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*Chapter II*  
*Literature Review*

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## II.1 Introduction

The oral absorption process from a pharmaceutical dosage form is complex. However, the major steps occurring during oral drug absorption can be regarded as part of a serial process:

- The dissolution of the drug from the dosage form
- The solubility of drug as a function of its physicochemical characteristics
- The drugs effective permeability across the intestinal wall.
- Its pre-systemic metabolism.

All of these processes can have direct effect relationships with intestinal site, gastric emptying and transit time dependence, which have significant effects on the rate and extent of drug absorption and therefore the safety and efficacy of the drug product.

Fundamental knowledge can be acquired about the above processes, which allows for efficient, scientifically supported formulation design. The key in any development process is to define the overall rate-limiting factor(s) to the oral absorption process of a drug product.

Carefully designed experiments for each of these processes allow mechanistic separation of this sequence of events, enabling identification of the rate-limiting step(s). Solubility, dissolution rate and intestinal permeability, are the major biopharmaceutic factors that affect the rate and extent of absorption of an oral drug product. The FDA has acknowledged the impact of these processes on drug product performance and is finalizing a guidance document that reflects the above scientific rational. This guidance will allow classification of drug candidates (Biopharmaceutics Classification System, BCS) based on solubility/dissolution and intestinal permeability characteristics, which will substantially facilitate the drug product development and approval process for a large group of drug candidates. Knowledge of this classification for a drug candidate early in the drug development program enables better risk assessment in starting clinical studies with a formulation that is not yet scaled up for full production. The goal of the biopharmaceutics (drug) classification system is to function as a tool for developing in vitro dissolution specifications for drug products that are predictive of their in vivo performance. The underlying scientific rational for the BCS has been discussed previously (Amidon et al, 1995; Amidon, 1996) and a broad variety of aspects related to its further development and application have compiled in a summary booklet published by the AAPS in 1997 (Amidon et al, 1997).

**Table II. 1      Drugs are proposed to be classified according to the following scheme**

Biopharmaceutics class	Solubility	Intestinal permeability
I	HS	HP
II	LS	HP
III	HS	LP
IV	LS	LP

HS: High Solubility; largest dose dissolves in #250ml of water over a pH range of 1–8.

HP: High Permeability; extent of absorption is > 80%.

Class-I drugs dissolve rapidly in an aqueous environment and are rapidly transported over the absorbing membrane. No strategies are required to increase their absorption. When the release of the active from the formulation is slower than the gastric emptying rate, good in-vitro-in-vivo-correlation (IVIVC) can be expected. The absorption (rate) of class-II drugs can be enhanced by accelerating the dissolution. Class-II drugs show IVIVC as long as the in-vivo dissolution rate is same as in-vitro. However, because the dissolution rate is critical for class-II drugs, the in-vivo absorption can be affected by several physiological fluctuations, like the volume and pH of the intestinal juices, the presence of bile salts, food, enzymes, and bacteria, the motility of the gut and the viscosity in the gut lumen.

For class-III drugs the absorption is rate limiting and in-vitro dissolution experiments cannot be used to predict in-vivo absorption. Also for class-IV drugs no IVIVC can be expected. It is up to the formulation scientist to increase the extent of absorption but also to improve the IVIVC. This will reduce the patient-to patient variability and improve the bioavailability and the predictability of pharmacokinetic parameters. It is clear that, depending on the classification of the drug, different strategies can be applied to increase or accelerate the absorption of a drug: either increasing the permeability of the absorbing membrane or increasing the amount of dissolved drug that is in contact with the absorbing membrane. For Class-III drugs, the permeation over the membrane is rate limiting. The strategy for class-III drugs is to increase the permeability of the absorbing membrane. Polar compounds and those that rely on some form of facilitated transport process generally display good absorption from the upper GI tract, but are poorly absorbed in the large intestine (or colon). As a consequence, their oral bioavailability can be affected by the limited absorptive site. In addition, the development of a modified release product, such as those designed to provide once-daily dosing, will be difficult, if not impossible. Hence, the concept of an '*absorption window*' has become popular (Corrigan, 1997).

Some drugs display region-specific absorption that can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile (Macheras et al, 1995).

Enhancing the gastric residence time (GRT) of a *narrow absorption window* drug may significantly improve the net extent of its absorption. This issue was demonstrated in a seminal experiment by Levy (1976) that compared the bioavailability of riboflavin when taken with Coca Cola, light cola, or water. The GRT of riboflavin attained by the glucose together with phosphoric acid in the Coca Cola was considerably larger than that produced by phosphoric acid alone in the light cola, while the GRT following intake with water was the shortest. There was a direct correlation between the prolonged GRT and enhanced bioavailability.

## *II.2 Regional Differences in Drug Absorption*

In 1985 Brockmeier et al. stated that little was known about the local absorption characteristics along the gastrointestinal tract for most drugs (Brockmeier et al, 1985). In the meantime, numerous studies have been published using the different techniques described in the last section. For several drugs no relevant differences between the observed gastrointestinal segments could be demonstrated: In human perfusion studies, for example, Gramatté et al. found that absorption of paracetamol was similar from the proximal and distal small intestine (Gramatté, T. and K. Richter, 1994). With the same technique, Delchier et al. found similar absorption rates for nicardipine from the jejunum and ileum (Delchier, et al, 1988). By means of the local instillation technique, Tay et al. demonstrated a consistent absorption of gepirone throughout all parts of the small intestine (Tay et al, 1992). However, in a number of studies published, more or less distinct site specific differences of drug absorption have been demonstrated. Amongst others, d'Agay-Abensour et al. found in human perfusion experiments that the absorption of 1-deamino-8-D-arginine vasopressin decreased in the order of stomach, duodenum and jejunum > distal ileum > proximal colon (d'Agay-Abensour et al,1993). Barr et al reported a decreased absorption of amoxicillin from the ileum compared to jejunum and ileum (Barr et al., 1994).

In colon no amoxicillin absorption could be observed (Barr et al, 1994). Jobin et al. and Godbilon et al. demonstrated that metoprolol was absorbed similarly from jejunum and colon but no absorption was observed from the stomach (Jobin et al, 1985). Ranitidine also shows site dependent differences in drug absorption, as reported by Williams's et al. and Gramatté et al (Williams et al, 1992, Gramatté et al, 1994). Williams et al. reported a similar absorption after local instillation of ranitidine into the stomach and the ileum, but slower absorption when the drug was instilled into the caecum. The results were confirmed and specified by the in vivo human perfusion studies performed by Gramatté et al., who found that the absorption rate of ranitidine decreased with the distance of the perfusion site from the mouth. Other examples of drugs with regional differences in rate and extent of absorption are allopurinol (Schuster et al, 1985), benazepril (Chan et al, 1994), ciclosporine (Drewe et al,1992), ciprofloxacin (Staib et al, 1989), Harder et al ,1990), glibenclamide (Brockmeier et al,1985), piretanide (Brockmeier et al,1986a; Brockmeier et al ,1986b), and sumatriptan (Warner et al,1995).

The observed regional differences in drug absorption can be associated with different phenomena. Generally, the extent of drug absorption in a particular gastrointestinal segment is determined by the rate of absorption, the available surface area and the transit time through the segment. Due to its large surface area, the small intestine is expected to be the primary absorption site for many drugs (Davis et al, (1986). However, there are examples of drugs reported in literature that are absorbed from the colon to a relevant extent, e.g. glibenclamide (Brockmeier et al,1985), theophylline (Yuen et al,1993), acetaminophen and phenylpropanolamine (Ishibashi et al,1999). In this case the high residence time in the large intestine compared to the small intestine might compensate for the less optimal surface area available for absorption in the large intestine (Waterman and Sutton, 2003).



### *II.3 Models for the investigation of intestinal drug absorption and absorption sites*

Drug discovery scientists use many techniques when evaluating the intestinal permeability of drug candidates during the drug selection process (Balimane et al., 2000).

#### *II.3.1 In-silico methods -Computer-Aided Drug design (CADD)*

#### *II.3.2 In-vitro*

##### *II.3.2.1 Excised tissue*

*II.3.2.1.1 Perfused intestinal segments*

*II.3.2.1.2 Everted sacs*

*II.3.2.3 Intestinal mucosa (stripped/Unstripped) mounted in Ussing chamber.*

##### *II.3.2.2 Isolated enterocytes*

##### *II.3.2.3 Membrane vesicles (BBMV, BLMV)*

*II.3.2.3.1 Caco-2 cells*

*II.3.2.3.2 Mardin-Darby canine kidney -MDCK cells/MDRI-MDCK-II*

*II.3.2.3.3 HT-29-MTX*

*II.3.2.3.4 TC-7*

*II.3.2.3.5 2/4/A1*

##### *II.3.2.4 Artificial membrane methods*

*II.3.2.4.1 Immobilized artificial membrane (IAM) Columns*

*II.3.2.4.1 Parallel Artificial Membrane Permeability Assay (PAMPA)*

#### *II.3.3 In-situ intestinal perfusion*

#### *II.3.4 In-vivo*

*II.3.4.1 Animals: Dog, Rat*

*II.3.4.1 Human*

### II.3.1 In-silico methods

There is a need to develop quantitative and predictive mathematical models that relate various physicochemical properties to intestinal permeability and absorption so that poorly absorbed compounds are eliminated in the initial stages of drug discovery. (Subramanian and Kitchen, 2006). The suitability of chemical structures could be determined even before the compound is synthesized. This could make it possible to save money, time and effort spent in bad compounds. It also has an ethical component in that it would avoid the need to use either animals or animal tissues to test absorption potential.

**Table II. 2      Outputs and Minimal Inputs for the Predictive ADME Software Packages (Bohets et al., 2001)**

MINIMUM INPUT	OUTPUT
<b>QMPRPlus<sup>TM</sup></b> (Quantitative Molecular Permeability Relationship) 2D/3D Structures	Log P, $P_{eff}$ , water sol., Molar volume, 2D/3D Molecular descriptors
<b>Gastroplus<sup>TM</sup></b> PKa, Solubility, $P_{eff}$ , Dose + Formulation, Diffusivity	Fraction of dose absorbed ( $F_a$ ), $F_a$ Vs time in different regions of the gut.
<b>iDEA<sup>TM</sup></b> (Physiological based absorption module) Rabbit intestinal segments permeability, Caco-2 P <sub>eff</sub> , efflux ratio, solubility, dose	$F_a$ , Rate & extent of absorption, $F_a$ Vs time in different regions of the gut.

### II.3.2 In-vitro Methods

#### II.3.2.1 Excised tissue

##### II.3.2.1.1 Perfused intestinal segments

Isolated intestinal segments comprise the absorptive cells and the underlying muscle layers. As it is commonly used, this technique only allows sampling from the mucosal side; drug disappearance is assumed to be equal to drug absorption. This assumption is valid when apical uptake is the rate-limiting step in drug absorption. (Sugawara et al., 1990).

#### Advantages

- Used to study segmental differences in drug absorption and metabolism without the interference from physiological factors such as, gastric emptying, surface area of the segment and/or small intestinal transit time.
- It may also be useful to evaluate the absorption of drugs whose poor solubility requires the use of complex dosing vehicles, which could not be presented to other *in vitro* systems such as, culture cells. (Hidalgo, 2001)

**Disadvantages**

- The determination of absorption based on luminal disappearance is potentially misleading.
- It requires large amounts of compound, relative to other *in vitro* systems.
- The number of intestinal segments that can be obtained from one animal is limited.
- As is the case with other excised tissue preparations, the viability of perfused intestinal segments is limited.
- Mucosal metabolism and mucosal accumulation could lead to an overestimation of true drug absorption, greater value in the elucidation of transport mechanisms.

As a result of these limitations, this technique is not likely to be useful as a Screening tool. (Hidalgo, 2001)

**II.3.2.1.2 Everted sacs**

The everted intestine sac, first described by Wilson and Wisemans, has been used to study drug absorption and metabolism (Wilson and Wiseman, 1954). The everted sac was one of the first *in vitro* techniques used to study intestinal drug absorption. It is prepared by inverting a piece of intestine using a glass rod.

**Advantages**

- Results are reported to have a better reproducibility compared to data obtained in Ussing chamber experiments.
- Other advantages are the relatively large surface area available for absorption and the presence of mucus and unstirred water layers.

**Disadvantages**

- Similar to the Ussing chamber, the tissue viability is limited to approximately 2 hours. (Maurer and Rump, 1991; Bouer et al, 1999; Sharma et al., 2002).
- A potential disadvantage of this approach is the presence of the muscularis mucosa, which is usually not removed from everted sac preparations. This might evoke an underestimation of the transport of compounds with a tendency to bind to muscle cells (Le Ferrec et al., 2001).

This technique was popular a few decades ago, but its utilization in recent years has been greatly reduced. It is unlikely that it will constitute an important absorption-screening tool in the future. (Hidalgo, 2001)

**II.3.2.1.3 Intestinal mucosa (stripped/Unstripped) mounted in Ussing chamber**

The using chamber was named after its inventor, the Danish professor, Hans Ussing, and the first application of the new technique was for studies of ion transport in frog skin (Ussing & Zerahn, 1951). Later, the Ussing chamber was utilized for the measurements

of drug tissue permeability to predict intestinal drug absorption (Grass & Sweetana, 1988; Ungell et al, 1998; Gotoh et al, 2005).

This model constitutes a bicompartamental system in which a compound can be exposed to either the mucosal or serosal surface and the rate of appearance in the other compartment can be measured by standard means of chemical detection. In this way the rates of transport or 'flux' across the epithelium can be readily determined. Absorption by paracellular passive diffusion is characterized by equal rates of transport from both mucosal and serosal surfaces, while carrier mediated 'active' transport is characterized by a significant enhancement in flux in one direction (Swaan et al., 1994; Hidalgo, 1993).

The removal of this muscle layer, a process known as stripping, is advantageous for two reasons. First, it removes an artificial permeability barrier, and second, stripped tissues can be oxygenated more efficiently. (Ungell et al., 1998)

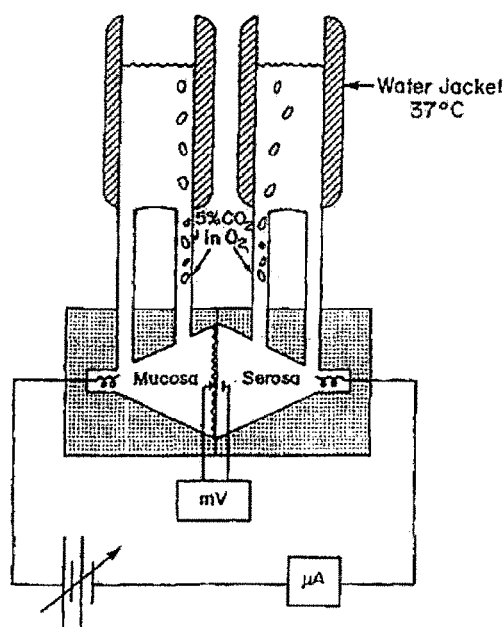


Figure II. 1 Schematic diagram of Using Chamber

### II.3.2.2 Isolated enterocytes

The process of cell isolation destroys many cells and greatly diminishes cell viability. (Pinkus, 1975). Because cells must be used as a suspension, they lack the polarity that characterizes intestinal mucosal cells *In Vivo*. Thus, isolated enterocytes can be used to study drug uptake, but not transepithelial transport or transport polarity. This technique is not commonly used because of its limited utility. (Hidalgo, 2001)

### II.3.2.3 Membrane vesicles (BBMV, BLMV)

Cell based assays are commonly used in *in-vitro* assays to predict the absorption rate of candidate drug compounds across the intestinal epithelial cell barrier. Cell membrane preparations include brush-border membrane vesicles and basolateral membrane vesicles. These preparations constitute simplified models to study mucosal absorption (Sugawara et al., 1991; Saitoh et al., 1988)

The assay determines the drug absorption rates ( $P_{app}$ ) across a cell monolayer. The Caco-2 cell line is heterogeneous and is derived from a human colorectal adenocarcinoma. Caco-2 cells are used as *in vitro* permeability models to predict human intestinal absorption because they exhibit many features of absorptive intestinal cells.

- Ability to spontaneously differentiate into polarized enterocytes that express high levels of brush border hydrolases and form well developed junctional complexes.
- Possible to determine whether passage is transcellular or paracellular based on a compound's transport rate. Caco-2 cells.
- Express a variety of transport systems including di-peptide transporters and P-glycoproteins (Pgp).
- Information can be gained on metabolism and potential drug-drug interactions as the drug undergoes transcellular diffusion through the Caco-2 transport model.

#### **Advantages:**

- Provides information on both passive and active permeability.
- Caco-2 assay shows a relationship with human intestinal absorption (HIA).
- Expression of transporters in Caco-2 cells alters with increased passage number.

#### **Disadvantages:**

- The Caco-2 cell line is extremely difficult to grow. It is a slow growing cell line and it tends to grow in clumps on top of one another.
- It is extremely laborious to culture these cells on the inserts. (Hidalgo, 2001).
- It is static, paracellular absorption might be underestimated and very low transport rates compared to the human small intestine is suggested (Barthe et al., 1999).

### II.3.2.4 Artificial membrane methods

A new approach for studying passive absorption of drugs is based on artificial membrane, i.e., liposomes, Parallel Artificial Membrane Permeability Assay (PAMPA) bio-mimetic lipid membrane and Immobilized Artificial Membrane (IAM)-HPLC.

#### **II.3.2.4.1 IAM -Immobilized Artificial Membrane columns**

Passive drug absorption across the gastrointestinal wall is governed by several molecular properties including lipophilicity, molecular size, charge, hydrogen bonding and solubility. Importantly, most of these properties are dependent on one another. Solubility

and permeability are considered in the framework of the biopharmaceutical classification system as fundamental to define the rate and extent of absorption of the active ingredient of a drug product.

Immobilized artificial membranes (IAMs) prepared from phosphatidylcholine analogs are used as stationary phases in liquid chromatography systems to model drug partitioning between an aqueous phase (mobile phase) and a cell membrane (IAM column). They simulate the hydrophobic and hydrophilic contribution of drug-membrane partitioning and can be used to as a fast screening column for predicting drug absorption.

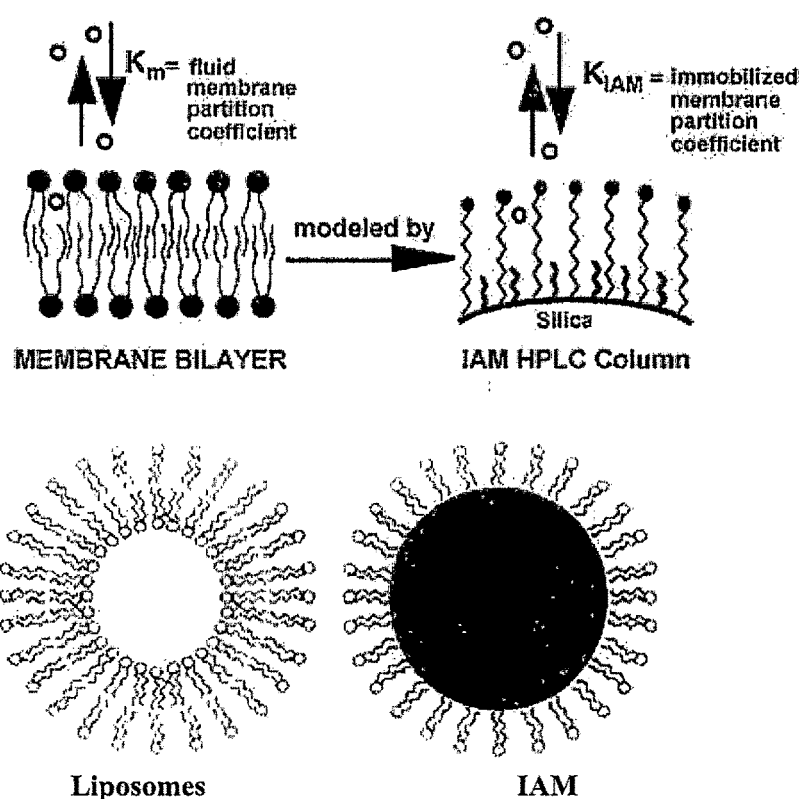
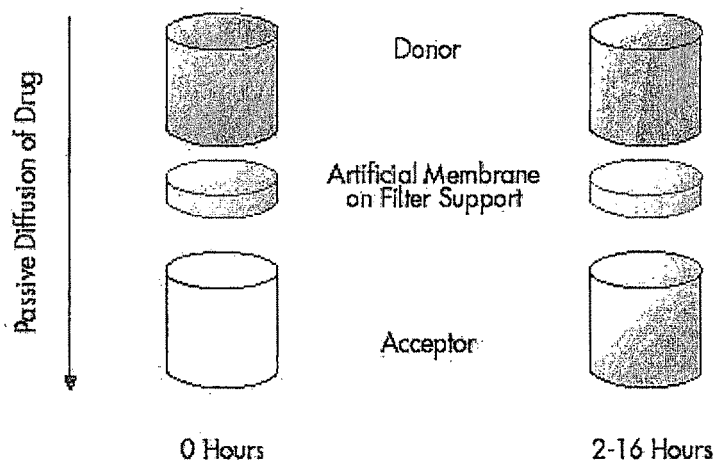


Figure II. 2 Membrane bilayers and IAM HPLC column

#### II.3.2.4.2 PAMPA- Parallel Artificial Membrane Permeability Assay

PAMPA is a non-cell based assay designed to predict passive, transcellular permeability of drugs in early drug discovery. The ability of compounds to diffuse from a donor compartment, through a membrane filter pretreated with a lipid-containing organic solvent, into an acceptor compartment is evaluated. These plates are particularly recommended for use in pre-ADME or Discovery programs requiring compound rank ordering or profiling.



**Figure II. 3 Individual Donor/Acceptor Well Assembly Before and After Incubation in PAMPA**

#### Advantages

- Fast, versatile, and low-cost.
- Helpful complement to cellular permeability.
- Provides information about passive-transport permeability that is not complicated by other mechanisms.
- High-throughput and flexible for the changing needs of drug discovery projects – no need to wait for cell growth.
- Useful as a front-line screen for ranking passive permeability.
- Amenable to examining absorption in different pH environments and has a broader dynamic range than Caco-2. Is useful for examining potential differences in absorption throughout the GI tract.

#### Disadvantages

- Should not be used to predict human intestinal absorption.
- Ineffective in predicting potential P-gp substrates.
- Use in conjunction with Caco-2 to find the root cause of poor absorption.

Recently, bio-mimetic artificial membrane permeation assay (BAMPA) is introduced as an improved version of PAMPA. It is an *in vitro* method to predict transcellular pathway permeation. In BAMPA, the composition of the lipid membrane is modified to mimic the intestinal brush border membrane. It is reported that the paracellular permeation could be predicted using the calculation model for molecular size-restricted diffusion within a negative electrostatic field of force. The Renkin function is employed as the molecular size-restriction function in their model.

### II.3.3 In-situ intestinal perfusion

One, or a combination of these models, is routinely used in permeability assessment in drug discovery. Within these techniques, single pass intestinal perfusion technique showed the most constant absorption rate and also a good correlation with human data using and similar perfusion technique (Fagerholm et al., 1996; Schugers et al., 1986). The artificially induced fluid movement on the intestinal absorption has also been studied in animals (Lennernas, 1995; Ochsenfahrt and Winne, 1974).

Rat single-pass intestinal perfusion is an *in situ* approach with intact anatomy and physiology. Thus, this approach is much more physiologically and pharmacologically relevant and input of drugs can be controlled in terms of concentration, pH and composition (Lu et al., 1992). The assessment of permeability by this technique has been used to predict human oral absorption for both passive and carrier-mediated transport of compounds (Amidon et al., 1988; Sinko et al., 1987). Its limitations include the technical difficulty, limited viability of tissue, and the need for larger amounts of compound for evaluation of drug absorption potential. From steady-state intestinal perfusion experiments in animals, dimensionless wall permeabilities have been estimated. Compounds with dimensionless intestinal wall permeability of 1.0 (equivalent to  $25 \times 10^{-4}$  cm/min) or higher have been shown to correspond to well absorbed drugs in humans, whereas drugs with dimensionless wall permeability of  $<0.1$  have been poorly absorbed. (Amidon et al., 1988; Fagerholm et al., 1996). Other approaches for rapid assessment of absorption potential include IAM (Pidgeon et al., 1995) and PAMPA (Kansy et al., 1998). The IAM chromatography offers the advantages of experimental simplicity and good correlations between IAM  $k'$  values and Caco-2 permeabilities have been reported. PAMPA is based on a 96-well microtiter plate technology and allows reasonable throughput, although it lacks similarity to natural membranes in that it does not possess pores or active transport mechanisms. It enables fast determination of the trends in the ability of the compounds to permeate membranes by passive diffusion and is thus suited for the screening of large libraries. A caveat of the IAM and PAMPA approaches is to remember that they will underestimate the absorption of compounds subject to active or paracellular transport *in vivo* and overestimate the absorption of compounds subject to efflux pump transport (White, 2000).

It has previously been demonstrated that a good correlation exists between permeability and the fraction of drug absorbed in the same species (Lennernas, 1998; Chiou, 1995). To date, one of the most commonly used assays to estimate a compound's absorption in human is to examine Caco-2 permeability. Although a general correlation does exist between Caco-2 permeability and drug absorption in humans, this model only works within certain limits. When drugs have low Caco-2 permeability or drugs are absorbed through carrier-mediated routes, many discrepancies can arise (Sun et al., 2002; Sun et al., 2004). On the other hand, the Caco-2 model is also limited because it does not account for the dose or the solubility of the drug in the intestinal lumen (Rubas et al., 1993) and cannot tell the differences between cellular transport and intestinal metabolism.



Indeed, this hypothesis has been confirmed by many reports from literatures for hundreds of compounds (Chiou, 1995; Zhao et al., 2003; Chiou, 1998). For drugs with low solubility, it has been shown that using an Ussing chamber with rat intestinal epithelium is more effective in predicting human fraction absorbed than using Caco-2 cells (Watanabe et al., 2004). However, up to date, the underlying mechanism of drug absorption similarity between the species has not been fully characterized. Therefore, the transporter expression profiles, especially for those transporters involved in carrier-mediated drug absorption process, will uncover the molecular mechanisms of drug absorption correlation between human and rat.

**Table II. 3 Models to determine intestinal permeability with advantages and limitations.**

SYSTEM	METHOD	EXAMPLES	ADVANTAGES	LIMITATIONS
<i>In vitro</i>	Artificial membranes – parallel artificial membrane permeation assay (PAMPA)	(Kansy et al., 1998)	Suitable for high-throughput screening (HTS)	Adequate for ranking of compounds in low, medium and high absorbability
	Subcellular fractions – brush border membrane vesicles (BBMV) and basolateral membrane vesicles (BLMV)	(Fan et al., 1998; Koga et al., 1998)	Useful for studying transcellular route	Extrapolation <i>in vivo</i> is difficult
	Cell cultures	(Caco-2, MDCK)	Validated for study of intestinal passive diffusion. Suitable for HTS. Allows study of carrier-mediated processes.	Less correlation with act carrier-mediated transport. Inter-laboratory variability
	Isolated tissues – ussing chambers, everted sacs		Complexity and characteristics closer to the <i>in vivo</i> situation	Less suitable for HTS
<i>In situ</i>	Continuous, single-pass perfusion	Animals (rat)	Good predictive performance for passive absorption	Non suitable for HTS. Less accurate estimation of performance of hydrophilic compounds
	Closed loop	(rat)	Good predictive performance for passive absorption	Hydrodynamic conditions different from <i>in vivo</i> situation
<i>In vivo</i>	Animals – rat, dog		Good predictive performance for passive absorption	Non suitable for HTS
	Human perfusion studies	(Lennernas et al., 1992)	Allows quantitative and mechanistic evaluation of drug absorption	Non suitable for HTS

Experimental methods, such as animal *in vivo* and ex vivo models have so far been evolved to estimate gastrointestinal absorption of drugs (Artursson, 1991; Hillgren et al.,

1995; Rubas et al., 1993; Salphati et al., 2001). One of the most used classic techniques employed in the study of intestinal absorption of compounds has been the single-pass intestinal perfusion (SPIP) model (Crouthamel and Sarapu, 1983; Sutton et al., 2001a), which provides experimental conditions closer to what is faced following oral administration. This technique has lower sensitivity to pH variations because of a preserved microclimate above the epithelial cells and it maintains an intact blood supply to the intestine (Hogerle and Winne, 1983; Shiau et al., 1985). Because water absorption and secretion during the perfusion may cause errors in the calculated Peff values, a non-absorbable marker to correct water flux is needed (Sutton et al., 2001). For this purpose phenol red is co-perfused with drug compounds.

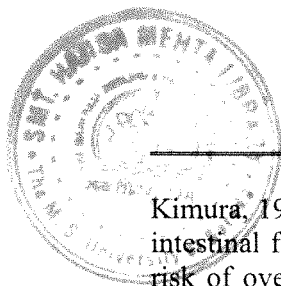
In-situ experimental methods are available and are used to predict the absorption of drugs *in vivo* (Hillgren et al., 1995; Fagerholm et al., 1996). The in-situ intestinal perfusion model has the obvious advantages over *in vitro* models of providing an intact lymphatic and blood flow circulation. However, from the pharmaceutical industry perspective the model is time consuming and suitable for high throughput screening. The passive component of absorption is independent of the active component in high stress perfusions and absorption is effectively all carrier mediated. Using single-pass, low mechanical stress perfusions, we have obtained evidence that the passive component of intestinal glucose absorption is mediated by the glucose induced activation and/or recruitment of GLUT-2 to the brush-border membrane.

Different techniques of intestinal perfusion are:

1. Single Pass Intestinal Perfusion (SPIP)
2. Recirculating Perfusion.
3. Oscillating Perfusion.
4. Closed Loop Perfusion

Among these, rat single pass intestinal perfusion (SPIP) technique is the most widely used, because of its proximity to *in vivo* conditions, lower sensitivity to pH variations because of preserved microclimate above epithelial cells, maintenance of intact blood supply to intestine, and good correlation with human absorption data.(Grassi and Cadelli, 2001; Salphati et al., 2001). Within these techniques, single pass intestinal perfusion technique showed the most constant absorption rate and also a good correlation with human data using and similar perfusion technique (Fagerholm et al., 1996; Schugers et al., 1986). Earlier studies have shown that the extent of absorption in humans can be predicted from an intestinal permeability values obtained by *in situ* perfusion in rats. (Amidon et al., 1988).

Among the various preclinical models that can be used to study drug absorption, *in situ* perfusion of small intestinal segments in anesthetized rats most closely mimics *in vivo* rat absorption studies. In contrast to for instance *in vitro* absorption models, the subsequent barriers a compound has to cross to reach the portal blood circulation are identical in the *in situ* and *in vivo* situation, which definitely contributes to the reliability of the *in situ* model. Although significant effects of anesthetic regimens on drug absorption in the experimental animal have been reported previously (Yuasa et al., 1993, Uhing and



Kimura, 1995), the intact blood supply and innervations with minimal interference of the intestinal function and architecture, guarantee optimal tissue viability, thus reducing the risk of overestimating drug absorption due to an impaired barrier function. The *in situ* technique also offers the unique possibility of studying the intestinal events in isolation without the complication of biliary excretion and enterohepatic circulation. In addition, as for the Ussing chamber technique, drug absorption in the different regions of the small intestine can be evaluated (Hu et al., 2000). Although *in situ* perfused rat intestine has been used previously for instance to compare the absorption characteristics of a small series of peptides (Kim et al., 1993), the model is not very amenable for increased throughput screening purposes. Nevertheless, the model is widely used for the selection of drug candidates and to confirm results obtained in simpler models of drug absorption, such as Caco-2, often lacking certain features (e.g. mucus layer) that may influence drug absorption. For example, the enhanced absorption of the antiviral agent adefovir when administered as the prodrug adefovir dipivoxil was demonstrated in Caco-2 monolayers (Annaert et al., 1997) and this effect was confirmed with *in situ* perfused rat ileum (Okudaira et al., 2000). In a study conducted by Stewart et al. (Stewart et al., 1995), the prediction of the fraction of dose absorbed in humans from rat intestinal perfusion data was demonstrated for a series of compounds with variable (5-100%) absorption in humans. In addition, a high correlation between effective permeability values determined in rat and human jejunum has been demonstrated (Fagerholm et al., 1996). In a recent review (Lennernäs, 1998), Lennernäs thus concluded that *in situ* perfusion of rat jejunum is a useful technique to classify compounds according to BCS, provided that appropriate reference compounds are included to account for interlaboratory variations in passively and actively transported drugs. Several modifications of the *in situ* technique have been developed and a comparison between these modifications was made by Schurgers et al. using theophylline as test compound. (Schurgers et al., 1986). In the 'closed loop' approach (Doluisio et al., 1969, Hasegawa et al., 1996); a drug solution is introduced into a 10-20 cm segment of the intestine that is tied off at both ends. The luminal solution is then sampled after a certain incubation time in order to determine the disappearance of drug from the lumen. Dynamic variants of this approach involving either oscillation or recirculation of the drug solution are used in order to better simulate the *in vivo* movement of luminal contents. One drawback of these approaches is that it is not always practical to determine the steady-state disappearance rate of drug from the lumen. For this reason, although larger amounts of test compound are required, the single-pass intestinal perfusion (Komiya et al., 1980), involving cannulation of the segment and perfusion with a drug solution at constant concentration and flow rate, is more often used. Adopting the parallel-tube model for rat intestinal perfusion experiments, effective permeability coefficients ( $P_{\text{eff}}$ , cm/s) can be calculated from the Area Under the Curve (AUC) ratio of the drug before ( $\text{AUC}_{\text{in}}$ ) and after ( $\text{AUC}_{\text{out}}$ ) passage through the segment, according to the following equation (Komiya et al., 1980; Levitt et al., 1988):

$$P_{\text{eff}} = \frac{(-Q_{\text{in}} \cdot \ln (\text{AUC}_{\text{out(corr)}}/\text{AUC}_{\text{in}}))}{A}$$

with  $Q$ , the flow rate of the perfusion medium, and  $r$  and  $L$  the radius and the length of the intestinal segment, respectively. It is recommended to correct outlet AUC for

intestinal water absorption/secretion by measuring area changes of the non-absorbable marker PEG-4000 (Hu et al., 1988). Determination of  $P_{eff}$  values is useful in that results from several studies have demonstrated a relationship between rat intestinal  $P_{eff}$  and the fraction of dose absorbed in man (Stewart et al., 1995; Lennernäs, 1997). It is well-known that the applied flow rate during the single-pass perfusion experiments determines the thickness of the so-called unstirred water layer (UWL, also 'aqueous boundary layer'), lining the apical (mucosal) side of the intestinal mucosa (Komiya et al., 1980; Zimmerman et al., 1997; Yuasa et al., 1988). Although the role of this UWL for intestinal drug absorption may be limited in humans (Lennernäs, 1997), experimental conditions during an *in situ* rat intestinal perfusion experiment are often such that diffusion across this UWL is rate-limiting for rapidly absorbed compounds (Yuasa et al., 1988).  $P_{eff}$  depends on the permeability across two barriers in series, namely  $P_w$ , the intrinsic permeability across the intestinal wall and  $P_{UWL}$ , the permeability across the UWL, and therefore one can write:

$$\frac{1}{P_{eff}} = \frac{1}{P_w} + \frac{1}{P_{UWL}}$$

There has been some debate about the physiologically most relevant flow rate and the thickness of the corresponding UWL and the fact that the flow rates applied are often too high (Barthe et al., 1999). Many studies use flow rates of  $\sim 0.2$  ml/min for rat intestinal perfusion experiments, and it was suggested that this is relevant based on flow rates used in human intestinal perfusions (2-3 ml/min) and the 10-fold smaller diameter of rat intestine (Fagerholm et al., 1996). The presence of this UWL also has consequences for calculation of intrinsic kinetic transport parameters from perfusion experiments. Johnson and Amidon have developed (Johnson and Amidon, 1988) the well established boundary layer approach to calculate  $P_w$  from the experimentally measured  $P_{eff}$  by factoring out the resistance across the UWL. The intrinsic membrane transport parameters ( $K_m$  and  $V_{max}$  for a carrier-mediated transport processes and  $P_m$  for passive transport) describing drug uptake and diffusion can then be obtained from  $P_w$ . It is noteworthy that domination of aqueous resistance during perfusion experiments can be avoided by keeping the ratio of outlet to inlet concentration greater than 0.85; on the other hand perfusion flow rate must be slow enough to allow for detection of significant differences between  $C_{in}$  and  $C_{out}$ . The boundary layer approach has been applied to calculate intrinsic transport parameters for instance for a series of  $\beta$ -lactam antibiotics (Hu et al., 1988) and for L- and D-methionine (Zheng et al., 1994). It should be mentioned that an alternative approach to the boundary layer method, namely a numerical aqueous resistance-nonlinear regression method, suitable for the calculation of permeability parameters for highly absorbed drugs (Sinko et al., 1996). The one major assumption that has to be taken into account with all of the above variants of the *in situ* intestinal perfusion technique is that disappearance of drug from the intestinal lumen accurately reflects drug absorption, i.e. appearance of the drug into the portal circulation. This however means that, if significant drug metabolism occurs, or if the drug extensively accumulates in the intestinal tissue, drug absorption will be severely overestimated. In order to obtain a more complete mass balance picture during *in situ* perfusion experiments, sampling from the mesenteric vein that is draining the blood from the perfused intestinal segment, often is performed. Although this approach is technically more complicated and requires substantial volumes of donor

blood to be infused in order to keep the blood volume of the animal constant, it has the major advantage that a direct measure of drug absorption is obtained. Also, pharmacokinetic analysis of differences between luminal drug disappearance rate and drug appearance rate in the portal circulation can give indications about retention and/or metabolism of the drug in the intestinal cells (Bohets et al., 2001). Some of the mechanisms may involve poor compound solubility in the gastrointestinal fluids, poor permeability across the gastrointestinal epithelium, insufficient stability in some gastrointestinal segments including enzymatic and non-enzymatic degradation, complexation, as well as, at times, pronounced hepatic first-pass extraction.

Its limitations include the technical difficulty, limited viability of tissue, and the need for larger amounts of compound for evaluation of drug absorption potential. From steady-state intestinal perfusion experiments in animals, dimensionless wall permeabilities have been estimated. Compounds with dimensionless intestinal wall permeability of 1.0 (equivalent to  $25 \times 10^{-4}$  cm/min) or higher have been shown to correspond to well absorbed drugs in humans, whereas drugs with dimensionless wall permeability of  $<0.1$  have been poorly absorbed. (Amidon et al., 1988; Fagerholm, et al., 1996).

### **II.3.4 In Vivo Methods**

In general, drug absorption in animals is believed to be a good predictor of absorption in humans.

#### **II.3.4.1 Animals**

##### **Advantages**

- Animals integrate all the biological factors that may affect drug absorption.
- Unlike *in vitro* systems, in which a correlation to *In Vivo* data must be established, this step is unnecessary when animals are used.
- The species used in absorption studies could be the same one used in pharmacology and/or toxicology evaluations.
- They also can be used to evaluate complex formulations, which would be very difficult to test *in vitro*.

##### **Disadvantages**

- The need for relatively large amounts of material.
- The complexity of the analytical methods needed for plasma analysis.
- The time-consuming and labor-intensive nature of experiments.
- They provide little mechanistic information on drug absorption.

#### II.3.4.2 Humans

A well established method to gain information on both, the absorption process and the site of absorption, is **the human intestinal perfusion** method. This technique uses a multiluminal tube which is placed in particular segments of the gastrointestinal tract (Godbillon et al., 1985; Gramatté et al., 1994; Gramatté and Richter, 1994; Gramatté et al., 1996). Similar to the in situ perfusion in laboratory animals, the tube is flushed with a solution of the test drug. The tube is also used to reaspirate the perfusion solution, which can then be analysed in appropriate drug assays. The disappearance of the drug from the solution as well as the drug concentration in blood samples can be used to determine the amount of drug absorbed. To avoid reflux of the drug solution beyond the desired segment and to exclude the contact with enzymes or other secretions of segments distal to the perfused segment, occlusive balloons can be employed [d'Agay-Abensour et al., 1993; Lennernas, 1997; Vidon et al., 1985]. While human perfusion experiments are well established for the detection of regional differences of permeability in the small intestine, a perfusion of the colon is hardly feasible by an intubation from the oral end. This is due to the enormous length of the tube necessary to reach the colon, and the high viscosity of the luminal content that hinders an aspiration of the perfusion solution from this segment.

Another method to examine regional differences in the absorption of a drug is its **local instillation** to a specific site of the gastrointestinal tract via a catheter (Williams et al., 1992; Brockmeier et al., 1986a; Brockmeier et al., 1986b). The site of instillation can be controlled either by endoscopy, fluoroscopy or pH-monitoring. By this means absorption of the drug from regions distal to the site of administration can be excluded (Rouge et al., 1996). This method provides only little mechanistic information on the absorption process, when only the final concentration of the drug in the blood is measured.

Conclusions regarding intestinal drug efflux or gut wall metabolism are hardly possible. Another drawback is that an endoscopic localisation of the tube is generally combined with a cleansing of the large intestine, resulting in non-physiological experimental conditions (Gleiter et al., 1985).

The administration of a drug to a specific site of the gastrointestinal tract can also be performed using a **high-frequency (HF) capsule**. This capsule with a size of 12 mm by 28 mm contains a latex balloon with a dissolved or suspended drug that is ruptured by a high-frequency signal, as soon as the capsule has reached the desired site of drug administration (Staib et al., 1989; Harder et al., 1990; Fuhr et al., 1994). The location of the capsule during its transit through the gastrointestinal tract is traced by X-ray. This method is also not adequate for mechanistic studies of the absorption process for the same reason described under local instillation via catheters.

Another method used for investigations on the absorption site of drugs is to trace an administered controlled-release dosage form via **pharmacoscintigraphy** (Kenyon et al., 1998; Kenyon et al., 1997; Wilding et al., 1991; Wilding et al., 1995). The gamma radiation emitted by tracers incorporated within the preparation (e.g. indium-111 (Wilding et al., 1991), samarium-153 or erbium-171 (Wilding et al., 1995), without

having an apparent impact on the formulation properties, allows one to observe the transit of the controlled-release product. Such studies provide an insight into the fate and integrity of delivery systems and enable the detection of the site of drug release from the dosage form (Wilding et al., 2001).

**Advantage:**

- An optimal presence of all physiological factors with impact on drug absorption.
- In combination with measurements of drug concentrations in the blood, regional differences in drug absorption can be demonstrated.

**Disadvantage:**

- Results obtained from in vivo studies do not provide sufficient mechanistic information on the absorption process due to a complex overlapping of numerous factors influencing the drug absorption (Rouge, N., P. Buri, et al. (1996)).
- All in vivo methods described are not practical for screenings or routine use, since the complex techniques are cost-intensive, time-restrictive, and require approval by ethics committees (Ungell, A.-L., 1997; Le Ferrec et al., 2001).

## ***11.4 Sources of Regional Differences in Drug Absorption***

Different mechanisms can be involved in the absorption of drugs from the gastrointestinal tract, including passive transcellular diffusion, paracellular diffusion, endocytosis and active transport, both in the absorptive and the secretory direction. For some drugs absorption is mediated by one of these routes exclusively, for others two or more mechanisms overlap.

Some absorption mechanisms provide potential explanations for regional differences in the rate and extent of drug absorption.

### **11.4.1 Passive diffusion**

As for passive diffusion, the pH partition hypothesis (Crevoisier and Buri, 1976) suggests a preferred absorption of acidic drugs in proximal regions of the gastrointestinal tract and an increased absorption of basic drugs in more distal regions. This is due to the pH gradient in the gastrointestinal fluids which alters the ratio between the protonated and unprotonated form of acidic and basic drugs. Since absorption of ionized compounds is assumed to be negligible in most cases, this ratio determines the amount of drug absorbed in a specific region of the gastrointestinal tract. Examples for this phenomenon are the basic  $\beta$ -adrenoceptor antagonists metoprolol (pKa: 9.5) and oxprenolol (pKa: 9.7) that are well absorbed from duodenum and jejunum but show no apparent absorption from the acidic milieu of the stomach [Jobin et al., 1985; Vidon et al., 1986].

However, these effects are based on pH-dependent differences in the lipid solubility of ionizable drugs and are not due to altered permeabilities of a specific substance in different segments of the gastrointestinal tract. Therefore, regional differences in the absorption of acidic and basic drugs will predominantly follow the rule described above, as long as the solubility and octanol-water partitioning remain sufficiently high over the physiological pH range of the gastrointestinal tract. For many drugs, however, this is not a realistic assumption (Brockmeier et al., 1985).

#### **II.4.2 Paracellular absorption**

Another possible source for regional differences in the absorption of drugs is the paracellular route. Instead of crossing the epithelial cells of the gastrointestinal tissues, substances can migrate across pores between the cells to be absorbed. This process is limited by transmembraneous proteins that are located between epithelial cells. These so-called tight junctions decrease the porosity of the epithelial cell layers, such that the paracellular route is only accessible to water and small hydrophilic molecules. This absorption mechanism is assumed to be of minor importance for the absorption of most drugs. However, it is considered to have relevance for the absorption of hydrochlorothiazide, cimetidine, 5-amino salicylic acid, small peptides and nucleoside analogues (Zhou et al., 1999; Thwaites et al., 1993; Park and Mitra, 1992). As the junctions between the epithelial cells become progressively tighter from the small intestine to the colon, the paracellular permeability decreases in that direction. This phenomenon is reported as an explanation for the decreasing permeability from jejunum to colon for hydrophilic  $\beta$ -adrenoceptor antagonists such as atenolol (Sasaki et al., 1994).

#### **II.4.3 Active transport processes**

For several drugs carrier-mediated transport is the major mechanism of absorption, for others it provides an additional absorption or secretion pathway. In both cases the saturability of the transporter can result in non-linear pharmacokinetics and dose dependent absorption. When the transporter carries the drug from the luminal side of the gastrointestinal tract to the blood side, a saturation of the carrier system might result in decreasing absorption with increasing doses, as described for cefatrizine (Yu and Amidon, 1999). In case of drug efflux carriers, increased absorption is assumed for increasing doses, as found for talinolol (Wetterich et al., 1996). For compounds undergoing carrier-mediated active transport in the absorptive direction, differences in the expression of the particular transporters throughout the gastrointestinal tract account for altered absorption from the respective region. When mechanisms apart from active transport play a negligible role in the overall absorption of a drug, any lack of expression of the carrier will result in the occurrence of so-called absorption windows. Absorption windows related to varying carrier expression have been reported for furosemide (Ritschel et al., 1991), riboflavin (Levy and Jusko, 1966; Klausner et al., 2002), levodopa (Deleu et al., 2002; Klausner et al., 2003) and several  $\beta$ -lactam antibiotics (Barr et al., 1994; Sanchez-Pico et al., 1989; Li et al., 1999; Yu et al., 1996; Bretschneider et al., 1999; Terada et al., 1997a, 1997b), such as amoxicillin, carindacillin, cefadroxil and cefatrizine. These drugs show site-specific absorption in upper parts of the gastrointestinal tract due to a lack of respective carriers (i.e. the amino acid transport systems LAT-2 and b0+ for levodopa (Gomes and Soares-da-Silva, 2002), and the peptide



transporters PEPT-1 and PEPT-2 for  $\beta$ -lactam antibiotics (Bretschneider et al., 1999) in lower intestinal segments (Sanchez-Pico et al., 1989; Ziegler et al., 2002).

For active transport processes in the secretory direction (i.e. intestinal drug efflux) no information is available in the literature dealing with a potential correlation between regional differences in the expression of the efflux pump P-glycoprotein within the gastrointestinal tract and regional differences in the absorption of P-glycoprotein substrates. However, opposite to the findings reported for substances transported by carriers from the luminal side to the blood side, the absorption of P-glycoprotein substrates must be assumed to decrease in regions with higher carrier expression.

Reports on the distribution of P-glycoprotein are controversial. In permeation study of the rat intestine Saitoh et al. found indications for a greater efflux in duodenum and jejunum compared to ileum and colon (Saitoh and Aungst, 1995). Other rat experiments published by Nakayama et al. suggested the highest efflux in jejunum (Nakayama et al., 2000). The results from rat studies published by Tamura, et al. and Makhey et al. are in contrast to these findings. Both working groups found that the P-glycoprotein function in ileum and colon was higher than in more proximal parts of the gastrointestinal tract (Tamura et al., 2002; Makhey et al., 1998). These findings are in accordance with studies in catfish, reported by Kleinow et al., who observed increasing P-glycoprotein levels from proximal to distal regions of the intestine (Kleinow et al., 2000). Finally, these results are in agreement with the PCR experiments published by Brady et al., who found that *mdr1*-mRNA levels in rat intestinal tissues increased from duodenum to jejunum and ileum. The highest mRNA levels were reported for the large intestine (Brady et al. 2002). The protein expression of P-glycoprotein in micropigs, however, was reported to be higher in proximal parts of the intestine than in more distal parts (Tang et al. 2002). The inconsistent results underline the demand for further investigations in this field.

## *11.5 Consequences for Dosage Form Design*

For several drugs regional differences in drug absorption result in decreased bioavailabilities. Therefore, one argument for the design of new controlled-release (CR) dosage forms can be an optimization of the drug delivery on the basis of the knowledge on preferred absorption sites for a specific drug (Klausner et al., 2002). When the occurrence of an absorption window limits the bioavailability of a drug, the goal for the design of an optimized dosage form is to increase the residence time within the gastrointestinal segment of preferred absorption. In literature, dosage forms are described that provide a targeted delivery of a drug to any of the three segments of the gastrointestinal tract, namely the stomach, the small and the large intestine (Rouge et al., 1996).

Enhancing the gastric residence time (GRT) of a Narrow Absorption Window (NAW) drug may significantly improve the net extent of its absorption. This issue was demonstrated in a seminal experiment by Levy (1976) that compared the bioavailability of riboflavin when taken with Coca Cola, light cola, or water. The GRT of riboflavin attained by the glucose together with phosphoric acid in the Coca Cola was considerably

larger than that produced by phosphoric acid alone in the light cola, while the GRT following intake with water was the shortest. There was a direct correlation between the prolonged GRT and enhanced bioavailability.

## *11.6 Gastrointestinal Transit*

The transit of a drug (formulation) through the GI tract will determine how long a compound will be in contact with its preferred absorptive site. In humans, the small intestine transit time is reasonably constant: at around three hours for a drug formulation (or for a meal) to pass from the stomach to the ileo-caecal junction (Davis et al., 1986). Transit through the colon is much longer and can be 20 h or more (Washington, et al., 2001). Hence, the time a drug will have in its absorption window can be relatively short, more so if the drug is preferentially absorbed in the proximal small intestine (e.g. jejunum) rather than throughout the small bowel. Consequently, the bioavailability of a drug, which is largely or exclusively absorbed from the upper GI tract, will be affected by factors that change GI transit. For example, the presence of food in the stomach will slow the rate of gastric emptying and will thereby keep the drug above or at the absorption window for a longer period of time. An increase in bioavailability might then be expected. However, if formulation excipients are used that increase the rate of transit in the small intestine (e.g. through an osmotic effect), the bioavailability can be reduced as observed with cimetidine, a polar drug that is almost exclusively absorbed from the small intestine (Adkin et al., 1995).

Some important drugs have absorption windows in the small intestine and, as a result, they often display low bioavailability after oral dosing. In addition, they are difficult to formulate into extended release products because on arrival in the colon (or even before), absorption will be low or non-existent. Efforts have been made to improve absorption, and various different strategies have been described in the scientific literature and in published patents.

## *11.7 Gastro-Retention*

In theory, an elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and for the drug to be released at an appropriate rate.

The strategies for delaying drug transit through the gastrointestinal (g.i.) tract fall into one of three categories:

- 1) Pharmacological,
- 2) Physiological and
- 3) Pharmaceutical; the first two being less attractive than the last because of toxicity problems.

**A pharmacological approach** involves the co-administration or incorporation of a drug into the dosage form. This drug delays gastro-intestinal emptying. Examples include antimuscarinics, e.g. propantheline, which are relaxants of the smooth muscle (Beermann and Groschinsky-Grind, 1978; Manninen et al., 1973) or a drug that changes motility, e.g. opiate analgesics or derivatives such as loperamide (Minami and McCallum, 1984). However, the potential side effects that may arise from such treatments on a routine basis would not be acceptable for regulatory approval.

**A physiological approach** is the use of natural materials or fat derivatives such as triethanolamine myristate (Groning and Heun, 1984, 1989), which stimulate the duodenal or jejunal receptors to slow gastric emptying. The use of large amounts of a 'volume filling' polymer such as polycarbophil (Harris et al. 1990a, b) can also cause a 'slowing down' response in terms of gastro-intestinal transit. A lesser-known phenomenon is the ileal brake (Van Citters and Lin, 1999). There are particular dietary components, for example, fats and fatty acids that are infused into the terminal ileum and can cause a slowing of intestinal transit. This 'braking' mechanism appears to be a feedback process for the improved digestion of dietary components. Studies have been performed in humans to identify optimal ileal brake activators (quality and quantity). One of which investigated whether ileal brake activators could alter the bioavailability of atenolol from the small intestine by slowing intestinal transit and thereby increasing the time available for absorption (Dobson et al., 2002). Oleic acid and a monoglyceride were formulated into modified release capsules that were targeted to the small intestine. The results showed that, in some volunteers, an increase in small intestine transit time led to an increase in the quantity of drug absorbed. However, drug absorption was related not only to the total time spent by the drug in the small intestine, but also other factors such as the proportion of such time spent at the ileo-caecal junction. This study highlighted the complexities of exploiting natural GI processes to enhance the oral bioavailability of drugs. Kroening et al. have recently reported that tapeworms can slow the transit of intestinal contents (Kroening et al., 2003). Of the tapeworm-secreted compounds tested, only luminal infusion of guanosine 3', 5'-cyclic monophosphate (cGMP) induced contractile patterns that mimicked those observed during tapeworm infection. As a consequence, it has been suggested that cGMP might be used in proprietary pharmaceutical formulations to improve drug absorption; 'Wisconsin investigators have filed for a patent on the idea of adding cGMP to drugs to lengthen the amount of time they spend in the gut and thus increase how much medicine a person absorbs' (<http://www.sciencenews.org/articles/20030322/fob6.asp>).

Unfortunately, the patent position will be less than certain because, in 1982, the *Escherichia coli* heat-stable toxin was reported to activate the cGMP system (Mathias et al., 1982), which altered motor activity thus slowing transit and enabled bacterial proliferation and invasion. Bacteria have other strategies that help to promote invasion. Fimbriae are long filamentous protein projections on the surface of certain organisms that allow them to adhere to receptors on the brush borders of villous enterocytes (Cleary et al., 2004). Caston et al. investigated the use of purified fimbriae from *E. coli* as a natural bioadhesive (Caston et al., 1990). The fimbriae were attached to small microspheres.

Encouraging data were reported for a rat model in terms of an increase in small intestine transit, but the system has yet to be investigated in humans.

Pharmacological and physiological approaches thus set out to delay gastrointestinal transit by modification of the rate of gastric emptying using 'passage-delaying agents'. By contrast, the pharmaceutical strategies attempt to achieve the same objective by actually retaining the dosage form at or upstream of its absorption site for as long as possible.

The main approaches that have been examined thus far are:

- low density of the GRDF that causes buoyancy above gastric fluid;
- high density which retains the dosage form in the body of the stomach that is anatomically lower than the pyloric sphincter;
- bioadhesion to gastric mucosa;
- swelling to a large size which prevents emptying of the dosage form through the pyloric sphincter.

Controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. Incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic (PK) and pharmacodynamic (PD) factors.

## **II.7.1 Pharmacokinetic aspects**

### **II.7.1.1 Enhanced bioavailability**

Once it has been ascertained that the compound in question is defined as NAW, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For e.g. the bioavailability of riboflavin and levodopa CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations (Klausner et al., 2002, 2003).

### **II.7.1.2 Enhanced first pass biotransformation**

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

### **II.7.1.3 Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum**

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, CR-GRDF may elevate absorption compared to the immediate and CR dosage forms.

#### II.7.1.4 Reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

#### II.7.1.5 Targeted therapy for local ailments in the upper GI tract

The prolonged and sustained administration of the drug from the GRDF to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

### II.7.2 Pharmacodynamic aspects

(Hoffman, 1998; Hoffman and Stepensky, 1999)

#### II.7.2.1 Reduced fluctuations of drug concentration

Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

#### II.7.2.2 Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

#### II.7.2.3 Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

#### II.7.2.4 Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

#### II.7.2.5 Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to development of microorganism's resistance.

## 11.8 Aim of the Thesis

The aim of the present study was to develop various gastro retentive drug delivery systems for a drug having region specific absorption. Alfuzosin was chosen as a model drug. Alfuzosin has a short half-life and shows the characteristic of being absorbed preferentially in the upper part of the gastrointestinal tract and, in particular, being absorbed in the duodenum and the jejunum (Maggi et al., 2000; Andrieu et al., 1995).

Alfuzosin is a functionally uroselective  $\alpha_1$ -adrenoreceptor antagonist. It can improve urinary voiding symptoms and increase urinary flow rates while causing few cardiovascular adverse effects. When administered as an immediate release (IR) formulation, alfuzosin must be administered twice or thrice daily associated with the following disadvantages (Kate and Greg, 2002):

- Vasodilatory – related events (dizziness, headache, hypotension, postural hypotension, malaise).
- Dose titration required so as to avoid first day effects.
- Dosage adjustment for elderly patients or those receiving concomitant anti-hypertensives.

In order to avoid the above disadvantages associated with an IR formulation, a prolonged release (PR) formulation is required that may produce small variations in peak and trough serum drug levels which may contribute to the lower frequency of cardiovascular adverse effects and may also improve patients perception of quality of quality of life.

A prolonged release (PR) formulation of alfuzosin is available in the market with the Brand name of UROXATRAL (strength – 10 mg) (Synthelabo).

*Key features of this PR formulation are:*

- Is available as a tri-layered tablet, in which the barrier layers (one swellable and one erodible) are applied to the planar surfaces of compressed tablets, producing a three-layered matrix with the active substance between two inactive layers.
- Hydrophilic polymers, contained in the inactive layers swell on contact with fluid resulting in an increased gastric retention and continuous release of alfuzosin over the dosage interval.
- Most of the absorption occurs in the proximal part of the gastrointestinal tract because of the slow dissolution and higher duodenal versus colonic permeability.

- Effect of food is that the extent of absorption is 50% lower under fasting conditions where as no food effect is observed with an immediate release formulation.

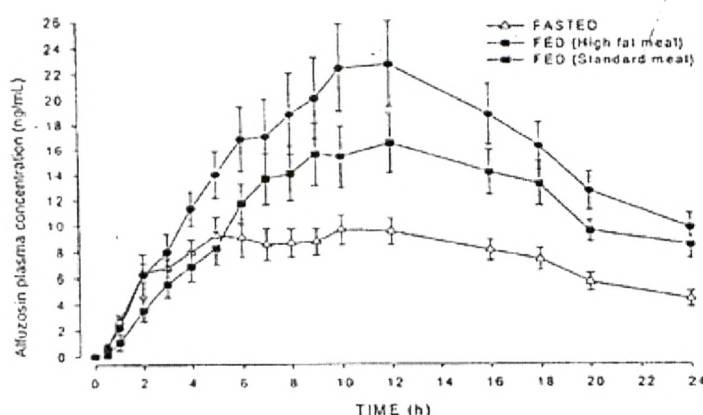


Figure II. 4 Effect of food on absorption of Alfuzosin Hydrochloride

Table II. 4 Transit profile (Mean  $\pm$  SD) of the tablet core for fasted and fed volunteers.

	Gastric emptying (Hours post-dose)	Colon arrival (Hours post-dose)	Small intestinal transit time (hrs)	Initial tablet disintegration (Hours post-dose)	Complete tablet disintegration (Hours post-dose)
Fasted (n=8)	0.59(0.35)	5.82(1.96)	5.23(1.66)	2.98(1.45)	18.30(5.01)
Fed <sup>a,b</sup> (n=8)	5.90(2.24)	11.70(0.96) <sup>a</sup>	5.99(5.76) <sup>a</sup>	2.92(0.51)	11.57(5.49)

<sup>a</sup> Data was available for only 2 subjects

<sup>b</sup> The timings shown are for tablet core; for the released material there was a delay (i.e.  $6.5 \pm 1.10$  hours posted dose for gastric emptying and  $12.67 \pm 1.51$  hours post-dose for colon arrival).

- Undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism. Following oral administration of  $^{14}\text{C}$  – labeled alfuzosin solution, the recovery of radioactivity after 7 days, expressed as percentage of the administered dose, was 69% in feces and 24% in urine.
- To be taken immediately after the same meal each day.

*From the above pharmacokinetic parameters of the PR formulation, we may conclude that,*

- The drug may have an absorption window especially in the upper part of gastrointestinal tract.
- More Prolonged gastric retention period may be required for better absorption of drug as there is a significant (50 %) difference in fasted and fed conditions with PR dosage form.



## 11.9 Prior Art

U. S. Patent No. 6,149,940 discloses a preparation of an alfuzosin once daily composition for oral delivery using a Geomatrix technology that has been developed by Jagotec-AG. The three-layer Geomatrix tablet described in this patent consists of a hydrophilic active matrix core containing alfuzosin hydrochloride and two inert, functional layers (one swellable layer and one erodible layer) whose function is to control the hydration and swelling rate of the core, and thereby slow down and linearize the dissolution of the drug. When the tablet comes into contact with gastric juices, it increases considerably in volume and thus remains in the stomach for a longer time. In this manner, most of the drug is absorbed in a controlled manner in the portion of the gastrointestinal tract having better absorption window. The alfuzosin is released in zero order from the dosage form developed using this technology. However, the manufacture of multi-layered tablets by this technology involves special facilities, is time consuming, complex to produce, and consequently relatively expensive (Maggi et al., 2000).

U.S.Pat. No. 5,589,190 discloses a pharmaceutical composition that includes an alfuzosin core. The core is coated with a coating whose dissolution is pH dependent, which thereby enables the release of alfuzosin to be modulated over the entire length of the digestive tract. The '190 patent teaches that the sustained release of alfuzosin is dependent on the nature and thickness of the coating. Further, the '190 patent discloses a combination of two types of tablets with different release rates that are filled into hard gelatin capsules for once-daily oral administration. These coated formulations, however, have disadvantages including the possibility of leakage of active ingredient from the coating and the need for strict process controls during their manufacture (Andrieu et al., 1996).

EP700285 discloses drug delivery compositions of alpha adrenoceptor blocking agents that have a biphasic drug release profile. This patent teaches matrix compositions using hydroxypropyl methylcellulose and a coating that is designed to dissolve under the conditions present in the colonic region (Illum et al., 1998).

U.S. Patent Applications No. 2006/0062846 and 2006/0062845 assigned to Cimex disclose a monolithic composition of alfuzosin which does not float in gastric fluid. The applications disclose compositions which show desired dissolution profile with more than 70% by weight of hydroxypropyl methylcellulose based on the weight of the total composition. The applications also disclose use of polyvinylpyrrolidone as a dry binder in the composition (Scheer and Mathias, 2006).

The WO 04/37228 patent application assigned to Ranbaxy discloses a sustained release oral dosage form that includes a single functional layer and, optionally, one or more nonfunctional layers adjacent to the single functional layer. The single functional layer includes alfuzosin or pharmaceutically acceptable salt, solvate, enantiomers or mixtures thereof and one or more release retarding ingredients. The release retarding ingredient may be one or more of cellulose polymer, methacrylate polymer, acrylic acid polymer, block copolymer, gum or polyethylene oxide. It discloses use of polyvinylpyrrolidone as a dry binder (Viswanathan et al., 2005).

French patent application 2 784 583 discloses a multi-layer tablet, improved in that it comprises an effervescent couple which generates carbon dioxide in contact with gastric fluids. These bubbles of carbon dioxide confer flotation properties to this tablet, which permit it to remain in the stomach in a less haphazard way. This flotation is completed by the presence of hydrophilic polymers, which swell and increase the volume of the tablet over time. Nevertheless, such a tablet remains complicated to produce industrially because it is necessary to work in an atmosphere of controlled humidity because of the effervescent couple. This also requires precautions to store the obtained products, given the presence of this effervescent couple, so that production is of higher cost. The effervescent couple used contains sodium whose content is not desirable particularly in the case of a low sodium diet, which is another drawback

Patent Application 20040115259 discloses a tablet containing Alfuzosin Hydrochloride permits guaranteeing optimum dwell time in the stomach of the individual by immediate flotation, a controlled release following a profile whose kinetics can vary and be adapted particularly between kinetics of the order of 0 and 1, and to complete retention by flotation the excipient being selected from at least one compound of the family of cellulose derivatives and/or derivatives of povidone and/or derivatives of polyvinyl acetate, and compression of this mixture with a force permitting obtaining a monolithic homogenous tablet (Bordes et al., 2004).

It was observed that preparation of sustained release alfuzosin formulation which is bioequivalent to the reference product available in various countries, specifically UroXatral® marketed by Sanofi in United States, is difficult due to unique nature of the formulation and specific absorption window of the drug in GI tract. The efforts to prepare bioequivalent composition using teachings of the prior art resulted in failure and most of the times undue experimentation.

## *II.10 Alfuzosin Hydrochloride*

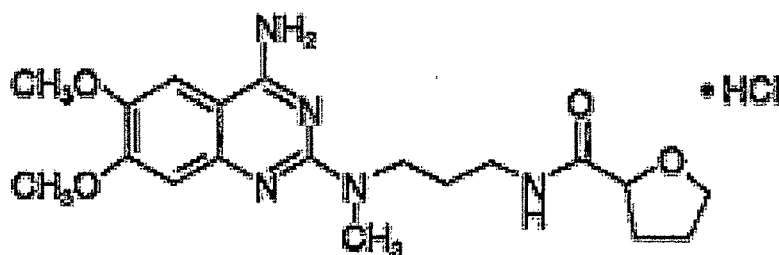
### **II.10.1 Description**

Alfuzosin hydrochloride is (R, S)-N-[3-[(4-amino-6, 7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2- furancarboxamide hydrochloride.

### **II.10.2 Empirical formula**



### II.10.3 Chemical structure



### II.10.4 Physicochemical Properties

**Appearance, Color:** A white or off-white crystalline powder.

**Solubility:** Freely soluble in water, sparingly soluble in alcohol and practically insoluble in Methylene chloride.

**Polymorphism:** Available in four polymorphic forms viz Anhydrous form, dihydrate form, trihydrate form and tetrahydrate form which are distinguished by XRD pattern.

**Molecular Weight:** 425.9

**Melting point:** 240°C

### II.10.5 Pharmacokinetics

#### II.10.5.1 Absorption

The absolute bioavailability of Alfuzosin HCl 10 mg ER tablets under fed conditions is 49%. Following multiple dosing of 10 mg under fed conditions, the time to maximum concentration is 8 hours.  $C_{max}$  and  $AUC_{0-24}$  are 13.6 (SD = 5.6) ng/mL and 194 (SD = 75) ng·h/mL, respectively. Alfuzosin HCl exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached with the second dose of Alfuzosin HCl tablets administration. Steady-state alfuzosin plasma concentrations are 1.2- to 1.6- fold higher than those observed after a single administration. The extent of absorption is 50% lower under fasting conditions.

#### II.10.5.2 Distribution

Alfuzosin is moderately bound to human plasma proteins (82% to 90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).

### II.10.5.3 Metabolism

Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

### II.10.5.4 Elimination

The mean half-life is 10.0 hours and the apparent total body clearance for is approximately 80 mL/min.

**Table II. 5 Pharmacokinetic data of Alfuzosin hydrochloride**

Parameter	Unit	ODAdults	IR
C <sub>max</sub>	µg/L	13.6 (SD = 5.6) ng/ml	
T <sub>max</sub>	Hours	8hr	0.5-3 hr(1.5 hr)
AUC <sub>0-24</sub>	ng·h/ml	194 (SD = 75) ng·h/ml	
Plasma Protein binding	%	82% to 90%	
Elimination Half life (T <sub>½</sub> )	Hours	10 Hours	3-5 hours
Volume of distribution V <sub>d</sub>	L/Kg	3.2 L/kg	2.5 L/Kg
Time for steady – state Plasma concentration	Hours	48 Hours	

## II.10.6 Clinical Pharmacology

### II.10.6.1 Pharmacodynamics

The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The static component is related to the prostate size. Prostate size alone does not correlate with symptom severity. The dynamic component is a function of the smooth muscle tone in the prostate and its capsule, the bladder neck, and the bladder base as well as the prostatic urethra. The smooth muscle tone is regulated by alpha-adrenergic receptors. Alfuzosin exhibits selectivity for alpha<sub>1</sub>-adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH.

### II.10.6.2 Adverse Reaction

The most commonly observed adverse events associated with the use of Alfuzosin HCl (extended-release tablets) in clinical trials, and which occurred more frequently than those which were associated with placebo were: Body pain, abdominal pain, dyspepsia, constipation, nausea, dizziness, hypotension or postural hypotension, syncope, bronchitis, sinusitis, pharyngitis, rash, tachycardia, chest pain, priapism, impotence.

### II.10.6.3 Indications and Usage

Alfuzosin HCl (extended-release tablets) is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. It is not indicated for the treatment of hypertension.

### II.10.6.4 Dosage and Administration

The recommended dosage is one Alfuzosin HCl extended-release 10 mg tablets tablet daily to be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

## II.11 Advantages of ER Vs IR

**ER versus IR Alfuzosin.** ER alfuzosin is administered once or twice daily, enhances patient compliance, and is associated with fewer adverse cardiovascular effects than IR alfuzosin. Buzelin et al. (1997) found that ER alfuzosin 5 mg twice daily was similar to placebo in the rates of drug-induced adverse cardiovascular effects. However, in elderly and hypertensive patients, ER alfuzosin was associated with a higher cumulative frequency of asymptomatic orthostatic hypotension than placebo-treated patients (Buzelin et al. 1997). In another report, Buzelin et al. (1997) compared ER alfuzosin 5 mg twice daily with placebo. The number of patient dropouts due to adverse effects was similar between both groups. ER alfuzosin did not cause first-dose syncope in any patient, probably because the ER formulation produced little fluctuation in serum alfuzosin concentrations over the dosing interval and relatively stable serum concentrations were maintained between doses (Van Kerrebroeck et al., 2000; Buzelin et al., 1997, Lukacs et al., 1996).

Van Kerrebroeck (2001) compared the efficacy and safety of 10 mg of ER alfuzosin given once daily without any dosage adjustment with 2.5 mg of IR alfuzosin thrice daily and placebo for three months, followed by an open-label extension period of up to one year. The three-month treatment portion of the study found that both formulations were equally effective in increasing peak urinary flow rate and improving patients' voiding symptom score and that both formulations were more effective than placebo. However, IR alfuzosin caused more vasodilatory adverse effects than the ER formulation (9.4% versus 3.4%), respectively. A greater percentage of patients treated with the IR drug discontinued treatment compared with those treated with the ER formulation (3.4% versus 1.4%, respectively).

## II.12 BPH

Benign prostatic hyperplasia (BPH) is the most common cause of voiding dysfunction, and one of the most frequent causes of disability in aging men. BPH is a nonmalignant neoplasm of prostatic epithelial and stromal tissue. Often inappropriately termed "benign prostatic hypertrophy," the disease process involves hyperplasia rather than hypertrophy.

Benign prostatic hyperplasia is a rare occurrence in men less than 40 years of age. After age 40 the prevalence of BPH is age-dependent (Berry et al., 1984) and approximately 50% of men greater than 50 years of age have moderate urinary difficulties due to the disease process (Bruskewitz, 1992). By age 85, approximately 90% of men will have BPH (Berry et al., 1984). Men of all races and cultures are afflicted (Walsh, 1984; Oesterling, 1992; Barry, 1990), suggesting the etiology of BPH may not be environmentally or genetically influenced.

Often BPH is present prior to the fifth decade of life; however, it is benign and unnoticed since patients are usually asymptomatic. Generally BPH becomes symptomatic commencing with the fifth decade of life. Identified risk factors for BPH are aging and normal testicular function (Ekman, 1989). Since the prostate surrounds the urethra, urinary symptoms are the signs of prostatic hyperplasia. Although BPH and prostate cancer often coexist, there is no evidence that men with BPH are more likely to develop prostate cancer (Greenwald et al., 1970).

### **II.12.1 Pathogenesis of BPH**

Aging and androgens are all that is required for the development of BPH. The disease is not seen in men who are castrated early in life, and castration actually promotes regression of BPH (Cabot, 1896; White, 1895). Testosterone, the major circulating androgen, diffuses into the prostate cells, and is predominantly converted to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase. More than 90% of testosterone in the prostate is of testicular origin with the remainder produced by the adrenal glands (Hawkins et al, 1980; Trachtenberg et al., 1980). Testosterone and DHT bind to androgen receptors and result in increased protein biosynthesis and hyperplasia. Thus, prostatic hyperplasia is dependent directly on androgen stimulation (Tymoczko et al., 1978).

Prostatic obstruction consists of two elements: the static and dynamic components. The static component is related to enlargement of the prostate gland, which requires the presence of DHT. Thus, the use of antiandrogens and more recently the 5-alpha reductase inhibitor finasteride (Proscar), approved in 1992 by the Food and Drug Administration (FDA) to treat BPH, are therapeutic options. The dynamic component originates from the tone of the prostatic smooth muscle and is under the influence of the sympathetic nervous system (Caine, 1986). Smooth muscle contraction in the urethra, prostate and bladder neck contribute to the voiding symptoms of BPH. Research in the animal model demonstrated that the rat prostate contracts in the presence of norepinephrine, an adrenergic agonist (Shapiro et al., 1992). Alpha-adrenergic receptors are abundant in the prostatic adenoma, prostatic capsule, and bladder neck (Caine et al., 1975), and these adrenergic receptors are primarily the alpha-1 type (Hieble et al., 1985; Caine et al., 1976). On the basis of these findings, the nonselective alpha-adrenergic antagonist phenoxybenzamine was studied as an agent to decrease muscular resistance to urinary outflow, and proved to be beneficial in the treatment of BPH (Barry, 1980). Consequently, the selective alpha-1 adrenergic antagonists (prazosin, terazosin and doxazosin) have been advocated for use in patients with BPH.

## II.12.2 Clinical Presentation

Patients with benign prostatic hyperplasia experience symptoms of prostatism which are considered either irritative or obstructive in nature (**Table II.6**). The symptomatology of BPH often varies, and significant intra- and interindividual variation in symptoms exists. Nocturia, urinary urgency and frequency and pain or burning on urination are typical irritative symptoms, while obstructive symptoms manifest with urinary hesitancy, straining or dribbling during micturition, and a weak or interrupted stream of urine. Initially, the bladder can expel urine past the prostatic blockage. Eventually the bladder is no longer able to compensate, which results in incomplete emptying and stasis of urine within the bladder. Patients may present with severe symptoms that are hallmarks of advanced disease, such as urinary retention, urinary tract infections, nephrolithiasis, hydronephrosis, gross hematuria and compromised renal function (Barry et al., 1992).

**Table II. 6 Urinary Symptoms of Benign Prostatic Hyperplasia**

<b>Irritative Symptoms</b>	<b>Obstructive Symptoms</b>
Dysuria	Hesitancy
Nocturia	Straining
Urgency	Dribbling
Frequency	Weak stream
Burning	Incomplete emptying

Physicians can help patients who have BPH develop an International Prostate Symptom Score (IPSS) to help guide treatment. The IPSS is based on the presence and severity of symptoms and is used worldwide.

The IPSS, along with quality-of-life scores and measurements from common diagnostic tests, can be used to help divide patients with BPH into stages. Knowing a patient's BPH stage serves as a guide for BPH management. These stages include:

**Stage 1.** Patients have no bothersome symptoms and no significant urine obstruction. In general, these patients do not need treatment at this time. They are observed closely by their physician (this is called "watchful waiting").

**Stage 2.** Patients have bothersome symptoms, but without significant urine obstruction. These patients can be treated with medication.

**Stage 3.** Patients have significant urine obstruction (which is defined as urine flow of less than 10 milliliters per second (mL/s) and persistent residual urine of more than 100 mL. The patient's physician may recommend a surgical procedure called transurethral resection of the prostate (TURP).

**Stage 4.** Patients may have complications of BPH such as chronic retention of stones in the bladder. These patients would definitely need TURP.

### **II.12.3 Tests Used to Diagnose BPH**

#### **Digital Rectal Examination**

A digital rectal examination (DRE) is a routine test that identifies an enlarged prostate. To perform a DRE, a physician inserts a lubricated, gloved finger into the rectum. An experienced urologist can easily detect the posterior and lateral lobes of the prostate through the thin rectal wall. A normal prostate gland is about the size of a chestnut. A prostate gland with BPH will feel soft. A benign enlarged prostate will feel smooth and elastic. The tissues of a cancerous prostate gland are usually denser. BPH occurs only within the prostate capsule. A physician may suspect cancer if there are hard nodules or firm areas in the prostate (Lepor HL et al., 2002; Scher HI., 2001).

#### **Diagnostic Tests**

Prostate specific antigen (PSA) is a protein produced by prostate cells. Normally, it is found in high concentrations in seminal fluid and in small quantities in the blood. PSA is a prostate specific substance (Scher HI 2001). The normal PSA value range is between 0 and 4 nanograms per milliliter (ng/mL). Recent research suggests that up to 30 percent of men who have a PSA score of 2.6 to 4.0 ng/mL may have prostate cancer (Lobel B, 2005). An elevated blood PSA level, while by no means diagnostic of cancer, is concerning because it indicates excessive breakdown and turnover of prostate cells. For this reason, men with elevated PSA levels should have additional diagnostic testing, most often including a prostate biopsy, to rule out prostate cancer (Scher HI, 2001). For more information on prostate cancer and PSA, see the chapter on Prostate Cancer.

#### **Uroflowmetry**

Uroflowmetry measures the time in which a given volume of urine is voided. Usually, a healthy man between the ages of 40 and 60 years voids 200 mL in about 11 seconds (a rate of 18 mL/s). A healthy man older than age 60 voids a little longer, more than 15 seconds (at a rate of 13 mL/s). A man with BPH may need 20 to 40 seconds to void 200 mL, depending on the severity of urethral constriction (Lepor HL et al 2002). Uroflowmetry can be done at home by using a measuring cup and a wristwatch that has a second hand. To perform uroflowmetry at home, drink lots of water. Then wait as long as you can to urinate. Measure the time it takes you to void 200 mL (about 7 ounces).

The volume of urine remaining in the bladder immediately after urination is completed is measured by a postvoid residual urine test. This test can be performed using ultrasound (a noninvasive technique) or a catheter (which is invasive). Increasing amounts of residual urine over time can indicate that the BPH has progressed and that there may be a need for surgery (Lepor HL et al., 2002).

### **II.12.4 Therapeutic Options**

Generally, if a physician has diagnosed an enlarged prostate but the patient has no symptoms, the patient does not require treatment. However, severity of symptoms is associated with a greater likelihood of the need for surgery. Because most men with BPH do not develop a significant urine obstruction, and because minor symptoms develop



slowly or not at all, urine flow studies are the preferred diagnostic tool to identify patients who do not require treatment. These patients can be followed by watchful waiting (Lepor HL et al., 2002). This strategy, particularly when considering the slow progression of BPH, provides the opportunity to use complementary approaches (such as nutritional therapy) with no risk of undertreating patients.

**Watchful waiting**

If BPH is not severe, the patient's condition will be monitored closely by his physician. A physician should confirm that a delay in treatment will not lead to irreversible complications. Several measures, such as decreased intake of fluids (especially before bedtime) and moderate intake of alcohol and caffeine (Lepor HL et al., 2002) can lessen severity of symptoms. Watchful waiting does not imply doing nothing. Quite the contrary, it provides an excellent opportunity to treat BPH with diet and nutritional supplements.

**Transurethral microwave thermotherapy**

Transurethral microwave thermotherapy (TUMT) is an alternative to surgery. This procedure uses a catheter tipped with a special antenna that delivers microwave energy to the prostate to selectively heat and kill prostate tissue. The microwave surgical instrument is designed so temperature and the depth of heating are precisely controlled. TUMT is an outpatient procedure performed while the patient is under sedation (not anesthetized). TUMT is an alternative for men with BPH who are not good candidates for surgery. Patients treated with TUMT have minimal, transient adverse effects that resolve spontaneously or resolve with medication. Symptom relief may occur within 3 weeks. One disadvantage of TUMT is the risk of retrograde ejaculation, a condition that occurs when semen enters the bladder rather than being ejaculated. While this does not affect the sensation of orgasm, it can cause infertility.

**Transurethral needle ablation**

Transurethral needle ablation (TUNA) uses low-level radiofrequency, at about 490 kilohertz (kHz), to cause the tissue that is to be ablated to reach a temperature of 50°C to 90°C. The procedure is carried out over the course of a few weeks. During TUNA, a catheter that is tipped with two flexible needles is inserted into the prostate through the penis. The needles are shielded at the base to avoid damaging the urethra. Radiofrequency energy passes from one needle to the other, destroying the prostate tissue between the needles. The progress of the procedure is viewed by transrectal ultrasound. TUNA can be performed as an outpatient procedure with the use of a local anesthetic and sedation (Lepor HL et al., 2002).

**Surgery**

Surgery is widely used for treatment of BPH that is causing significant obstruction to urine flow. Surgery for BPH can be done through a transabdominal incision or through an endoscopic device inserted into the urethra (TURP). About 90 percent of all surgeries performed for BPH are TURP procedures. TURP is the standard against which other interventions are judged.

During TURP, the physician uses an instrument called a resectoscope. The resectoscope is tipped with a small wire loop. The loop is used to snip off obstructing pieces of the prostate gland and then to cauterize the wound to minimize bleeding (although there may still be some bleeding). TURP has been shown to be an effective treatment; after TURP, symptoms are usually much improved. However, BPH may recur. Also, some men may eventually have erectile dysfunction (impotence). Additionally, most patients will experience some degree of incontinence, which will usually disappear in a short time.

Most patients will remain in the hospital for about 3 days after undergoing TURP. Once the patient is released from the hospital, his recovery period is short and he usually experiences significant relief of his symptoms. The most common, unavoidable, and permanent adverse effect of TURP is retrograde ejaculation.

TURP can also be performed using a laser. Studies have shown that photovaporization of prostate tissue using a focused laser (the Greenlight PV Laser System) results in reduced prostate size with a very low incidence of adverse effects (Kumar SM, 2005). Alternatively, a procedure called transurethral vaporization of the prostate (TUVP), in which the tissue is vaporized, can be performed. In TUVP, vaporization electrodes deliver high heat directly to the prostate tissue by means of a grooved roller bar. The heat vaporizes the tissue much like a laser. This is a relatively new technique that is showing clinical promise and has been adopted by many experienced urologists.

If it is necessary to remove a portion of the prostate gland, a partial prostatectomy may be performed. This procedure is open surgery performed while the patient is under general anesthesia. During the operation, the surgeon removes only the enlarged part of the prostate gland. This surgery should not be confused with a radical prostatectomy, in which the entire prostate gland is removed. Radical prostatectomies are performed in men with prostate cancer.

The current clinical philosophy concerning BPH is to postpone any form of surgery for as long as possible to avoid complications that may jeopardize the patient's quality of life. Stopping the progression of prostate enlargement through diet and pharmacotherapy should be the first approaches in the treatment of BPH (Djavan et al., 2002; Schulman, 2001).

## **II.12.5        Drugs Used to Treat BPH**

### **5-Alpha-reductase inhibitors.**

Prostate cells produce 5-alpha-reductase, which converts testosterone into DHT. DHT is much more potent than testosterone at promoting prostate growth. The drug finasteride inhibits 5-alpha-reductase 2, but not 5-alpha-reductase 1. The drug dutasteride inhibits both 5-alpha-reductase 1 and 5-alpha-reductase 2 and is considered more effective (Occhiato et al., 2004).

**Testosterone inhibitors.**

Prostate cells require androgens for survival. Chemical castration is achieved by using medications such as leuprolide and goserelin, which inhibit testosterone. Leuprolide and goserelin are luteinizing hormone-releasing hormone agonists (LH-RH agonists) that cause chemical castration. Although LH-RH agonists shrink an enlarged prostate gland and are used to treat advanced prostate cancer, they are expensive and have unpleasant side effects. As a result, LH-RH agonists are rarely used to treat BPH (Anonymous, 2005; Sugimura, 2004; Tarlatzis and Bili, 2003).

**Alpha-blockers**

Antihypertension drugs called alpha-blockers act on the nervous system to relax arteries by inhibiting excitatory impulses to muscle cells. The smooth muscle cells in the prostate gland have alpha-receptors, so alpha-blockers are sometimes used to relax the muscle and reduce symptoms. Alpha-blockers used to treat BPH include terazosin, prazosin, and doxazosin. A newer alpha-blocker, tamsulosin, can be taken once a day and is effective in treating patients with BPH who have moderate to severe symptoms (Debruyne et al., 2004; Debruyne et al., 2002; Dunn et al., 2002). Many alpha-blockers can cause impotence. If impotence results with one drug, switching to a similar drug may end the undesirable side effects (Tahmatzopoulos and Kyprianou, 2004; Kyprianou, 2003).

**Aromatase inhibitors**

Aromatase, the enzyme that converts testosterone to estrogen, can also be inhibited to try to prevent the age-related rise in estrogen. The use of aromatase inhibitors among men with BPH, however, is subject to some controversy. A number of studies have shown that the aromatase inhibitor anastrozole, when used in conjunction with 5-alpha-reductase inhibitors, increased the level of testosterone in animal models of BPH (Sciarra and Toscano, 2000; Suzuki et al., 1998). Some doctors consider this to be counterproductive among men who have BPH. However, studies of a newer aromatase inhibitor known as mepartricin (not yet approved in the United States) suggest that the drug lowered estrogen levels without affecting levels of other sex hormones (Boehm et al., 1998). Anastrozole is a US-approved aromatase inhibitor (although it is not approved to treat BPH). Obviously, more research is needed into the synergistic effects of 5-alpha-reductase inhibitors (such as dutasteride) used in conjunction with aromatase inhibitors (such as anastrozole) in men. It is also important to keep in mind that maintaining youthful testosterone levels is extremely important in aging men.

### *II.13 Commercial Status of Gastric retention Technologies*

(Jose et al., 2005; Jose Gutierrez et al, 2003)

There are few companies that have focuses efforts on the gastric retention technologies:

**DepoMed, Inc.** has developed technology that consists of swellable tablet. After ingestion of the tablet it swells and achieves sufficient size to resist gastric emptying, while simultaneously providing controlled release of the drug. Two of the products that DepoMed has developed include Metformin GR<sup>TM</sup> and Ciprofloxacin GR<sup>TM</sup>.

Perhaps one of the most publicized of the commercial gastric retention programs is that offered by DepoMed .Inc. The chief technology is in essence the incorporation of a swelling excipient that provides the tablet with some limited swelling properties. DepoMed gastric retention programmes extend over 5 published patents. Their primary gastric retention technology is defines as the formulation of drug candidates into tablets utilizing polymer matrix composed of hydrophilic polymers, swelling upon contact with water to such a size, which promotes gastric retention of the dosage form in the stomach during the fed state. The technology aims at controlled drug delivery in the GI tract based on diffusion mechanisms. Therefore, gastric retention would seem to be an additional benefit here, as opposed to the underlying principle of the technology. The technology does offer advantageous such as the potential ease of manufacturing and processing. The tablet swells in the stomach environment to a size larger than the pylorus within 1 hour.

The products that DepoMed are developing include Gabapentin GR<sup>TM</sup> (currently in Phase I clinical trials) indicated for the management of seizures and post-herpes pain. The current dosing strategy for the medication is 3 to 4 times a day. DepoMed is utilizing a once daily dosing strategy with combination of gastric retention and controlled drug delivery to reduce the multiple dosing of the current medication. Another candidate under development is Glumetza GR<sup>TM</sup> (completed Phase III clinical trials) indicated for the treatment of type II diabetes. Furosemide GR<sup>TM</sup> is a loop diuretic and has entered Phase II clinical trials. DepoMed is also working with ActiveBiotics to develop a gastric retention dosage form for Rifalazil, which is intended for the treatment of gastrointestinal disease.

**Alza Corporation** has developed a gastro-retentive platform for the OROS system, which showed prolonged gastric residence time in a dog model as the product remained in the canine stomach at 12 hours post dose and was frequently present at 24 hours. In humans, in the fasted state the average gastric residence time was for the same system was 33 minutes.

**Pfizer Pharmaceuticals** has patents for gastric retention technology that uses extendable arm, but has no product.

**Merck & Co., Inc.**, has patents describing technologies using various unfolding shapes to encourage gastric retention.

**Kos pharmaceuticals, Inc.**, technology is based on the superporous, superabsorbent hydrogels. Superporous hydrogels contain densely concentrated small pores that produce capillary channels that absorb water quickly. The rapid absorption results in dramatic swelling that is much faster than a conventional hydrogel.

**SkyePharma** produces Geometrix systems which are tablets with a wide range of predictable and reproducible drug-release profiles. The systems claim to allow the simultaneous release of two different drugs from one tablet but at different rates. They can supposedly deliver an initial burst of a drug for fast therapeutic effect, followed by controlled release at constant rate, or deliver a drug to specific sites within the patient's digestive system, either via a single or multiple dose release. The tablet contains a combination of layers, each with different rates of swelling, gelling and erosion. When the tablet is first swallowed, the drug concentration is high, but the surface area is small. AS time goes by and the core swells, the surface area expands to compensate for the decrease in drug concentration.

**West pharmaceuticals** have a patent using microspheres and claiming gastric retention. Their commercial technology is based on low-density microspheres with a bioadhesive coating. The technology of the patent claims the composition of a microsphere comprising an active ingredient in the inner core of the microsphere, a rate controlling layer of a water insoluble polymer, and an outer layer of a bioadhesive agent in the form of a cationic polymer.

One of the latest gastric retention technologies to have become commercially known is **Intec Pharma's** GRDF platform, claimed to be a simple foldable polymer-based matrix system. The device is administered contained within a capsule, which unfolds in the stomach, with the size-restricting passage through the pylorus.

**Teva Pharmaceutical Industries** has a patent for providing gastric retention of a bisphosphonate drug. The device comprises a non-hydrated hydrogel, a superdisintegrant, and a tannic acid.

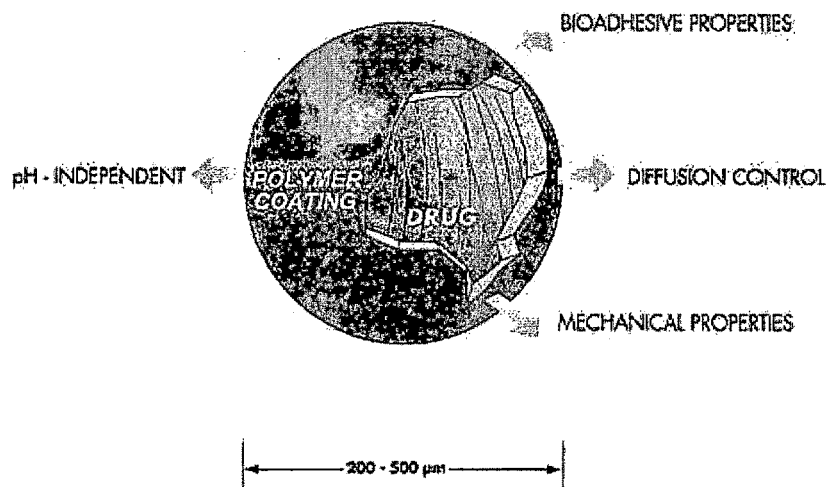
**Madopar** is an HBS floating system produced by Roche, not available in US but available in Europe and Australia, and contains 200 mg levodopa and 50 mg benserazide. The formulation consists of a capsule designed to float on the stomach contents. Following dissolution of the gelatin shell, a matrix body is formed consisting of the active drug and other substances. The drug diffuses as successively hydrated boundary layers of the matrix dissipate.

**Valrelease** is a floating capsule containing diazepam produced by Roche. The formulation is an HBS system, also prolonging gastric retention and is used as once-a-day dosage form comparable to the previous three-times-a-day non-floating dosage form.

**The alginate -containing preparations such as Gaviscon (GSK) and peptic (Ivax)** preparations are designed for the suppression of gastro-oesophageal reflux. They consist of alginate that gels in the gastric environment due to the carbonate or bicarbonate content. These systems are called rafts as the viscous layer can ride the stomach waves.

Flamel's Micropump® technology is a controlled-release system which permits either extended, or both delayed and extended delivery, of small molecule drugs. It is suitable in particular to drugs with a narrow window of absorption from the upper part of the small intestine.

Flamel's Micropump® technology consists of a multiple-dose system containing 5,000 to 10,000 microparticles per capsule or tablet. The 200-500 microns diameter-sized microparticles are released in the stomach and pass into the small intestine, where each microparticle, operating as a miniature delivery system, releases the drug by osmotic pressure at an adjustable rate (controlled for Micropump® I or delayed for Micropump® II) and over an extended period of time.



**Figure II. 5 Flamel's Micropump® Technology**

The design of the Micropump® microparticles allows an extended transit time in the small intestine with plasma mean residence time extended up to 24 hours, which is especially suitable for short-lived drugs known to be absorbed only in the small intestine. The Micropump® microparticles' design can be adapted to each drugs' specific characteristics by modifying the coating thickness and composition (including the excipients encapsulated with the drug) for improved efficacy (i.e., extending therapeutic coverage), reduced toxicity and/or side effects (i.e., reduced C<sub>max</sub> or peak drug concentration in the plasma) and improved patient compliance (once-a-day regimen). Such adaptations can be particularly useful in the context, for example, of chronotherapy.

Flamel has proven in human studies (up to and including Phase III clinical trials) the extension of the release of four small molecule drugs, known to be only absorbed in the upper part of the small intestine:

- Proton pump inhibitors for the treatment of gastroesophageal conditions, including heartburn and other symptoms of gastroesophageal reflux disease (GERD);
- Genvir™, acyclovir for the treatment of Acute Genital Herpes (positive results in Phase III);
- Metformin XL, an anti-diabetic for the treatment of type II diabetes (positive results in Phase I);
- An undisclosed ACE inhibitor co-developed with Servier Monde (confidential); and,
- Augmentin SR, an antibiotic (confidential).

**Other marketed preparations are:**

**Topalkan** – aluminum- magnesium antacid preparation and  
**Almagate Flot-Coat** – antacid preparation.

The fact that these companies are working on such platform devices highlights the need for gastric retention to improve delivery of successful 24- hour release dosage forms considering the effect of transit time.

### *11.14 Patterns of gastric emptying*

Patterns of gastric emptying are dependent on several characteristics of the ingested material, particularly nutritive and physical properties, so that solids, nutrient-liquids and non-nutrient liquids empty from the stomach at different rates (Malbert and Ruckebusch 1988; Horowitz and Dent 1991).

#### **Liquids**

Gastric emptying of liquids is critically dependent on volume ingested, as well as the osmolarity and nutrient content. Non-nutrient and low-nutrient liquids empty relatively rapidly from the stomach with an overall mono-exponential pattern i.e. the volume of liquid that enters the duodenum in a given time is approximately proportional to the volume remaining in the stomach (Hunt and Spurrell, 1951). Consequently, the rate of emptying is influenced by intragastric volume and posture. In contrast, high-nutrient containing liquids are retained in the distal stomach for longer periods and empty more slowly as a results of feedback from small intestinal receptors (Lin et al., 1993). Posture and intragastric volume appear to have minimal influence in the latter case. Gastric emptying of a nutrient liquid consists of an initial phase, during which the emptying may be faster, followed by a linear emptying phase when 2-3 kcal per minute are delivered into duodenum, essentially irrespective of the source of those calories (Elashoff et al., 1982; Horowitz et al., 1993a). In addition, to caloric density, characteristics of the nutrient itself may influence the rate of emptying e.g. fructose is a less potent inhibitor of gastric emptying than glucose (Moran and McHugh, 1981).

When evaluated a second-by-second basis emptying of the stomach content is predominantly a pulsatile, rather than continuous, phenomenon- both antegrade and retrograde flow occur frequently and there is substantial variation in the characteristics of individual flow pulses (Malbert and Mathis 1994; Hausken et al., 1998).

#### **Solids**

The emptying of digestible solids fro the stomach proceeds at a much slower phase than that of nutrient and non-nutrient liquids and is characterized by an initial "lag phase" during which little or no emptying occurs (Collins et al.,1983). The lag phase, which is usually 20-60 min in duration, is accounted for by an initial retention of the solid in the proximal stomach, followed by redistribution to the antrum. If the viscosity of the meal is increased sufficiently, the ability of the stomach to discriminate between large and small particles is impaired so that large particles may be delivered in the duodenum (Russell and Bass, 1985). Larger(>3 mm) indigestible solids were thought not to empty from the stomach until the return of migrating migratory complex, however, it is now clear that they may empty much earlier than this (Stotzer and Abrahamsson, 2000).The amount of nutrient liquid consumed with the solid affects the rate of solid emptying (Heddle et al.,1989a; Urbain et al.,1989). In a mixed meal, comprising solids and liquids, up to 80%

of the liquid phase empties before the solid (Horowitz et al., 1989b), indicating that the stomach is capable of discriminating between solids and liquids.

### Fat

Food high in fat is handled differently by the stomach and can, therefore, be considered separately from liquids and solids. Fat represents a challenge as it is liquid at room temperature and coalesces to form large globules in the stomach. In the erect posture fat may float in other gastric contents because of its low density and be 'retained' in the uppermost part of the stomach (Edelbroek et al., 1992c; Horowitz et al., 1993b). Because of its high nutrient density of fat, it can markedly slow emptying of other meal components (Meyer et al., 1986). The rate of emptying of fats, as for digestible solids and aqueous nutrient liquids, is regulated by feedback from the small intestine triggered by fatty acids (Meyer et al. 1994b; Feinle et al., 2003a). Because of the requirement for digestion and the potential for 'layering' of fat on the top of other, more dense, meal components it is likely that the slowing of gastric emptying induced by fat will be greater when it is ingested before, rather than with, a meal.

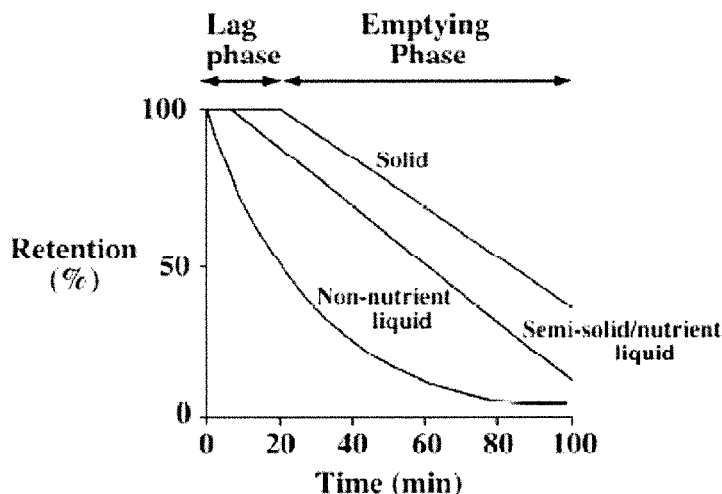
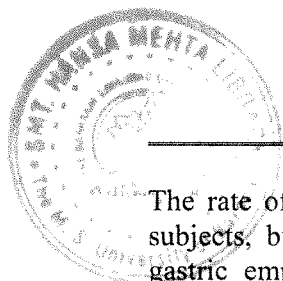


Figure II.6 Scintigraphic gastric emptying curves for solid (pancake) and nutrient liquid (10% glucose). Solid empty in linear fashion following a lag phase while nutrient liquids empty in a mono-exponential manner with minimal lag.

### II.15 Factors Influencing Gastric Emptying

Various studies have found similar factors to have contradictory effects on gastric emptying. The differences are difficult to explain but could be attributed to the measurement technique, various inclusion criteria, size, pre-existing drug treatment; and also composition and caloric content of test meals.





The rate of gastric emptying of either liquids or solids varies widely between healthy subjects, but under controlled situations is relatively reproducible. Reproducibility of gastric emptying in pathological conditions has not been studied satisfactorily. The volume and composition of ingested food determines the rate of gastric emptying (Velchik et al., 1989). Gastric emptying of liquids is rapid (half-time is about 12 minutes so that 95 % is emptied within one hour) (Cote, 1992). An increase in caloric content generally slows gastric emptying so that the rate of delivery of calories into the duodenum is relatively constant (Hunt and Stubbs, 1975). It is estimated that nearly 50% of a solid meal remains in the stomach after two hours.

The temperature of the ingested meal is not important for liquids, which conduct heat rapidly, but may delay the emptying of hot or cold semisolid or solid meals, which have a higher thermal inertia. Gastric emptying occurs more rapidly in the morning than in the evening (Goo et al., 1987), so that longer fasting may be needed to obtain an empty stomach later in the day.

Gastric emptying is slightly slower in healthy older subjects (over 70 years of age) of both sexes (Horowitz et al., 1984), even though the absorption of oral drugs does not seem to vary with age (Horowitz et al., 1984; Divoll et al., 1982).

The results of studies of the effect of body weight on gastric emptying of solids and liquids are inconsistent. Accelerated (Wright et al., 1983), delayed (Horowitz et al., 1983) and unchanged gastric emptying (Sasaki et al., 1984) have all been reported. The differences in emptying rates are difficult to explain, but it appears that moderate obesity is not a major modifying factor, although the emptying of solids may be delayed in obese subjects who are at least 63 % in excess of ideal weight (Horowitz et al., 1983). Whether changes in gastric emptying are a primary cause of obesity is unknown.

The influence of gender on gastric emptying is controversial. Some authors have found similar gastric emptying rates for men and women (Petricing and Flachs, 1990; Horowitz et al., 1984), others have found slower gastric emptying in women than in men (Datz et al. 1989; Hutson et al., 1989). The difference could be attributed to the phase of the menstrual cycle at the study time, as the rate of solid gastric emptying decreases linearly during the menstrual cycle towards the luteal phase (19-28th day). The emptying of liquids does not differ between the two phases of the cycle (Petricing and Flachs, 1990; Gill et al., 1987).

Factors such as age, sex and body weight may be significant for the pharmacokinetics of oral drugs; however it is less likely that they influence the volume of remaining perioperative gastric contents.

Pregnancy is believed to delay gastric emptying, and anaesthetic technique is modified accordingly. However, the majority of studies have not shown delayed gastric emptying of liquids in women presenting during the first or second trimester for terminations of pregnancy, at elective caesarean section (Macfie et al., 1991), and at first and third postpartum day (Gin et al., 1991). These results indicate that guidelines for fasting of

fluids in elective pregnant patients need not be different from those in nonpregnant patients.

Gastric emptying of solids has not been studied satisfactorily in pregnancy as use of the scintigraphic method is unacceptable. Recently, high-resolution ultrasonography, presumably capable of noninvasively identifying the stomach contents, found delayed gastric emptying of solids during active labor (Carp et al., 1992).

Pain and emotional stress are believed to cause delay in gastric emptying, but it is difficult to quantify the effect (Kaus and Fell, 1984; Thompson, 1988). Other factors such as body temperature, noise, light and previous experience may modify the response. Inducing vertigo or immersion of a hand in ice cold water produces elevations of plasma betaendorphin, sympathetic stimulation, and causes a delay in gastric emptying in volunteers (Thompson, 1988). However, the gastric intubation used in these studies could in itself delay gastric emptying because it unfortunately combines the effects of physical stimulus with emotional stress. Ischaemic pain induced by the submaximal effort tourniquet test also delays gastric emptying of semisolids as assessed by the scintigraphic method (Petring and Madsen, 1991).

In contrast, pain may have less effect on the emptying of liquids as intermittent immersion of the feet in ice water did not influence absorption of paracetamol in healthy volunteers (Thoren et al., 1989). Additionally, paracetamol absorption in patients with pain awaiting emergency orthopaedic surgery was almost identical both to that observed in the same patients before discharge from hospital and to that observed in healthy volunteers (Mark et al., 1984; Steedman et al., 1991).

The perception of pain intensity is influenced by personality variables and other sociocultural factors (Thompson, 1988). Accordingly, preoperative delay in gastric emptying occurred only in patients who became apprehensive, while less anxious patients did not show any change in paracetamol absorption (Simpson and Stakes, 1987). However, other studies in patients with pain are needed.

The patient's mobility and posture prior to anaesthesia may also be significant. Lying on the left side delays gastric emptying of liquids (Nimmo and Prescott, 1978). Movement between sitting and standing position produces the most rapid gastric emptying of both liquids and solids (Moore et al., 1988).

Abstinence from smoking has no major effect on gastric emptying of liquids in habitual smokers (Petring et al., 1985). Intubation-aspiration studies performed with a double-lumen gastric tube found no difference in the aspirated gastric volume in smokers refraining from smoking in the fasting period compared with either patients smoking cigarettes in the fasting period (Adelho et al., 1985) or nonsmokers (Adelho et al., 1987).

#### **The influence of premedication**

Premedication can be the most important factor responsible for changing the rate of gastric emptying in patients awaiting anaesthesia. Sedative drugs may delay gastric

emptying as drowsiness and sleep is accompanied with decrease in gastrointestinal motility. The most striking delay in gastric emptying occurs with the administration of opioid analgesics (Mark et al., 1984; Minami and McCallum, 1984), including short-acting drugs such as alfentanil (Milligan et al., 1988), but the mechanism by which this occurs is not understood. The existence of opioid receptors in both the brain and gastrointestinal tract makes it difficult to determine whether the effect is central or peripheral. It was originally postulated that agonist/antagonist opioids (kappa(k) agonists, and mu(m) antagonists) such as buprenorphine and nalbuphine might not delay gastric emptying; however, this has been disproved by several paracetamol absorption and scintigraphic studies (Adelhof et al., 1985; Yukioka et al., 1987). The action of opioids on gastric emptying is reversed by naloxone (Nimmo, 1984), but a large dose of naloxone induces a paradoxical, inhibitory effect on basal gastric emptying (Adelhof et al., 1985).

It appears that anxiolytic drugs do not delay gastric emptying. Gastric emptying measured by paracetamol absorption is unchanged following a single dose of diazepam (Adelhof et al., 1984; Adelhof et al., 1985). A study using oral diazepam even showed enhanced gastric emptying (Schurizek et al. 1988).

The anticholinergic activity of certain antihistamines (e.g., diphenhydramine) delays gastric emptying. However, a single, modest but sedative intravenous dose of chlorpromazine does not alter gastric emptying of liquids (Petring et al., 1987).

**Table II. 7 Medications that affect Gastric Emptying** (American Gastroenterological Association, 2004)

<b>Delay gastric emptying</b>
Opioid analgesics
Anticholinergic agents
Tricyclic antidepressants
Calcium channel blockers
Progesterone
Octreotide
Proton pump inhibitors
H <sub>2</sub> receptor antagonists
Interferon alfa
L dopa
Fiber
Sucralfate
Aluminum hydroxide antacids
β adrenergic receptor agonists
Glucagon
Calcitonin
Dexfenfluramine
Diphenhydramine
Alcohol
Tobacco/nicotine
Tetrahydrocannabinol
<b>Accelerate gastric emptying</b>
Prokinetic agents
Metoclopramide
Erythromycin/ clarithromycin
Cisapride
Domperidone
Tegaserod
β adrenergic receptor agonists

*Conditions that lead to abnormal gastric emptying are (Matthies and Donohoe, 1998):*

1. Neurogenic
  - a) Postsurgical (esp. vagotomy with/without partial/subtotal gastrectomy, *etc.*)
  - b) Diabetes
  - c) Medication/Drugs
  - d) Infection (*Trypanozoma cruzi*, VZV, EBV)
  - e) Neurologic disorders (Stroke, Multiple sclerosis)
2. Myogenic
  - a) Scleroderma/Polymyositis/SLE
  - b) Progressive muscular dystrophy
  - c) Amyloidosis
3. Other etiologies
  - a) Zollinger Ellison Syndrome
  - b) Gastritis/Peptic ulcer disease
  - c) Anorexia nervosa
  - d) Endocrine disorders (Hypothyroidism, CRF)
  - e) Abdominal Radiation
4. Idiopathic

## *II.16 Methods Used To Study Gastric Emptying*

Gastric emptying in man has been studied for approximately 160 years and many techniques have been employed. Investigations of gastric emptying require the use of precise, well-defined methods where the choice of technique is determined by a number of factors. A variety of techniques are available to study gastric emptying non-invasively, all of them having specific advantages and disadvantages

**Table II. 8      Methods used to study gastric emptying (Petric and Blake, 1993)**

<b>Radiologic</b>	liquid barium sulphate
	enteric-coated barium granules
	"barium burger"
	radioopaque spheres
<b>Intubation-aspiration</b>	saline load test
	serial intubation and aspiration
	multiple sampling
	multilumen tube perfusion and aspiration
<b>Radioisotopic Ultrasound</b>	solid phase emptying
	liquid phase emptying
<b>Absorption kinetics of orally-administered solutes</b>	paracetamol
	ethanol
	glucose
<b>Ferromagnetic tracer</b>	
<b>Epigastric impedance</b>	
<b>Applied potential tomography</b>	

**Intubation**

The simplest intubative gastric emptying test is the saline load test. This, however, has the disadvantage of not taking the gastric secretion into account. Utilizing this test, 750 ml of physiological saline solution is given through the gastric tube and if >200 ml can be recovered after 30 min it indicates abnormal gastric retention (Hunt and Spurrell, 1951; Goldstein and Boyle, 1965; Dubois et al., 1978). The use of a non-absorbable marker in the test volume, as polyethylene glycol or phenol red, makes it possible to estimate the amount emptied and the contribution of gastric secretion.

Intubation techniques have previously provided information of both liquid and solid gastric emptying (Hunt and Spurrell, 1951) while the complexity and subject inconvenience has limited their use.

Intubation techniques, for example, were originally used to study the transport of water, ions and nutrients, though in recent years they have been used to investigate gastrointestinal drug absorption (Jobin et al., 1985). The technique involves the positioning of a tube, after administration via the oral or rectal route, at a predetermined site within the gut. Drug in solution or suspension is applied via instillation or infusion through the tube and blood samples are collected and subsequently analysed to quantify drug absorption. This process can be repeated at different sites within the gut in order to map the absorption characteristics of the drug on a region-by-region basis (Godbillon et al., 1985; Williams et al., 1992; Warner et al., 1995). Such techniques, however, are highly invasive and unpleasant for the volunteer and have been shown to perturb normal gastrointestinal physiology by altering gastrointestinal motility (Read et al., 1983), which in turn has ramifications for the relevance of absorption data collected using this approach

**Breath test**

Both stable ( $^{13}\text{C}$ ) and radioactive ( $^{14}\text{C}$ ) carbon isotopes, bound to various substrates, can be used for measurement of liquid or solid gastric emptying (Ghoos et al., 1993). Octanoic acid (a medium chain triglyceride) is the mostly used substrate for labelling of solid meals, and acetate can be used as a substrate to label liquid meals. When the digested meal is emptied into the duodenum, the carbon-labelled substrate is rapidly absorbed and metabolised in the liver to be exhaled as  $\text{CO}_2$ . By applying mathematical calculations on the exhaled carbon isotope levels, gastric emptying parameters are indirectly assessed (Ghoos et al., 1993).

**Paracetamol absorption**

Liquid gastric emptying can be estimated by the paracetamol absorption test. Paracetamol is rapidly absorbed from the small intestine and gastric emptying is the rate-limiting step since no absorption takes place in the stomach (Heading et al., 1973; Näslund et al., 2000). Drug absorption tests require repeat blood samples to capture the rise of the plasma drug concentration. Parameters expressing gastric emptying rate can then be derived from the generated time-concentration curves.

**Radiology**

The discovery of the Röntgen rays in 1895 opened completely new non-invasive ways to study the motility of the GI tract. A pioneer work was presented by Cannon 1898, in a study of gastric motility in cat. Using bismuth contrast medium mixed with the food, he described the influence of food intake on gastric motility (Cannon, 1898).

Radiological examinations for evaluation of upper GI motility with barium meals are simple to perform at any radiology department. Most of the techniques are non-invasive and well tolerated by the patients. The volume of the residual barium in the stomach can only be assessed in qualitative terms and the method is therefore considered insensitive for any but the most severe gastric motility disorders.

A variety of sophisticated remote control drug delivery devices have been developed to obtain absorption data under normal physiological conditions (Staib et al., 1986; Lambert et al., 1991; Gardner et al., 1997). One such device, the high frequency capsule, consists of a small plastic capsule containing a latex balloon filled with drug in the form of a solution or suspension (Staib et al., 1986). The capsule is swallowed with a small dose of radio-opaque agent, barium sulphate, to assist with its localisation within the gastrointestinal tract by X-rays. On reaching the desired release site within the gut, the capsule is activated via an external high frequency pulse, which leads to rupture of the balloon and drug release.

Gastric emptying studies using radionuclides began in the mid 60s. The far most known report came from Griffith et al who used a  $^{51}\text{Cr}$ -labelled porridge meal and a scintiscanner for gamma ray detection (Griffith et al., 1966).

Another, but more complicated method using a stationary scintillation detector was developed by Brömster et al (Brömster et al., 1966, 1968) as a modification of a method utilised for absorption studies (Lundh, 1957). Using this methodology, the test meal consisted of a nutrient liquid formula tagged with  $^{131}\text{I}$ -human serum albumin (HSA). The radiotracer was rapidly absorbed in the duodenum, which diminished the acquisition disturbances from the radioactivity in gut segments near the stomach, but correction was needed due to resecretion of  $^{131}\text{I}$  into the stomach.

The early methods for assessing gastric emptying by radionuclide techniques were hampered by several factors caused by equipment and available radionuclides. Up to 10 min were required for the scintiscanner to accomplish a scan, which made the method inaccurate, especially in subjects with rapid gastric emptying. Data were graphically collected as marks on a recording paper showing the stomach distribution, which had to be manually counted. The early gastric emptying radionuclides were far from optimal for radiation safety reasons. They had long physical half lives ( $^{51}\text{Cr}$  27.7 days,  $^{131}\text{I}$  8 days) and high-energy emissions ( $^{51}\text{Cr}$  320 keV,  $^{131}\text{I}$  364 keV and also a high amount of beta-particles). As radioiodine also accumulates in the thyroid, the gland had to be blocked before the examination.

The introduction of gamma cameras for gastric emptying tests (Harvey et al., 1970) made many subsequent acquisitions possible which improved the accuracy in patients with

rapid gastric emptying or dumping. An important step forward came with the availability of  $^{99m}\text{Tc}$ , which both reduced the radiation doses and increased the imaging quality (Calderon et al., 1971).

Methodological development for simultaneous testing of both liquid and solid gastric emptying began with the work of Heading et al (Heading et al., 1974, 1976) by labelling the liquid and solid components of the meal with radioisotopes emitting different photon-energies which could be separately detected. To overcome the problems with dissociation of the solid phase marker, Meyer et al developed a technique employing in vivo  $^{99m}\text{Tc}$ -sulphur colloid labelled chicken liver (Meyer et al., 1976). The in vivo labelling of the solid phase is, for natural reasons, not a practical method and in vitro labelling of solids with  $^{99m}\text{Tc}$ -sulphur colloid or  $^{99m}\text{Tc}$ -albumin colloid have been shown to be reliable alternatives (Wright et al., 1981; Rinetti et al., 1982; Taillefer et al., 1987).

A variation on the remote control theme has been devised in the form of the InteliSite capsule (Gardner et al., 1997; Pithavala et al., 1998). This capsule can be followed in vivo using gamma scintigraphy, thereby overcoming the need for repeated X-rays and the high radiological burden associated with monitoring the intestinal position of the high frequency capsule. Moreover, the InteliSite capsule has been designed such that it is not restricted to carrying liquids, but also powder formulations. In practice, though, complete powder emptying from the device has been difficult to achieve (Cook et al., 1998), especially in the colon where agitation and fluid volume are usually limited. The recently described InteliSite Companion and Enterion capsules (Wilding et al., 2000), which are engineered to actively expel their contents, may overcome the shortcomings of the earlier devices in delivering powders. Such devices, however, are expensive and are further limited by the fact that each individual capsule can only be used once.

### **Ultrasonography**

Gastric emptying, wall motion, transpyloric flow and gastric accommodation have been studied by different ultrasonography techniques (Bateman and Whittingham, 1982; King et al., 1984; Brown et al., 1993; Gilja et al., 1996). Assessment of gastric emptying can be performed by measurements of the changes in antral cross-sectional area (Bolondi et al., 1985). The few studies performed by parallel measurements of gastric emptying with ultrasonography and scintigraphy have demonstrated good agreement between the methods, both for liquid and solid meals (Hveem et al., 1996; Benini et al., 1999). Ultrasonographic measurements of gastric emptying are, however, time-consuming and dependent on a skilled operator.

### **MRI**

Magnetic resonance imaging (MRI) can be used for gastric motility examinations, permitting the study of both liquid and solid emptying (Schwizer et al., 1992, 1994; Feinle et al., 1999), as well as gastric contractions and accommodation (Borovicka et al., 1999; Kunz et al., 1999; Schwizer et al., 2002). The first reports described liquid gastric emptying using Gd-DOTA (gadolinium tetraazacyclododecane tetraacetic acid) as an MRI marker (Schwizer et al., 1992, 1994; Fraser et al., 1994) while evaluation of solid gastric emptying with MRI technique can be performed without the use of contrast agents (Feinle et al., 1999).

### *II.17 Effect of food on drug absorption*

How food affects drug absorption is a subject that did not achieve full recognition in scientific and regulatory circles until 1977, when the first major review on this topic was published (Welling, 1977). Since that time, the number of studies examining various aspects of food drug interactions has increased, and the topic has been extensively reviewed, both in terms of interactions of particular drugs or families of drugs (Pfeifer, 1993; Sorgel and Kinzing, 1993; Welling, 1989, 1993; Welling and Tse, 1982; Williams et al., 1993), and in terms of relating the effects of those interactions to clinical consequences (Lasswell and Loreck, 1992; Neuvonen and Kivistc, 1989; Neuvonen et al., 1991; Wix et al., 1992).

It is important to consider drug-food interactions because the pharmacokinetics of a prescribed drug may be affected when co-administered with food. Recently, Welling (Welling, 1996) classified drug-food interactions into 5 categories: those causing

- reduced,
- delayed,
- increased and accelerated absorption,
- and those in which food has no effect.

The variable, but clinically important, effects of food have long been recognized. Some of the drug-food interactions reported in the literature during the past decade are listed in Table II.10. Some drugs belong to more than one category: for example, aspirin (acetylsalicylic acid), avitriptan, libenzapril, cilazapril and pidotimod, whose absorption may be both reduced and delayed in presence of food. On the other hand, the absorption of midazolam and triazolam is delayed and the extent of bioavailability is increased when ingested with grapefruit juice. There are other instances in which the rate of absorption [measured as peak plasma drug concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $t_{max}$ ) values] may be decreased or delayed but the overall bioavailability remains unchanged. Also there are few interactions in which the rate of drug absorption is slightly enhanced or accelerated, but the bioavailability is not significantly modified by food (Bianchetti et al., 1995; Granneman and Mukherjee, 1992; Dingemanse et al., 1998; Lukkari et al., 1996; Delhotal-Landes et al., 1988).



**Table II. 9      Physiological interactions due to ingested food and fluid which may influence drug absorption (Welling, 1989)**

Physiological function	Effect of food	Possible effect on drug absorption
Stomach emptying	Decreased rate with solid meals, fats, high temperature, acids, solutions of high osmolarity. Increased rate with large fluid volumes	Absorption generally delayed, may be reduced with unstable compounds, may be increased due to drug dissolution in stomach. Absorption increased with large fluid volumes
Intestinal motility	Increased	Faster dissolution and decreased diffusional path promotes absorption. Shorter transit time may reduce absorption
Splanchnic blood flow	Generally increased, but may be decreased by ingestion of glucose	Absorption increased with faster blood flow. Variable effects on first-pass metabolism, depending on drug
Bile secretion	Increased	Absorption may increase due to faster dissolution or decrease due to complexation
Acid secretion	Increased	Increased absorption of basic drugs provided they are acid stable. Decreased absorption of acid labile compounds.
Enzyme secretion	Increased	Increased or decreased absorption depending on drug characteristics
Active absorption process	Increased	Active drug absorption may be reduced by competitive inhibition

## II.17.1 Increased or Accelerated Absorption

### II.17.1.1 Increased solubility

#### II.17.1.1.1 Due to increased GI Transit Time

##### II.12.1.1.1.1 Inhibitory effects due to

- Nervous reflexes
- Harmonal feedback

**Nervous reflexes:** Breakdown products of **protein digestion** elicit inhibitory enterogastric reflexes; by slowing the rate of stomach emptying, sufficient time is ensured for adequate protein digestion in the duodenum and small intestine.

Either **hypotonic or hypertonic fluids** (especially hypertonic) elicit the inhibitory reflexes. Thus, too rapid flow of nonisotonic fluids into the small intestine is prevented, thereby also preventing rapid changes in electrolyte concentrations in the whole body extracellular fluid during absorption of the intestinal contents.

**Hormonal Feedback from the Duodenum Inhibits Gastric Emptying—Role of Fats and the Hormone Cholecystokinin:** Not only do nervous reflexes from the duodenum to the stomach inhibit stomach emptying, but hormones released from the upper intestine do so as well. The stimulus for releasing these inhibitory hormones is mainly fats entering the duodenum, although other types of foods can increase the hormones to a lesser degree. On entering the duodenum, the fats extract several different hormones from the duodenal and jejunal epithelium, either by binding with “receptors” on the epithelial cells or in some other way. In turn, the hormones are carried by way of the blood to the stomach, where they inhibit the pyloric pump and at the same time increase the strength of contraction of the pyloric sphincter. These effects are important because fats are much slower to be digested than most other foods. Precisely which hormones cause the hormonal feedback inhibition of the stomach is not fully clear. The most potent appears to be cholecystokinin (CCK), which is released from the mucosa of the jejunum in response to fatty substances in the chyme. This hormone acts as an inhibitor to block increased stomach motility caused by gastrin. Other possible inhibitors of stomach emptying are the hormones secretin and gastric inhibitory peptide (GIP). Secretin is released mainly from the duodenal mucosa in response to gastric acid passed from the stomach through the pylorus. GIP has a general but weak effect of decreasing gastrointestinal motility. GIP is released from the upper small intestine in response mainly to fat in the chyme, but to a lesser extent to carbohydrates as well. Although GIP does inhibit gastric motility under some conditions, its effect at physiologic concentrations is probably mainly to stimulate secretion of insulin by the pancreas. In summary, hormones, especially CCK, can inhibit gastric emptying when excess quantities of chyme, especially acidic or fatty chyme, enter the duodenum from the stomach.

In the fasting state, gastric motility passes through cycles of migrating motor complexes (MMC). Each cycle lasts 2-3 h and comprises four phases, of which phase 3, the “housekeeper wave”, is the strongest. Non-nutrient liquids pass through the stomach largely independent of MMC, but the solids are moved from the stomach into the small intestine mainly during the phase 3. Depending on when a solid meal is ingested relative to the MMC, the gastric residence time may vary from a few minutes to 2-3 h (Ewe et al., 1989). Ingested food changes gastric motility to a postprandial pattern, during which time gastric residence time is increased, particularly by solid meals and by chyme of low pH, high osmolality, and high-fat content. Residence time is also influenced by hot meals. On the other hand, delayed gastric emptying might increase systemic availability of compounds that have poor solubility at acidic gastric pH by permitting more material to dissolve in the stomach before passing into the small intestine.

Drugs that have an intestinal absorption that increases when they are administered with food include those that have an incomplete absorption as a consequence of their poor solubility in the GI fluids. The increased intestinal uptake results from the delayed gastric emptying [therefore longer gastric residence time (GRT)].

It has been shown that food enhances the bioavailability of nitrofurantoin in dosage forms that exhibit poor dissolution characteristics (Rosenberg and Bates, 1976). Increased nitrofurantoin absorption may be attributed to better dissolution of the weakly acidic

nitrofurantoin molecule by food-induced slow stomach emptying, as judged from studies employing anticholinergic pretreatment (Melander, 1978; Welling, 1977).

Prolonged stomach retention may also increase the absorption efficiency of drugs that are absorbed by saturable mechanisms or that exhibit an 'absorption window' effect, by prolonging the time during which the drug is in contact with the active site.

Increased absorption of riboflavin (Levy and Jusko, 1966) and riboflavin-5'-phosphate (Levy and Jusko, 1966) in the presence of food, particularly after high drug doses, has been shown to be consistent with a site-specific saturable absorption mechanism.

A remarkable food effect involved the lipophilic hypolipidemic compound CGP 43371 (Sun et al., 1994). Administration of single 800 mg capsule doses of CGP 43371 after breakfast caused an 11-fold increase in peak plasma drug levels. As CGP 43371 is absorbed mainly from the ileum, delayed gastric emptying would enable more compound to disintegrate and dissolve before reaching this absorption site. It is proposed that CGP 43371 dosage should be modified relative to food intake.

#### ***II.17.1.1.2 Bile induced solubilization***

An increased secretion of bile salts which may increase the dissolution rate (Lennernas and Fager, 1997). The secretion of bile salts results from food intake, which causes contraction of the gallbladder and the subsequent release of bile salts into the duodenum. Typically, bile salt concentrations fall within the 1 to 4 mmol/L range under fasted conditions and between 10 and 20 mmol/L in the fed state (Dressman et al., 1990). However, the concentration of bile salts should be above the critical micellar concentration (CMC) in order to influence the drug transport (Dongowski et al., 1996). Furthermore, the micellar interaction between lipophilic drugs and bile salts appears to be much weaker than that between bile salts and hydrophilic drugs (Yamaguchi et al., 1986).

Some of the classic examples of drugs whose absorption is favored by bile salts are cyclosporine (Lindholm et al., 1990), halofantrine, griseofulvin and danazol (Charman et al., 1997). In the case of manidipine, the increased bioavailability in the fed state has been attributed to its high lipophilicity and a solubilisation effect produced by food and bile secretions (Rosillon et al., 1998).

This is believed to be the mechanism that explains the increased bioavailability of griseofulvin (Welling, 1977), cefuroxime (Mackay et al., 1992) and fenretidine (Doose et al., 1992) with a meal containing fat. Griseofulvin is an antifungal drug with very low water solubility and hence poor bioavailability. Absorption of griseofulvin has been shown to be increased by high-fatty meals but not by high-protein or high-carbohydrate meals (Welling, 1977). As griseofulvin is an extremely lipophilic molecule, its dissolution and hence absorption may be accelerated directly by the presence of fat in the meal and indirectly by fat-stimulated bile secretion.

Previous studies have shown that bioavailability of cefuroxime is increased by food (Williams and Harding, 1984). In a subsequent mechanistic study, hyoscine butylbromide had no effect on cefuroxime absorption whereas cholecystokinin resulted in a 20%

increase in cefuroxime C<sub>max</sub> and AUC values (Mackay et al., 1992). These results lead to the conclusion that bile release, but not gastric emptying, may be at least partially responsible for increased cefuroxime absorption in the presence of food.

#### ***II.17.1.1.3 Increased Secretions***

In addition, the larger volume of the gastric fluid induced by food intake may increase the solubility and dissolution of the drug. In the case of saquinavir (a novel protease inhibitor), the increased bioavailability following a meal has been attributed in part to the increased solubilisation induced by increased gastric pH (Barry et al., 1997). Given the physicochemical characteristics of a drug, its modified solubility, and hence its GI absorption in the presence of food, may be governed by a combination of 2 or more factors. For example, rufinamide is a new antiepileptic drug characterized by a moderate solubility (63 and 59 mg/L, respectively, in 0.1 mol/L HCl and simulated intestinal fluid) and relatively large partition coefficient ( $\log P = 0.88$ ), indicating a relative lipophilic behaviour of the compound (Cardot et al., 1998). Cardot et al. (1998) suggest that the modified solubility of rufinamide in the presence of food may be caused by a larger volume of gastric fluid and stimulated biliary secretion. In the case of bropiramine (Emori et al., 1995), the increase in dissolution, which increased the bioavailability, was thought to result from a longer GRT and larger volume of the gastric fluid.

#### ***II.17.1.1.4 pH***

Another good example is itraconazole. It is a weak base ( $pK_a = 3.7$ ), has high lipophilicity ( $P = 460000$ ) and is almost insoluble in water and dilute acids (less than 5 mg/L). [92] Zimmermann et al. (1992), concluded that the facilitated absorption of itraconazole in the fed state is contributed by low stomach pH, long GRT and a high fat content of the coadministered meal. However, the same meal would increase the dissolution rate and absorption of a weak acid nonsteroidal anti-inflammatory drug (NSAID) [e.g. ibuprofen] (Pargal et al., 1996).

### **II.17.2 Decreased first pass Metabolism**

Food ingestion affects splanchnic blood flow, but the degree and direction of change vary with the type and size of meal (Welling, 1996). A high protein meal has been shown to cause a 35% increase in splanchnic blood flow, whereas a liquid glucose meal causes an 8% decrease (Svensson et al., 1983). In most cases after solid meals, one would expect splanchnic blood flow to increase. Increased postprandial splanchnic blood flow has been touted as one of the mechanisms involved in decreased first-pass metabolism, and hence increased systemic availability of some high hepatic first-pass drugs, such as propranolol and metoprolol (Axelson et al., 1987; Melander and Mclean, 1983; Olanoff et al., 1986).

Another mechanism by which absorption of a drug may be increased is the lowering of first-pass metabolism by food (Ingwersen et al., 1993). This has been well documented for lipophilic basic drugs. A classic example is propranolol. Large increases in AUC are seen when it is administered with food. The mechanism for its interaction is based on the relationship between hepatic blood flow and hepatic clearance. As the extent of first-pass metabolism is directly related to the hepatic extraction ratio, it implies that the magnitude

of the extraction ratio increases as the efficiency of hepatic metabolism increases (Welling, 1989).

Other examples where concomitant food intake causes a marked increase (an average of approximately 50%) in the oral bioavailability of certain high hepatic first pass drugs, include labetalol (Daneshmend and Roberts, 1982), dixyrazine (Liedholm et al., 1985), zuclopenthixol (Aaes-Jorgensen et al., 1987), propafenone (Axelson et al., 1987) and diprafenone (Koytchev et al., 1996). This phenomenon has been referred to as the food effect. Not all high first-pass drugs are affected by food in this way (Melander and McLean, 1983; Melander et al., 1988), and so far no criterion has been found to distinguish drugs exhibiting the food effect from others which do not.

Thus the oral bioavailability of basic, highly extracted drugs is increased when they are taken with food (Tam, 1993). Although the underlying mechanisms are not entirely understood, food may influence drug bioavailability by changing splanchnic blood flow and/or first-pass metabolism in the liver.

Most GI absorption occurs directly from the lumen of the GI tract. During this process, drug molecules move across the epithelial cell lining of the GI tract and enter into the adjacent capillary network associated with the splanchnic circulation, leading to the portal circulation (Welling, 1989). The rate of blood flow through the splanchnic capillary bed will, therefore, have a marked effect on the absorption of drugs (Basu, 1988). Ingestion of food increases splanchnic blood flow and hence enhances drug absorption as a larger fraction of drug bypasses the liver during absorption (Mao and Jacobson, 1970; McLean et al., 1978, 1981). Thus, postprandial increases in splanchnic blood flow rate may be implicated in decreased first-pass metabolism, and, therefore, an increase in bioavailability could be observed for drugs which are subject to extensive first-pass metabolism and saturable hepatic clearance. Oral coadministration of digoxin and certain calcium antagonists results in an increase in digoxin absorption (Dunselman et al., 1988). It has been reported that at least part of this interaction is mediated by the capacity of these drugs to alter intestinal blood flow in humans (De Mey et al., 1990; Carlton et al., 1996). Evidence for this was obtained in rat perfusion studies in which a calcium antagonist increased jejunal permeability to digoxin. Increased mesenteric blood flow was visually apparent in this *in situ* system compared with control (digoxin alone) [D. Fleisher, unpublished data].

Clinical data show that a significant increase in drug absorption with coadministered grapefruit juice is mediated by inhibition of CYP3A4-mediated drug metabolism by furanocoumarins (Ameer and Weintraub, 1997). Since oral grapefruit juice does not alter drug plasma concentrations when the drug is administered intravenously, the case for an intestinal interaction, although not proven, is made stronger.

Grapefruit juice has been shown to inhibit the metabolism of dihydropyridine calcium channel blockers. Systemic availability of orally administered felodipine was increased more than two-fold by co administered grapefruit juice (Bailey et al., 1991). A less pronounced effect was observed with nifedipine. This effect has been linked to inhibition

of cytochrome P-450 III A4 by flavonoids present in grapefruit juice. In a study of men with borderline hypertension, felodipine and dehydrofelodipine systemic availability increased 2.5 and 1.7 fold, respectively, when felodipine was taken with grapefruit juice relative to water (Bailey et al., 1991). Under the same conditions, plasma levels of nifedipine and dehydrononorfedipine increased 1.4 and 1.2 fold. The results with felodipine were reproduced in another study in nine healthy middle-aged men (Edgar et al., 1992). The interaction with grapefruit juice may be due to inhibition of first-pass oxidative metabolism by flavonoids in the grapefruit juice, but the precise mechanism of interaction has not been identified.

### **II.17.3 Physiological responses**

Interestingly enough, a recent study suggests that the mechanism of the 'food effect' may also involve physiological responses to the sight and smell of food in addition to mechanisms activated by food ingestion. Power et al. (1995) investigated the pharmacokinetics of propranolol in the presence and absence of sensory exposure to an appetizing meal without eating it ('teasing') in both dogs and humans. They observed that low-intensity teasing resulted in significantly lower AUC and C<sub>max</sub> compared with fasting, confirming food effect patterns known to occur in dogs. On the other hand, high intensity teasing resulted in significantly greater AUC and C<sub>max</sub> compared with fasting, thereby reproducing in dogs the increase in propranolol AUC known to occur with food ingestion in humans. An increased intestinal absorption may also involve the up-regulation of carrier-mediated transport systems that occurs in response to high-protein meals (Gidal et al., 1996).

### **II.17.4 Formulation Factors**

The release of drug from some formulations may also be affected by the concomitant intake of food. This is of great clinical relevance to extended release formulations, as the drug absorption-time profile and, therefore, the clinical effect is controlled by drug release from the formulation (Abrahamsson et al., 1998). In addition, enteric-coated preparations may partially release their drugs in the stomach if taken with meals (Dressman et al., 1990). Evidence is also available from sustained release theophylline products in which drug release is substantially influenced (either increased leading to dose-dumping or decreased) by the concomitant intake of food (Jonkman, 1989). Thus, food can be a significant determinant in the efficacy and safety of controlled release oral products which exhibit a pH-sensitive release pattern. It is recommended that drug formulations requiring acidic pH or rapid release should not be taken with meals.

*In vitro* studies have shown that drug release is controlled by tablet erosion for poorly soluble drugs (Alderman, 1984). The importance of tablet erosion as a determinant of drug release has also been confirmed in *in vivo* studies by gamma-scintigraphy (Abrahamsson et al., 1998, 1993). Abrahamsson et al. (1998) suggested that the potential factors that might induce a more rapid erosion are vigorous motility induced by food and the physicochemical effects of food components and gastric secretions.

Studies (Shameem et al., 1995; Katori et al., 1996; Sako et al., 1996; Aoki et al., 1994) suggest that the destructive mechanical forces of GI tract play a significant role in drug release from controlled release dosage forms. In patients in the fed state, drug release may be further increased because of an increase in the mechanical stress of the GI tract caused by food intake; however, the magnitude of release depends upon the gastroduodenal transit time (Aoki et al., 1994) and the wet strength or hardness of the controlled release dosage formulations (Katori et al., 1996; Sako et al., 1996). Thus, the *in vivo* release of a drug from a multiple unit controlled release product that is structurally weak is larger than that from single unit products (Katori et al., 1996). In addition, the *in vivo* drug release is dependent upon the erosion/dissolution rate which in turn depends on the destructive conditions (e.g., pH, agitation intensity) of the GI tract (Shameem et al., 1995; Sako et al., 1996).

Shameem et al.(1995) found that under mild destructive conditions (paddle method at 10 rpm), 2 different controlled release tablets of paracetamol (acetaminophen) which differed in erosion rates showed similar *in vitro* release rates. However, under highly destructive conditions (rotating basket method at 150 rpm), the tablet with the faster erosion rate showed a faster release rate, both *in vitro* and *in vivo*. Similar results have been obtained for controlled release granules of paracetamol which differed in hardness. Katori et al.(1996) found similar release rates for both hard and soft granules of paracetamol under mild destructive conditions in official dissolution tests; however, soft granules showed a faster release rate in the rotating dialysis cell method.

As drug release is controlled by tablet erosion, it implies that the absorption rate of some drugs may be related to or controlled by the erosion of the hydrophilic matrix tablets (Abrahamsson et al., 1998, 1993). In the case of nifedipine, a poorly soluble drug, tablet erosion (which can be affected by food) leads to an increased absorption rate and elevated C<sub>max</sub> (Abrahamsson et al., 1998). The faster absorption of nifedipine has been attributed to an effect of food on the drug-release mechanism, i.e. tablet erosion and increased solubility in the GI tract induced by food (Abrahamsson et al., 1998).

Similar conclusions were reached by Ueno et al. (1989) in an earlier study. Ueno et al. suggested that the increased serum concentrations of nifedipine in the fed state were caused by increased wettability of the sustained release dosage form and increased solubilisation of the drug in the gastric milieu. Furthermore, as tablet erosion has been found to be slower in the more distal parts of the GI tract, a slower drug absorption is observed there (Abrahamsson et al., 1993). In fact, the absorption profiles of controlled release dosage forms show biphasic patterns, with the second phase showing extremely low absorption (Sako et al., 1996). Necroscopic studies have shown that the suppression of drug absorption in the second phase is caused by the termination of drug release from dosage forms in the colon (Sako et al., 1996).

### **II.17.5 Meal Effects on Drug Diffusivity**

The effect of meal viscosity on drug absorption will depend on whether or not there exists site-specific absorption, particularly if absorption is limited to the upper portions of the small intestine (Pao et al., 1998; Reppas et al., 1991). If the drug exhibits site-specific

absorption, then meal-induced decrease in diffusivity ( $D$ ) may impede drug absorption as the drug moves past the absorption site. However, the effect of initial meal viscosity on  $D$  tends to diminish as the meal moves down the small intestine, an effect attributed to digestion and the release of GI fluids. Therefore, if the drug is absorbed throughout the small intestine, then meal viscosity should have little effect on the extent of drug absorption. When present, altered drug absorption associated with meal viscosity appears to be attributable primarily to altered fluid flow dynamics rather than to altered GI motility (Reppas et al., 1991; Rhie et al., 1998). However, only modest changes in gastric emptying rate are observed when viscosity increases above 15,000 cp. Accordingly, viscosity-induced delays in gastric emptying are primarily seen when comparing changes that occur within the lower range of potential viscosity values ((Reppas et al., 1991). For this reason, viscosity effects on drug bioavailability are generally considered to be primarily a consequence of the effect of viscosity on  $D$  (Carver et al., 1999). This relationship can be explained by the Noyes-Whitney equation, where the drug dissolution rate ( $dm/dt$ ) is directly proportional the diffusion coefficient ( $D$ ).

### **II.17.6 Other examples of combined effect**

Conflicting results were reported with the onchocerciasis agent amocarpine (CGP 6140) (Lecaillon et al., 1991). In male Guatemalan patients, systemic availability increased 20% when the drug was taken with a copious breakfast compared with during fasting. When the dose was increased to 1200 mg, both the peak plasma levels and the systemic availability of amocarpine were increased approximately three fold when the drug was given after a standard breakfast, relative to fasting (Lecaillon et al., 1990). The remarkable increase in absorption due to food after the high dose of amocarpine may be related to the greater degree of solubilization by the meal or to decreased presystemic metabolism. Substantially increased absorption due to food was reported for the lipophilic antiprotozoal agent atovaquone (Rolan et al., 1994). Peak atovaquone plasma levels increased over fivefold and systemic bioavailability increased over threefold when the drug was given after a high-fat breakfast compared with during fasting. Complimentary studies using a variety of conditions led to the conclusion that the food effect with atovaquone was probably due to combined effects of bile release and also to increased solubility resulting from the fatty meal.

Absorption of cefetamet pivoxil was delayed by food. Mean peak plasma levels occurred at 4.8 h compared to 3 h during fasting. Overall bioavailability and peak plasma levels increased approximately 25-30% (Blouin and Stoeckel, 1993). A similar effect was observed when cefetamet pivoxil was administered 1 h after a standard breakfast, although plasma profiles were similar when drug was administered with or before a standard breakfast (Tam et al., 1990).

Following a 7.5 mg/kg dose of the macrolide antibiotic clarithromycin to infants and children either fasting or after ingesting milk and/or hash brown potatoes, peak plasma levels were 4.6 and 3.6 mg/ml after non fasting doses, respectively (Gan et al., 1992). Systemic availability increased by 40%. In a study of adults, food taken immediately before a 500mg clarithromycin dose increased absorption by approximately 25% (Chu et



al., 1992). In both of these studies, plasma levels of the major active metabolite 14-hydroxyclearithromycin were moderately increased.

Absorption of the heterocyclic steroid derivative danazol (Charman et al., 1993), and also of the retinoid fenretidine (Doose et al., 1992), is substantially increased by food. Systemic availability of danazol from a capsule dose was increased over threefold by food in healthy female subjects, whereas bioavailability and peak plasma levels of fenretidine increased threefold following a high-fat meal compared with during fasting (Doose et al., 1992). Administration of fenretidine in an oil suspension to fasting subjects yielded intermediate values. Further examination of the effect of meal composition showed that a high fat meal resulted in plasma fenretidine bioavailability three times greater than did a carbohydrate meal, with a high protein meal yielding intermediate results.

Itraconazole systemic availability increased two to three fold following a standard breakfast compared with during fasting (Van et al., 1989). In contrast to itraconazole, absorption of fluconazole was relatively insensitive to food, both C<sub>max</sub> and AUC being slightly reduced or unchanged by meals. Although these divergent results are consistent with previous data on these agents, there is no mechanistic explanation for their different behavior. In six healthy volunteers, levodopa absolute bioavailability from an immediate release dosage form was 86.4 and 80.4% from fed and fasting treatments, respectively. Levodopa availability from a controlled release dosage form was 71% and 63.6% from fed and fasted treatments, respectively (Wilding et al., 1991). Although the controlled release dosage form yielded lower absolute bioavailability, the food effect was similar for both formulations. A diet rich in insoluble fiber (DRIF) increased levodopa plasma levels by 30% in patients after two weeks on a DRIF diet compared with baseline (Astarloa et al., 1992). Thus, the DRIF may serve the useful purpose of relieving constipation, and also of increasing plasma levels and presumably the effectiveness of levodopa.

Peak plasma nifedipine concentrations were increased 1.8 and 2.4 fold by low-fat and high-fat meals, respectively (Kleinbloesem et al., 1993). Overall systemic availability was increased 1.2 fold by both treatments. The increased nifedipine plasma levels appeared to be without effect on blood pressure relative to the fasting state, but mean heart rate increased by 10 beats/min after both post prandial doses compared to 5 beats/min during fasting. A dramatic food effect occurred with oral micronized progesterone (Simon et al., 1993). Repeated doses of micronized progesterone were administered in capsules for 5 days to 15 healthy postmenopausal women, either 2 h before or immediately after a standard breakfast. Peak day 1 and day 5 plasma levels of progesterone were increased twofold by food. Increased progesterone absorption with food was attributed either to a direct drug-food interaction in the GI tract, or to increased blood flow to the liver, causing decreased presystemic clearance.

Oltipraz, for example, is a highly lipid-soluble antischistosomal agent that is practically insoluble in aqueous medium. Administration of 500-mg tablets to fasting humans resulted in barely detectable blood levels (Ali et al., 1984<http://ipet.aspetjournals.org/cgi/content/full/303/3/889-B3>). When administered in

conjunction with either a low- or high-fat meal, the drug was rapidly absorbed and reached very high blood levels. The mechanism underlying this significantly increased absorption is not known but is speculated to arise from increased solubilization of the drug by bile acids secreted in response to the meal or effects on stomach emptying.

Similar to observations with cefetamet pivoxil (Blouin and Stoeckel, 1993; Tam et al., 1990), food had a positive effect on the new ester- type oral cephalosporin S-1108 (Saito, 1993). Systemic availability of S-1108 was increased approximately 1.5 fold, and peak plasma levels increased 1.2 fold following a Japanese style breakfast. Ceruletide diethylamine had no effect on S-1108 absorption, but  $t_{max}$  was delayed. Ranitidine had a negative effect. Thus, neither increased bile flow nor increased gastric pH seems to contribute to food-related increase in S-1108 absorption. A dramatic interaction was observed with the piperazine derivative dopamine reuptake inhibitor vanoxerine (Ingwersen et al., 1993). Administration of 100 mg of vanoxerine to healthy men after low-fat and high-fat breakfasts increased systemic availability 1.8 fold and 3.6 fold, respectively. Despite the considerable increase in systemic availability after the high-fat meal,  $C_{max}$  was increased less than two-fold because of delayed absorption. One subject who was virtually unaffected by food intake was a poor metabolizer of debrisoquine, which suggested that decreased first-pass metabolism, possibly related to increased splanchnic blood flow, may have contributed to the food effect in other subjects.

Absorption of the nootropic agent vinpocetine and also the 5-hydroxytryptamine 1a partial agonist zalospirone is modestly increased by food (Klamerus et al., 1993; Lohmann et al., 1992). Administration of vinpocetine tablets 10 min before and 10 and 30 min after starting a standard breakfast increased systemic availability 1.6, 1.7 and 2.0 fold relative to fasting. Peak plasma levels and areas under plasma curves of zalospirone were increased approximately 1.4 fold by food in both young and elderly subjects (Klamerus et al., 1993). Plasma levels were almost doubled in elderly subjects relative to young subjects. The results of these studies led to the recommendation that both vinpocetine and zalospirone be taken with or after meals.

The last drug listed in this category reflects the dramatic positive effect that food can have on circulating drug profiles. Systemic availability of a novel antiprotozoal agent 566C80 was increased 3.3 fold, and  $C_{max}$  was increased 5.4 fold, when administered after food (Hughes et al., 1991). In attempts to elucidate the mechanism of this interaction, 566C80 was given during fasting, with meals of varying fat content, as an aqueous suspension, as an oily emulsion, and after an infusion of cholecystokinin octapeptide (CCK-OP) (Rolan et al., 1994). Results from these studies led to the conclusion that increased absorption of 566C80 after food could be quantitatively accounted for by dietary fat.

## **II.17.7 Other factors which may be responsible are:**

### **II.17.7.1 Mixing Contractions (Segmentation Contractions)**

The maximum frequency of the segmentation contractions in the small intestine is determined by the frequency of electrical slow waves in the intestinal wall, which is the

basic electrical rhythm. Because this frequency normally is not over 12 per minute in the duodenum and proximal jejunum, the maximum frequency of the segmentation contractions in these areas is also about 12 per minute, but this occurs only under extreme conditions of stimulation. In the terminal ileum, the maximum frequency is usually 8 to 9 contractions per minute.

#### II.17.7.2 Peristalsis in the Small Intestine

Chyme is propelled through the small intestine by peristaltic waves. These can occur in any part of the small intestine, and they move toward the anus at a velocity of 0.5 to 2.0 cm/sec, faster in the proximal intestine and slower in the terminal intestine. They normally are very weak and usually die out after traveling only 3 to 5 centimeters, very rarely farther than 10 centimeters, so that forward movement of the chyme is very slow, so slow in fact that net movement along the small intestine normally averages only 1 cm/min. This means that 3 to 5 hours are required for passage of chyme from the pylorus to the ileocecal valve.

#### II.17.7.3 Control of Peristalsis by Nervous and Hormonal Signals

Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenum causing stretch of the duodenal wall, but also by a so-called gastroenteric reflex that is initiated by distention of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine. In addition to the nervous signals that may affect small intestinal peristalsis, several hormonal factors also affect peristalsis. They include gastrin, CCK, insulin, motilin, and serotonin, all of which enhance intestinal motility and are secreted during various phases of food processing. Conversely, secretin and glucagon inhibit small intestinal motility. The physiologic importance of each of these hormonal factors for controlling motility is still questionable.

The function of the peristaltic waves in the small intestine is not only to cause progression of chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa. As the chyme enters the intestines from the stomach and elicits peristalsis, this immediately spreads the chyme along the intestine; and this process intensifies as additional chyme enters the duodenum. On reaching the ileocecal valve, the chyme is sometimes blocked for several hours until the person eats another meal; at that time, a gastroileal reflex intensifies peristalsis in the ileum and forces the remaining chyme through the ileocecal valve into the cecum of the large intestine.

Resistance to emptying at the ileocecal valve prolongs the stay of chyme in the ileum and thereby facilitates absorption. Normally, only 1500 to 2000 milliliters of chyme empty into the cecum each day.

## *II.18 Design of Gastro retentive Dosage forms*

### **Optimal GRDF:**

In designing GRDF's, the following characteristics should be sought:

- Retention in the stomach according to the clinical demand
- Convenient intake
- Ability to load substantial amounts of drugs with different physicochemical properties and release them in a controlled manner
- Complete degradation particularly in the stomach
- FDA approved compounding ingredients
- No effect on gastric motility including emptying pattern, or other local adverse effects e.g. on the gastrointestinal wall
- Prolonged shelf-life
- Inexpensive industrial manufacture.

### **II.18.1 Size exclusion method**

During the past few years, there has been major concern in trying to address, in animals and/or in humans, the relationship between the size of solids and their gastric emptying during the digestive phase (Kelly, 1919; Hinder and Kelly, 1977; Meyer et al., 1981, 1985; Bechgard and Christensen, 1983; Takahashi et al., 1985; Gruber et al., 1987; Itoh et al., 1986). This question has brought certain confusion due to the likely irrelevant extrapolations from the dog results (generally accepted 2-mm cut-off size) to the human stomach, and from the fate of digestible food solids to that of undigestible dosage forms.

In fact, while it has been clearly established that the size of meal suspended particles must be about 0.5 mm in dogs and about 1.0 mm in men to allow emptying in duodenum (Kelly, 1919; Meyer et al., 1981, 1985).

**Length:** Smith and Feldman showed no significant difference in emptying of markers, 2 and 10 mm in length, of constant 2-mm diameter, from the fed stomach in man and concluded that gastric emptying of indigestible solids in humans is not influenced by the length of the particles used (Smith and Feldman, 1986).

**Pellets:** Pellets as contrast to tablets, with a smaller size were only retained for  $1.2 \pm 1.3$  hours in the fed stomach but on the other hand they do minimize the variation between fed and fasting mode (Shell et al., 2003).

Davis et al, observed a gastric emptying time for 50 percent of the pellets of 1 mm and under ( $t_{50\%}$ ) in the fed state of 2 to 3 hours (Davis et al., 1987).

O'Reilly found that 7 to 10 mm pellets excited in 3 to 4 hours (O'Reilly et al., 1987).

With multiple pellets or bead formulations, gastric emptying times generally increase with particle size. The longest mean gastric emptying times for these pellets were still shorter than the mean gastric emptying time for single unit nondisintegrating tablets.

**Tablets:**

**Khosla and Davis** investigated the GE of 7-, 11-, and 13 mm tablets from the fed stomach and showed GE times of less than 1 hour for 7 mm tablets in two of five subjects, suggesting that large tablets can empty from the fed stomach (Khosla and Davis, 1990).

**Timmerman and Moes** identified a gradual cut-off of 13 mm for retention in the fed mode, with mean gastric emptying times of approximately 6 hours for tablets of 12-18 mm and no clear trend in the mean or decreased variation with increasing particle size throughout the size range studied (Timmerman and Moes, 1993).

With 12 mm enteric coated hydroxypropyl methyl cellulose tablets, Davis et al, determined that the gastric emptying times after light and heavy breakfasts were  $5.1 \pm 0.8$  and  $7.7 \pm 0.7$  hours, respectively. After the light breakfast, 4 of the 16 tablets emptied from the stomach in less than 3 hours (Davis et al., 1988).

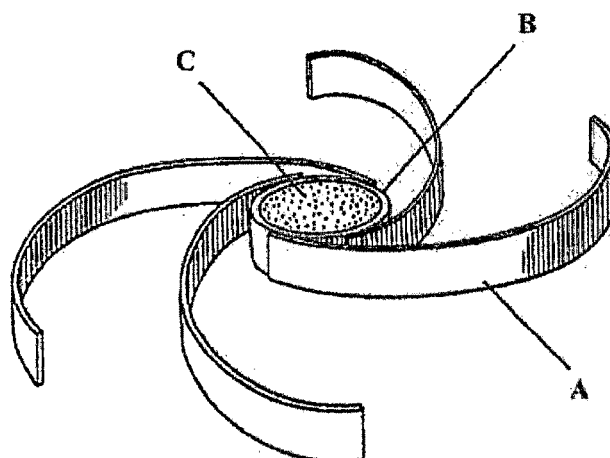
**Garg and Sharma** reported that tetrahedron and ring shaped devices have a better gastric residence time as compared with other shapes. The diameter of the dosage unit is also equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm (Garg and Sharma, 2003).

## II.18.1.1 Unfoldable, Extendible, or Expandable Systems

### II.18.1.1.1 *Systems unfolding in the stomach*

**Concept**

Systems that unfold in the stomach have one or more noncontinuous compressible retention arms. The retention arms are initially folded to make the whole system smaller. With the arms folded, the system can be fit into gelatin capsules or the folded arms are expanded to make the whole system too large to resist gastric transit (Curatolo and Lo, 1991).



**Figure II. 7** Partially unfolded dosage form modified from Curatolo and Lo. The retention arms (A), which have the ability to retain in the stomach on their own, are adhered to a receptacle (B) that holds a controlled release tablet (C). The arms induce gastroretentivity of the dosage form.

#### **Improvements to be made**

Since the device has to be emptied after all the drug is released, it is important to connect the compressible retention arm to the drug-delivery module using a biodegradable polymer. One of the problems noted with this type of device is that such biodegradable polymers may start degradation, albeit to a very small extent, during the folded state in storage; for this reason, the retention arms may not open up in the stomach. No animal studies have been done to determine how long they can stay in the stomach. In addition, even if they work as planned, the design of this type of device is so elegant that it requires a great deal of attention to produce, and so they may not be cost-effective.

#### **II.18.1.1.2 Systems extending to Complex geometric shapes**

##### **Concept**

Studies have shown that devices that extend in the stomach to certain geometric shapes can prolong gastric retention time (Cadwell et al., 1988; Cargill et al., 1988, 1989; Fix et al., 1993). The geometric shapes include a continuous stick (Cadwell et al., 1988), a ring (Cadwell et al., 1988), and a planar membrane (Cadwell et al., 1988). Since these devices should be small in the beginning for easy swallowing, they have to be compressible to a small size and expandable to a size large enough to prevent emptying through the pylorus. In one study, the longest length of the final dimension of devices varied from 2 cm to 5 cm while the shortest length was around 2 cm (Cadwell et al., 1988).

##### **Improvements to be made**

In beagle dogs, some of these devices showed extended gastric residence time (longer than 24 h) in the fasted condition (Curatolo and Lo, 1991; Cargill et al., 1988, 1989; Fix et al., 1993). In humans and larger dogs, however, the devices emptied from the stomach

much faster (Fix et al., 1993). The median gastric residence time of a tetrahedron –shaped device in man was 6.5 h and 3h in the fed and fasted states, respectively. This study points to the need of a gastric retention study in humans. More importantly, it also points to the fact that this approach is based on trial and error; for this reason, it is rather difficult to optimize a geometric shape for maximum gastric retention in humans. While an increase in flexural moduli resulted in an increase in gastric retention, it alone does not appear to be a dominating factor for extended gastric retention (Cargill et al., 1989). In addition, to make the system removable after use from the stomach, biodegradable systems have to be used; this may cause the same problem as observed with the unfolding systems.

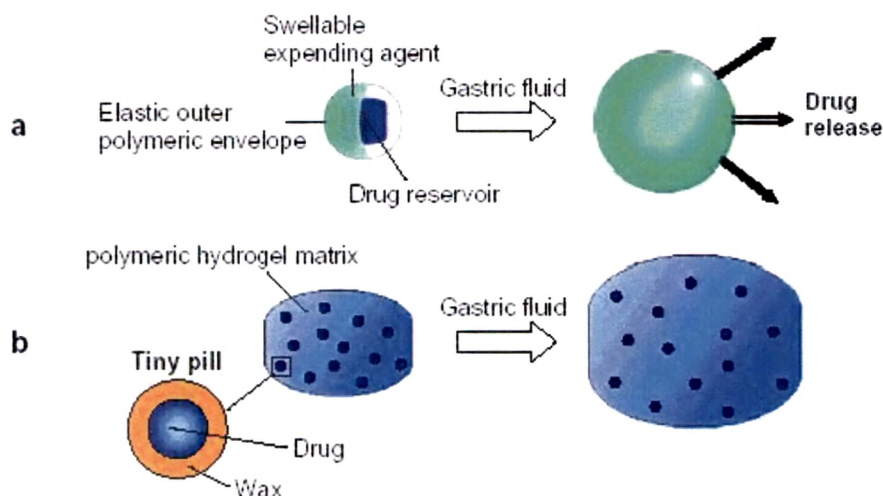
### ***II.18.1.1.3 Systems expanding to larger Sizes***

#### **Concept**

The idea here is to make devices that are small enough for easy swallowing but expandable upon contact with gastric juice to size sufficient to cause retention of the device in the stomach (i.e., to a size too large to pass through the pylorus). The concept is shown in fig 14. This type of device is made to a size slightly larger than the diameter of the pyloric canal i.e., about 1 cm to 4 cm, usually 2 cm in humans until completion of the prescribed therapeutic regimen (Michaels, 1974). Because the systems have to be removed from the stomach eventually, they have to be made either degradable or deflatable.

The main component of swellable systems is the agent that causes swelling of the device. Swelling can be achieved by several methods. First, one can employ hydrogels that swell upon contact with water (Johnson and Rowe, 1971; Urquhart and Theeuwes, 1984). Second, the swelling can also be achieved by wrapping the osmotic expanding agents (such as sugars, sugar derivatives and salts) or swellable expanding agents (such as swellable resins and hydrocolloid) with semipermeable membranes or polymer membranes that are substantially non hydratable but permeable to both drug and body fluids (Mamajek and Moyer, 1980). Third, solidified and liquefied gas at ambient temperature can be used as a swelling agent (Michaels, 1974; Michaels et al., 1975). The liquefied or solidified gas in a compartment will vaporized at physiological temperature to produce gas that inflates the device from a collapsed state to an expanded state. Gases that have a boiling point lower than 37 degree centigrade can be used. Examples of such gases are diethylether (boiling point of 34.6 degree centigrade), methyl formate (boiling point of 31.5 degree centigrade), tetramethyl silane (boiling point of 26.5 degree centigrade), iso- pentane (boiling point of 27.9 degree centigrade) perfluoropentane isomerse (boiling point of 31 degree centigrade), n-pentane (boiling point of 36 degree centigrade), and diethenyl ether (boiling point of 28 degree centigrade) (Michaels et al., 1975).





**Figure II. 8** Swellable systems developed by Mamajek and Moyer (a) and Urquhart and Theeuwes (b)

#### Improvements to be made

Devices that are designed to imbibe fluid and expand two-to fifty-folds have been proposed, but they were not tested in animals (Urquhart and Theeuwes, 1984), so their effectiveness in gastric retention remains to be seen. One of the major problems with the hydrogel approach is that swelling of the dried hydrogels, especially in the size of ordinary tablets and capsules, takes a few hours, and they may be emptied from the stomach even before reaching a fully swollen state. Second, the increase in size after swelling may not be large enough to make the device retained in the stomach over an extended period. For emptying from the stomach, the hydrogels have to be degradable or erodible. For systems utilizing osmotic or swellable expanding agents, a substantial portion of the expanding agents inside the polymer envelope has to be removed from the device; the removal of gases based on vaporized gases will be even bigger problem. These variables have not been worked out to make an effective gastric retention device, and no animal experiments have been done to show efficacy of this approach. As with unfolding systems, the manufacturing of these devices may be much more difficult than with other dosage forms.

#### II.18.1.2 Superporous Biodegradable Hydrogel Systems

This approach is based on the swelling of unique hydrogel systems. The principal difference of these devices from those described earlier is that the extent of swelling of superporous hydrogels is far beyond that obtained by other systems. The swelling ratio (volume of the swollen gel/volume of the dried form) can easily be over 1,000, compared with the only two- to fifty-fold increases obtained with other expanding systems. Because of their unique superswelling property, superporous hydrogels will be treated separately. To understand this system, it is necessary to understand how hydrogels and superporous hydrogels are different.



**II.18.1.2.1 Hydrogels and superporous Hydrogels**

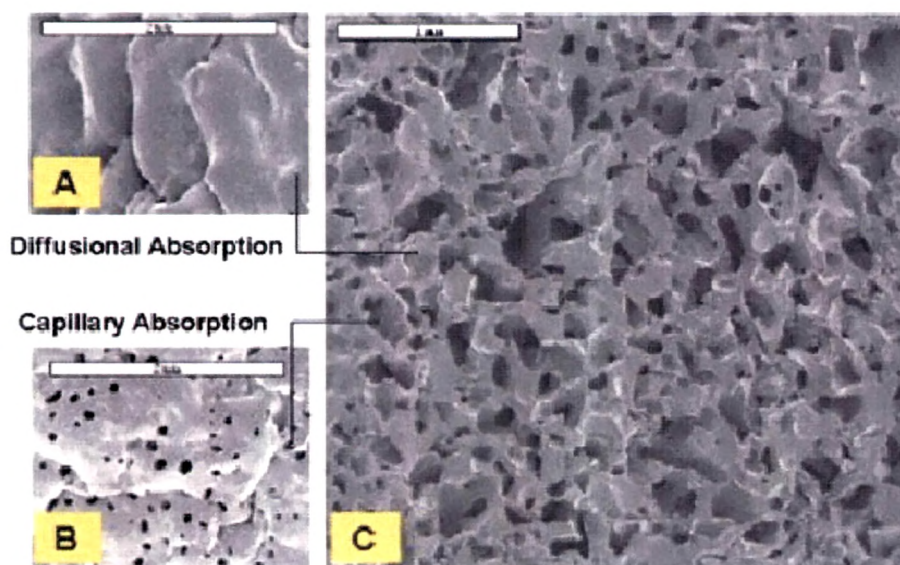
Both hydrogels and superporous hydrogels can be made either by crosslinking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of crosslinking agents. The main difference between the two types of hydrogels is pore size.

**II.18.1.2.1.1 Conventional Hydrogels**

Conventional hydrogels made by bulk polymerization lead to production of a glassy, transparent polymer matrix that is very hard. When immersed in water, such as glassy matrix swells to become soft and flexible. Although it allows the transfer of water and some low-molecular-weight solutes, this kind of swollen polymer matrix (i.e., hydrogel) is considered nonporous. The pores between the polymer chains are in fact the only spaces available for mass transfer, and the pore size is within the range of molecular dimensions (a few nanometers or less) (Chirila et al., 1993). Hydrogels that are prepared by solution polymerization can be considered porous, and the pore size depends on the type of monomer, the amount of diluent in the monomer mixture (i.e., the monomer-diluent ratio), and the amount of crosslinking agent (Barvic et al., 1967). As the amount of diluent (usually water) in the monomer mixture increases, the pore size also increases up to the micrometer range (Chirila et al., 1993). Hydrogels with an effective pore size in the 10 nm – 100 nm range and in the 100 nm – 10 mm range are called microporous and macroporous hydrogels, respectively (Chirila et al., 1993; Oxley et al., 1993). In practice, hydrogels with pores up to 10 mm can be described as either microporous or macroporous hydrogels. When the hydrogels are dried, they become glassy and no pores are observed even by scanning electron microscope. Figure 16A shows the surface of dried hydrogel cut in half. No pores are seen on the dried macroporous hydrogels. Due to the hydrogel's glassy nature, absorption of water into the gel by diffusion is a very slow process. For dried hydrogel the size of ordinary tablets, the swelling takes several hours.

**II.18.1.2.1.2 Superporous Hydrogels**

Superporous hydrogels are a new type of hydrogel that have numerous supersize pores inside (Park and Park, 1994; Chen, 1997). Superporous hydrogels have numerous pores while conventional hydrogels show no pores throughout the matrix even under SEM. The size of pores in superporous hydrogels is larger than 100 nm, usually in the range of several hundred micrometers, and can be up to the millimeter range. Even after drying, the pores of the superporous hydrogels remain connected to each other to form capillary channels. Because of this, dried superporous hydrogels can swell extremely fast upon contact with water and can swell to a very large size. Unlike conventional hydrogels, superporous hydrogels can swell to an equilibrium size in less than a minute regardless of size. It is this fast swelling property that is important in the application of hydrogels as a gastric retention device.



**Figure II. 9** Scanning Electron Microscope comparing Superporous Hydrogel (SPH) to a Conventional Hydrogel. (A) Surface of Conventional Hydrogel (B) Surface of a typical Superporous hydrogel (C) Cross- section of a typical Superporous Hydrogel

#### II.18.1.2.1.2.1 Superporous Hydrogel Systems

##### Concept

The main concept here is to utilize the superswelling properties of superporous hydrogels to extend gastric retention time. The superporous hydrogels can also be made biodegradable, eg. degradable by pepsin in the stomach. As drug is released or after the entire drug is released, the superswollen hydrogel degrades and eventually empties from the stomach. As mentioned above, the swelling ratio of superporous hydrogels is in the range of several hundred at a minimum and can be much higher than 1000. This means that each dimension can be increased 10 times.

About a decade ago, enzymes, digestible swelling hydrogels were developed for potential application as a gastric retention device for oral drug delivery (Park, 1988). Subsequent animal studies showed that the swelling hydrogels could remain in the canine stomach for upto 60 h as determined by direct visualization using ultrasound, X-Ray, and Fluoroscopic imaging techniques (Shalaby et al., 1992). The enzymes- digestible swelling hydrogel formulation was used to deliver flavin mononucleotide (FMN) for upto 50h (Shalaby et al., 1992). FMN is known to be absorbed only from the upper small intestine. Thus, the blood concentration of FMN maintained for longer than 24H (upto 50h) was due to gastric retention of the hydrogel in the stomach. When flavin mononucleotide was administered in a capsule without the hydrogel device, the blood level decreased to zero within 6 h. One problem with using swelling hydrogels in this study was that dried hydrogels (which are in a glassy state) did not swell fast enough in the stomach. Thus, when dried hydrogels were administered to dogs, they were all

emptied in about 30 min. Other large objects such as magnetic stirring bars, a few centimeters in length, were also emptied in less than 30 min (Shalaby et al., 1992). Others also observed that large nondigestible objects, such as nondisintegrating radiotelemetry capsules (or Heidelberg capsules) 7 mm in diameter x 20 mm in length with a density of 1.5, were readily emptied (in about 30 min) from the stomach (Mojaverian et al., 1991). The dried hydrogels were partially swollen for two hours before administration of the hydrogel formulation to avoid premature emptying. Since then, attention has been focused on developing superporous hydrogels that swell in less than a minute so that swelling kinetics do not pose a problem.

Hydrogels have remained in the stomach for more than 24 h even in the fasted state due to their unique properties (Shalaby et al., 1992). Hydrogels are flexible and yet maintain a certain mechanical strength. As we examined gastric retention of various types of hydrogels, we noticed that they were under the continuous influence of gastric contractions (Shalaby et al., 1992). Figure 18 shows how hydrogels remain in the stomach despite continuous gastric contractions pushing the hydrogel to the pylorus. Due to their slippery and flexible nature, hydrogels could escape gastric contractions (Shalaby et al., 1992).

#### **Improvements to be made**

There are several properties that the superporous hydrogel formulation should possess in order to function as gastric retention devices. These are fast swelling, large size, surface slipperiness, and mechanical length. For human applications, these factors need to be optimized. In dogs, hydrogels stayed in the stomach withstanding housekeeper waves when their size was about 2 cm in diameter x 2 cm in length, or larger (Shalaby et al., 1992). The use of superporous hydrogels allows a dosage form that is small enough for easy swallowing and becomes large enough for gastric retention after swelling. According to Houghton et al., the maximum gastric pressure in the fasted and fed state, following a solid or a liquid meal, ranges from 80 mm Hg to 100 mm Hg in humans (Houghton et al. 1988). Thus, any superporous hydrogel dosage form should have mechanical strength to withstand pressure. To eliminate problems associated with the weak mechanical strength of highly swelling hydrogels, superporous hydrogel composites that maintain high mechanical strength even after fast swelling to a large size were developed (Chen, 1997; Park and Park, 2001). While many parameters that are thought to be important for gastric retention have been worked out for superporous hydrogel systems, it still remains to be seen whether they would work in humans as well as in dogs. Only after human trials can further improvements be made.

#### **Work Done**

- **Retention by expanding system**

The pioneering design of GRDF's based on unfolding to a large configuration, was conducted by Laby (1974) for veterinary applications. These DFs were constructed for ruminants and particularly for releasing in a controlled manner bloat-preventing surfactants in bovine. The ring shape devices were shown to protect the cows against bloat, but their size of 15x 3 cm (length x diameter) was too large for human use.

Another unfolding DF for ruminants was developed by Brewer and Griffin (1980). This DF is fabricated as an optionally multilayer insoluble polymeric sheet that opens from one configuration to the other due to resiliency. The sizes vary according to the ruminant species e.g. for sheep a size of 0.2x 6x 4 cm as thickness x length x width, may be suitable. Such devices for sheep typically weighed 8 g and contained 3.5 g of drug. Relevant drugs such as anthelmintics may be incorporated into the polymer sheet. Studies using such devices which contained a nondegradable polymer, loaded with morantel citrate or levamisole HCl showed in-vitro release of the drug for a few months, with protection in sheep from worms for similar times.

A second generation of the above DF's (Griffin, and Brewer, 1981) has the same configuration but the DF's degraded after 6-12 weeks in the rumen due to addition of degradable polymers to the matrices. Prolonged rumen retention as well as in vivo CR of an anthelmintic drug, parbendazole was proven by sacrificing sheep and measuring the DF's drug contents.

Johnson and Rowe (1971) suggested the first GRDF's for human use on the basis of expansion in the stomach. The GRDF is a tablet comprised of thiolated gelatin, a cross linking agent and a drug. Once the DF reaches the stomach the thiolated gelatin hydrates, swells and crosslink's to form a matrix too large to pass through the pylorus.

Michaels (1974, 1975) described swelling DF's intended for human use by constructing tubular GRDF's from a swelling retention arm bonded to a chamber which contains a drug reservoir, a pressure generating compartment and a pressure responsive flexible bladder in between. The pressure generating compartment contains a liquid with boiling point close to body temperature or a solute with a high osmotic pressure. In the stomach, the pressure inside the compartment is elevated due to creation of gas or diffusion of liquid thus its volume is increased. Thereby the pressure is exerted on the bladder to reduce the volume of the reservoir consequently inducing controlled release; and the retention arm is expanded to a size larger than the pyloric sphincter. After the drug release, bioerosion or gradual diffusion of gas out of its compartment enables achievement of "collapsed" state followed by expulsion from the stomach. The GRDF is administered in a gelatin capsule.

A gas generating expanding membrane device was investigated by Sinnreich (1991) to resist emptying of the dosage form in the fasted state. The dosage form consisted of a membrane bag, which was typically polyvinyl alcohol, into which was placed the medicament, in particular, baclofen, and an agent that generated gas in the presence of gastric acid, such as sodium bicarbonate. Acid also could be incorporated into the dosage form to allow for a time lag in permeation of the acid or variation in gastric pH with food or proton pump inhibitors. This dosage form expanded to approximately 2.5 cm in diameter and remained inflated until the gas source was depleted. This dosage form delivering baclofen was then investigated in dogs (Wilson et al., 2001) and in humans (Cumming et al., 2001). Radiopaque strings were incorporated into the dosage form for visualization by X-ray in dogs, and gas in the dosage form also could be seen with

fluoroscopy. All dosage forms inflated in dogs whether in the fed or fasted states within hour. Deflation occurred in to hours in the fed state and in to hours in the fasted state. In the fasted state, five of six dosage forms remained in the stomach for at least 7 hours, whereas one emptied at 2 hours. The dosage form remained in the fed stomach for at least 10 hours in five of six dogs and emptied in 6 to 7 hours in the remaining fed beagle. The bioavailability of baclofen from the extended release dosage form was comparable with the immediate release form with a diminished  $C_{max}$  and extended  $t_{max}$  (Wilson et al., 2001). To study this system in humans (Sinnreich, 1991), samarium was incorporated into the dosage form, and it was then neutron activated (Wilding et al., 1995) to visualize its transit by gamma scintigraphy (Cumming et al., 2001). The dosage form was administered to 13 healthy volunteers in the fasted low-fat (low calorie) and high fat states (high calorie) and compared with immediate release baclofen administered fasted and with a high fat meal. When administered with the high fat meal, all systems remained in the stomach at 16 hours, and 7 of 13 remained at 24 hours. After a low fat, low calorie meal, all except one system remained at the stomach at 4 hours, four had emptied by 6 hours, 60 % remained at 16 hours, and one remained in the stomach at 24 hours. In the fasted state, three had emptied in 2 hours, and four still remained in the stomach at 16 hours. While the results for the low fat, low calorie meal was not entirely consistent, it is the most extended case of gastric retention under these conditions to appear in the literature. The plasma profiles in the high fat state were 90 percent of that of the immediate release dosage form, and for the low fat state, the bioavailability was 80 %.

#### • Swelling GRDFs

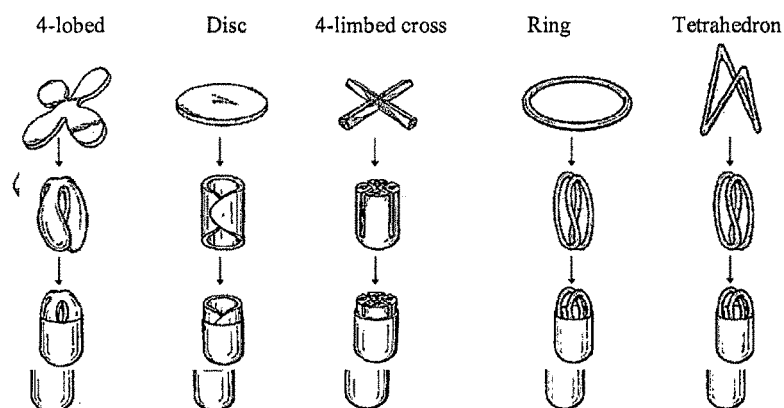
Mamajek and Moyer (1980) designed a GRDF comprised of an envelope from an elastic or nonelastic nonhydrable polymeric, membrane, which is drug and body fluid permeable. The envelope contained a drug reservoir and an expanding agent i.e. a swellable resin or hydrocolloid which causes expansion by osmotic pressure. Such devices of size larger than 1.5 x 1 cm were retained in the dog stomach for prolonged periods of time, typically more than 12 hours. Models of drugs such as poldine methylsulfate and haloperidol, had prolonged pharmacodynamic actions when administered in such GRDFs in comparison to conventional (Dosage form) DF.

Urquhart and Theeqwes (1984) developed a DF with the very high swelling ratio, exhibiting a 2 – 50 fold volume increase. Controlled release of the drug is achieved by incorporation into wax walled tiny pills dispersed throughout a hydrogel. Bio erosion of the DF enables its evacuation from stomach.

Shalaby and Co-workers developed albumin-crosslinked polyvinylpyrrolidone hydrogels with swelling and degradation properties which can be controlled by adjusting the degree of vinylic functionality of the albumin crosslinker. A dog study showed that a bulk-degrading hydrogel with the size of 2.7 \* 2.7 cm (Length \* Diameter) in the dried state swelled after 2.5 hour in the stomach to a length of 3.6 cm and was retained there for more than 60 hours. Administration of riboflavin- 5- phosphate containing hydrogels to dog maintained elevated blood concentration for upto 54 hours, thus yielding a 3.7- fold increase in bio availability in comparison to oral bolus (Shalaby and Park, 1990; Shalaby et al., 1992).

### • Unfolding GRDFs

Caldwell and co-workers (Caldwell et al., 1988) developed geometric configurations like continuous stick, ring, tetrahedron, planar disc, planar multilobe and string. These devices had the desired in vivo circumference, larger than 5 cm, to ensure gastro-retentivity. In vivo results in beagle dogs showed that the tetrahedron and the rigid ring showed retention (>90%) of more than 24 hours (Fiz et al., 1993). The smaller geometrical figure, a 2-cm arms tetrahedron, was further evaluated in American foxhounds, larger dogs weighing 30-40 kg, and in humans. In American foxhounds, half of the tetrahedral left the stomach in less than 2 hour and only 17% of the tetrahedral were retained in the stomach for 24 hours. In human volunteers, the tetrahedral left the stomach in the fasting state quickly with a median GRT of 3 hour and a range of 0.5-6 hour. In the fed state, most of the tetrahedral (90%) left the stomach in less than 10 hour with a median GRT of 6.5 hour and a range of 3.5 to more than 12 hour.



**Figure II. 10** Different geometric forms of unfoldable systems proposed by Caldwell et al.

Pagony and Zentner (1993) addressed the problem developed by Caldwell et al. They found that the prolonged stress applied during storage, reduces the resiliency and impedes the ability of the GRDFs to expand to the large configuration in the stomach. They designed bioerodible thermoset covalently cross linked elatomeric poly (ortho-esters) with a prolonged shape memory. Thus a three dimensional network structure induced dimensional stability and resiliency after compression for extended periods of time.

Sonobe et al. (1991), developed configurations that may be constructed with at least three coplanar limbs extending from a centre, e.g. cylindrical -shape, cross- shape or Y-shape. Such GRDFs were retained in beagle dogs fed stomach for more than 24 hours. Exploratory nicardipine CR tablets which were attached to such GRDFs had significantly higher bioavailability in comparison to identical CR tablets.

The work of Curatolo and Lo (1995) presents an unfolding spiral or coil configuration GRDF. It is designed as a receptacle means that holds a drug reservoir formed as a tablet or capsule, and one or more retention arms attached to it. The retention arms, in the form of fibers or ribbons, have the ability to stay in the stomach on their own. They are



characterized by: unfolding or uncoiling in the stomach to reach a circumference of more than 3 cm. GRDFs according to this invention, which had four short retention arms arranged concentrically around a tablet, were retained for more than 24 hour when administered to fasting beagle dogs, which were fed their normal food 7 hour post administration. On the other hand, devices having a single long retention arm arranged concentrically around the tablet were not consistently retained in the stomach. Administration of glipizide CR tablets incorporated into such GRDFs to fasting beagle dogs, which were fed 12 hours post dose, showed elevation of almost 2 fold in the bioavailability when compared to identical CR tablets. Another finding was that resilient polyethylene fibers with dimensions of 10 x 0.1 cm (length x diameter) were retained in stomach of beagle dogs for more than 24 hours. However, attachment of identical fibers to tablets shortened the GRT of the combination to that of the tablet alone.

Klausner and co-workers (Klausner et al., 2002,2003; Klausner, 2002) designed rectangular shaped unfolding GRDF's, which uses a combination of rigid components with large dimensions e.g., 5 x 2 cm, to enhance gastreretivity. The GRDF's are compounded from thin polymeric membranes: a drug-polymer matrix is surrounded by rigid polymeric strips, all covered from both sides in a sandwich form, by identical membranes, which connect and maintain them intact. Each separate component is designed to evacuate from the stomach rapidly while the combination of them all in this platform yields prolonged GRT (Friedman et al., 2001). The GRDFs were retained in the stomach of dogs and humans for prolonged and comparable time spans for at least 5 hours. In both species non-disintegrating tablets and large dimension low rigidity DFs were used as control groups. Pharmacokinetic evaluation in dogs, of riboflavin (Klausner et al., 2002) and levodopa (Klausner et al., 2003) incorporated into the GRDFs has shown increased bioavailability in comparison to non-gastreretentive CR-DFs. Moreover studies in healthy volunteers demonstrated enhanced pharmacodynamic actions i.e. diuresis and natriuresis, of frusemide (Klausner et al., 2003) and an extended absorption phase of levodopa in comparison to a nongastreretentive CR-DF, Sinemet CR, by about 2 hour (Shell et al., 2002).

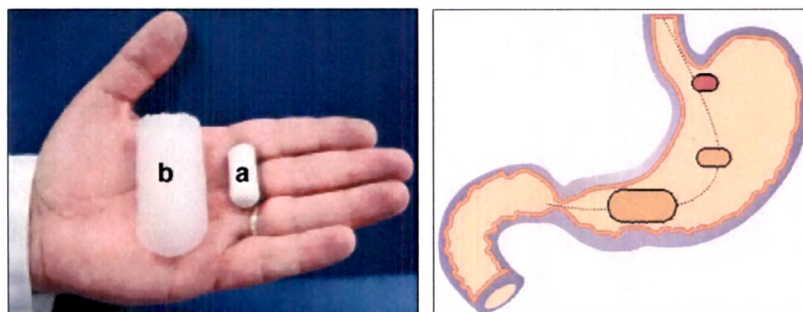
The GRDFs developed by Shell and co-workers (Shell et al., 2002; Gusler et al., 2001; Gusler and Berner, 2000; Louie-Helm et al., 2001) are swelling tablets which take advantage of the physiological fact that the fed mode prolongs GRT of DFs. Studies in fasting beagle dogs of GRDFs fabricated according to this invention, with dimensions of 19 x 8 mm (length x diameter) showed rapid evacuation of less than 90 min from the stomach, while administration with 50 g food prolonged GRT to 4-5 hour. A study involving human subjects evaluated GRT of swelling tablets with dimensions of 4x4 mm or 6x6 mm (length x diameter) and showed brisk emptying of less than 1 hour in the fasting state. However, following a heavy breakfast of 1500 kcal, 80% of the contents of all the tablets were retained for 4 hours, and in 5 of the ten subjects the tablets were retained for 6 hours or more. In four of the five subjects the tablets were retained for 10 hours or more (Shell et al., 2002). An experiment on other swelling GRDF's in accordance with this invention showed mean GRT values of less than 5.9 and mean upper gastrointestinal tract transit time of less than 9.5 hours (Gusler and Berner, 2000). Pharmacokinetic performances of metformin and ciprofloxacin swelling GRDFs were

compared to immediate release tablets following a standard breakfast of 500 kcal in healthy volunteers. Ciprofloxacin GRDF showed equal bioavailability, longer  $t_{max}$  and lower  $C_{max}$  (Louie-Helm et al., 2001). Metformin GRDFs released the drug for 6 to 9 hours in vitro. They had a diameter of 9 mm and swelled in vitro to 150% of their original size within 15 min. The in vivo findings showed that metformin GRDFs had a 17% or less increased mean bioavailability, lower  $C_{max}$  and about 2 hour longer  $t_{max}$  when compared to the immediate release tablet (Gusler et al., 2001).

Another recent GRDF is pouch with internal dimensions of 2 x 2 cm to 2.5 x 2.5 cm, administered while incorporated into a capsule. After intake of high fat meal these pouches were retained in the human stomach for over 16 hours (Wilson et al., 2002).

#### • Superporous Hydrogel

Chen and co-workers (Chen and Park, 2000; Chen et al., 2000; Park and Park, 2001; Klausner et al., 2002) designed unique superporous hydrogel composites with which combine a high swelling rate and ratio of more than 10 times the original weight of the dried matrix with substantial mechanical strength. The rapid swelling occurring within 20 min., prevents premature emptying from the stomach by “housekeeper wave. An in vivo beagle dog study showed that SPH composite, previously demonstrated to swell in simulated gastric fluid to a size of 3.5 x 2.4 cm (length x diameter), was retained and maintained intact in the fed stomach for more than 24 hour. Administration to fasting dog showed rapid evacuation.



**Figure II. 11** On the left, superporous hydrogel in its dry (a) and water-swollen (b) state. On the right, schematic illustration of the transit of superporous hydrogel. Gutierrez-Rocca et al.

Park and Oark (1998) developed superporous hydrogels, a class of lightly cross-linked hydrogels with larger pores greater than 100 micrometer in diameter. These superporous hydrogels were developed as open-channel hydrogel foam with a foaming agent, such as protein or Pluronic, and a gas or a chemical foaming agent. The monomers were selected to allow substantial swelling and may include polyacrylic acid, polyacrylamide, polyhydroxyethyl methacrylate, or hydroxypropyl methacrylate. These hydrogels remained in the stomach for 2-3 hours in fasted dogs, which is longer than most systems but has limited utility. When given with food to beagles, however, to allow an initial time for swelling in the fed state, these hydrogels remained in the stomach for 24 hours.



## **II.18.2 Intragastric Floating Systems (Low Density systems)**

The concept of FDDS was described in the literature as early as 1968 (Davis, 1968), when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pills having a density of less than 1.0 g/ml so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating delivery system.

The main concept here is to use devices in which density is lower than that of water so that the devices can float on top of the gastric juice. This is expected to prolong the gastric residence time and thus increase the bioavailability of drugs that are mainly absorbed in the upper part of GI tract. The devices may acquire low density after administration to the stomach or possess low density from the beginning.

### **II.18.2.1 Hydrodynamically Balanced System (HBS)**

#### **Concept**

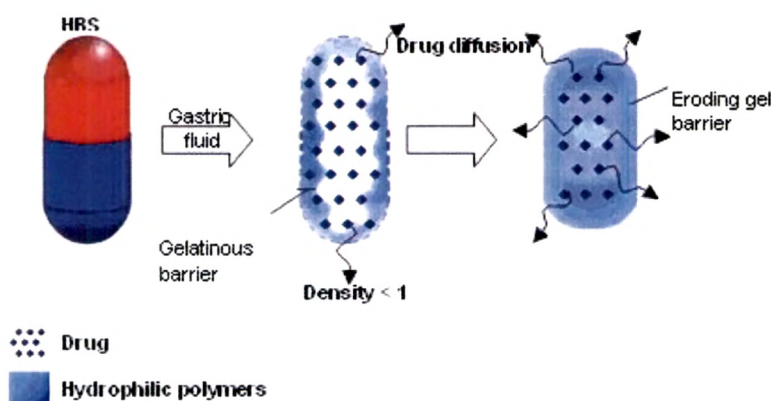
A hydrodynamically balanced system (HBS) was the first formulation that used the floating property of a device with density lower than that of water (Sheth and Tossounion, 1978). HBS is simply a capsule containing a mixture of drug, gel-forming hydrophilic polymers (e.g. hydroxypropylmethyl cellulose), and such other excipients such as hydrophobic fatty materials (e.g., stearates) (Sheth and Tossounion, 1978, 1979, 1984; Khattar et al., 1990; Babu and Khar, 1990; Menon et al., 1994). Upon contact with gastric fluid after oral ingestion, the capsule shell dissolves and the drug-hydrocolloid mixture absorbs water and swells to create a soft gelatinous outside surface barrier. Since the relative integrity of the overall shape is maintained, the density of the system at this stage becomes  $<1$ , mainly because of the presence of a dry mass in the centre as well as the presence of stearates, which slow down the penetration of water to the inside. As the hydrated outer layer is eroded, a new gelatinous layer is formed. During this process, the drug in the hydrated layer is thought to be released by diffusion. Figure II.12 describes this process.

#### **Improvements to be made**

The potential limitation of this approach is that the floating concept in an HBS is rather passive, i.e., it mainly depends on the air captured in the dry mass inside the hydrating gelatinous surface layer. The presence of a small amount of fatty material, added to impede wetting, also aids buoyancy. Because of this passivity, the buoyancy of an HBS largely depends on the characteristics and amount of hydrophilic polymer used (Oth et al., 1992). To make a better floating HBS, many investigators tried other combinations of hydrophilic polymers (e.g., agar (Bolton and Desai, 1989, 1991), carrageenans (Bolton and Desai, 1989), and alginic acid (Bolton and Desai, 1989)) and hydrophobic materials (e.g., oil (Bolton and Desai, 1989, 1991) and porous calcium silicate (Yuasa et al., 1996)). Floating capabilities of various excipients were also examined by Gerogiannis et al. (1994, 1993). Since it was difficult to achieve both good buoyancy and a desirable release property, a modified version of an HBS was developed. Double layered floating systems were proposed to optimize floating capabilities and drug release profiles

separately (Oth et al., 1992; Franz and Oth, 1993). The drug layer was a typical HBS and the buoyant layer comprised excess amount (80%) of HPMC.

Floating of an HBS has been visually observed in vivo using endoscopy in a few human volunteers (Khattar et al., 1990). The floating HBSs were shown to have slightly longer gastric residence times than nonfloating devices (Babu and Khar, 1990). In the subjects who took a meal once before administration, the capsules containing double layered HBS were emptied from the stomach at the end of the digestive phase, i.e., in approximately 3 hours. On the other hand, when the subjects were given meals before completion of the previous digestive phase, the system remained in the stomach for more than 10 h as examined by gamma scintigraphy (Oth et al., 1992). Such a long gastric retention, however, may not be related to the floating property. The gastric residence time can be prolonged for any dosage form as long as food is maintained in the stomach. While the concept of an HBS is attractive, it has not been really developed into an effective gastric retention device, except for one commercial product. For the floating device to be useful, it has to remain in the stomach even in the fasted state. But this may be extremely difficult, since the floating system requires the presence of gastric juice, which may not be available in the fasted state. Thus, at least with the knowledge we have the floating system has inherent limitations when used as a gastric retention device in the fasted state.



**Figure II. 12** Hydrodynamically balanced system (HBS). The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier

### II.18.2.2 Gas-Generating Floating systems

#### Concept

Since one of the main limitations of an HBS appeared to be the lack of a good floating mechanism, systems with an improved buoyant property have been designed. The gas-generating floating systems lower density by generating gas bubbles in the matrix.

Usually carbon dioxide is generated from sodium bicarbonate at an acidic pH (Groning and Heun, 1984; Atyabi et al., 1996). For this reason, acids, e.g., citric or tartaric acid, are included in the formulation. The system may be composed of single- or multilayers in various geometries such as membranes or spheres. The gas generating unit can be incorporated in any of the multiple layers (Hilton and Deasy, 1992; Groning and Heun, 1984; Phuapradit and Bolton, 1991; Ingani et al., 1985). Alternatively, the gas generating unit can be loaded inside microparticles such as ion-exchange resin beads (Atyabi et al., 1996), which can be loaded with bicarbonate and coated with a semipermeable membrane. On contact with gastric juice containing hydrochloric acid, carbon dioxide is released, which causes floatation of the device (Atyabi et al., 1996).

In a human study, the semipermeable membrane-coated beads showed prolonged residence times over the non coated control during a 150 min observation period. Floatable microbeads can also be prepared using multiple layers. The inner layer was made of two separate layers of sodium bicarbonate and tartaric acid, and the outer layer was a swellable membrane layer. Initially the system has a density larger than 1 and thus it sinks. As water permeated into the inner effervescent layers, sodium bicarbonate and tartaric acid are mixed together to generate carbon dioxide gas and this lowers the density to less than 1 g/mL.

#### **Improvements to be made**

The results of *in vivo* studies employing gas generating floating systems have not been consistent. Some studies showed moderate –i.e., up to 25% - increase in bioavailability of riboflavin (Ingani et al., 1985). In a study of drug absorption kinetics and bioavailability of acetaminophen in humans, the gas generating formulation did not show any significantly different bioavailability from that of a regular tablet in both fasted and fed conditions (Phuapradit and Bolton, 1991). In yet another human study, the bioavailability of amoxicillin trihydrate was actually reduced by 20% with the buoyant device (Hilton and Deasy, 1992).

The main problem here is that the persistence of the buoyant property has not been carefully examined in most of the devices. For this reason, it was suggested that the initial bulk density of the dosage unit and changes of the floating strength with time should be characterized prior to *in vivo* comparison between floating and non floating units (Timmermans and Moes, 1990; 1994). The real issue to be considered here is that all the dosage forms, whether buoyant or not, is expected to be emptied from the stomach in the fasted state by the housekeeper waves. Human studies using Gamma Scintigraphy showed that floating capsules, or floating tablets, generally have short (<2h) gastric retention times under fasted conditions but may have prolonged ( $\geq 4$  h) gastric retention times under fed conditions (Davis, 1986). Thus, it appears that, as with other devices, the presence of food prolongs the gastric retention time of the floating device. Most human studies with floating single unit dosage forms showed the same trend in the presence of food (Khattar et al., 1990; Mazer et al., 1988).

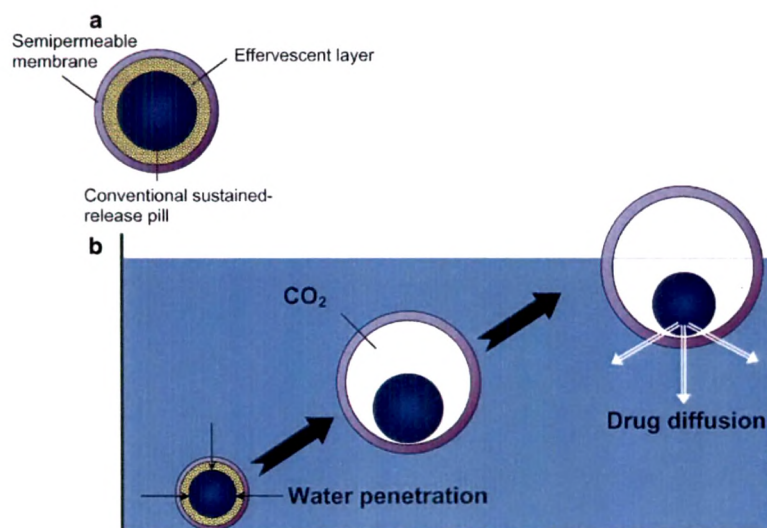


Figure II. 13 Schematic representation of “floating pill” proposed by Ichikawa (a). The penetration of water into effervescent layer leads to a CO<sub>2</sub> generation and makes the system float (b).

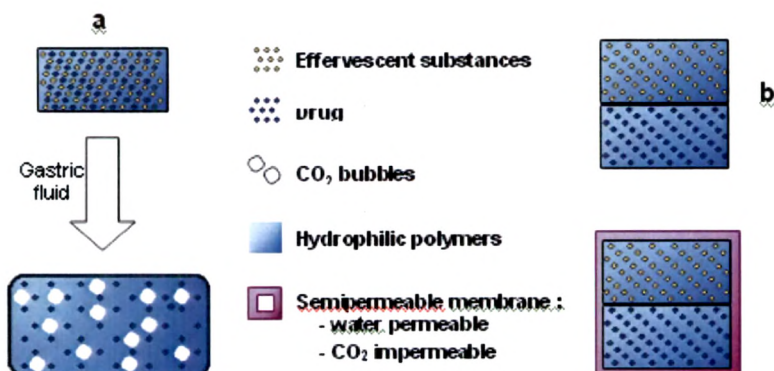


Figure II. 14 Gas-generating systems. Schematic monolayer drug delivery system (a). Bilayer gas-generating systems, with (c) or without (b) semipermeable membrane

### II.18.2.3 Volatile Liquid / Vacuum Containing Systems

#### II.18.2.3.1 Intragastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment, as shown in Figure II.15



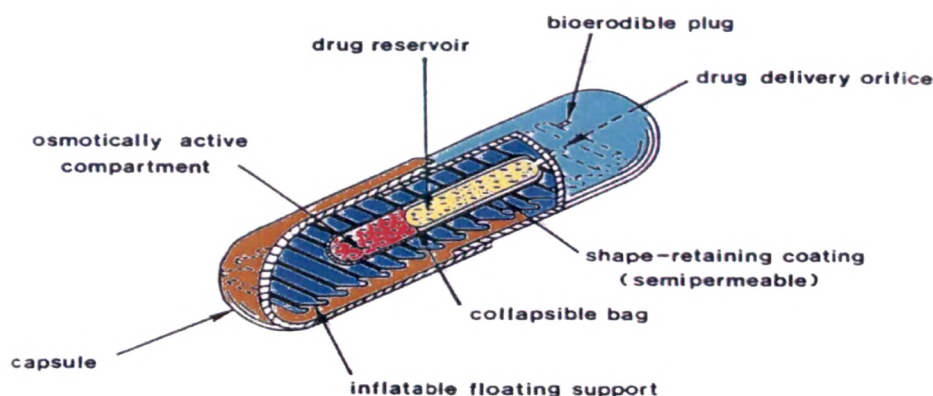


Figure II. 15 Intra Gastric Floating Gastrointestinal Drug Delivery Device

#### II.18.2.3.2 Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Figure II.16.

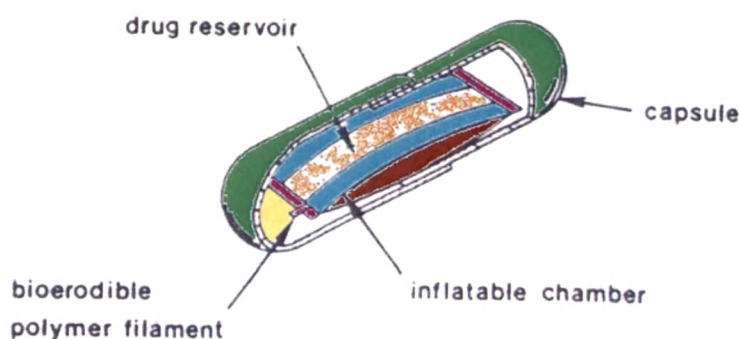


Figure II. 16 Inflatable gastrointestinal delivery system

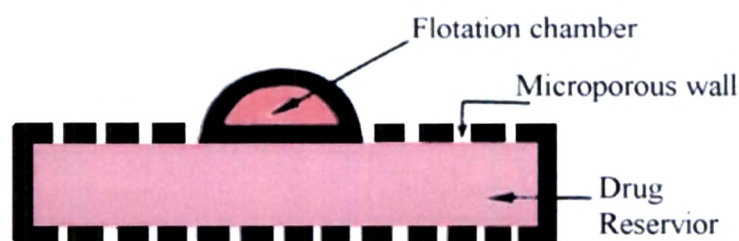
#### II.18.2.3.3 Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid

that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodable plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Figure II.17.



**Figure II. 17 Intragastric osmotically controlled drug delivery system**

#### ***II.18.2.3.4 Low- Density Core Systems***

##### **Concept**

In this type of system, the core materials are made of low density materials such as empty hard gelatin capsules, polystyrene foams, pop rice grains, or concave molded tablet shells (Watanabe et al., 1976). By providing a buoyant property from the beginning, the device is thought to have a better chance to stay afloat in the gastric juice. The external surfaces of the low density materials are coated with drugs and subsequently with a variety of polymers, such as cellulose acetate phthalate or ethylcellulose, to control drug release characteristics. Low density systems can also be produced using hydrogel matrices, such as agar, carrageenan, and alginic acid that contain light mineral oil (Bolton and Desai, 1989; Desai and Bolton, 1991). The presence of entrapped oil and air provides the buoyancy effect.

Low density floating systems have often been prepared as microparticles. Because of the low density core, some microparticles are called microballons (Kawashima et al., 1991, 1992; Jayanthi et al., 1995; Thanoo et al., 1993).

Radiographic study in humans showed that the microballons were dispersed in the upper part of the stomach and were retained there for over 3 h against peristaltic action.

#### **Improvement to be made**

This type of device has the same limitation as any other low density device. It may well be that gastric retention is not controlled by low density alone. Davis et al. examined the effect of density on gastric retention (Davis et al., 1986). Their study showed that light pellets (density of 0.94 g/cm<sup>3</sup>, diameter of 0.7 mm – 1.0 mm) emptied from the stomach at a slightly slower rate compared to heavy pellets ( density of 1.96 g/cm<sup>3</sup>, diameter of 0.7 mm – 1.0 mm) in three of 4 subjects with a large inter individual difference. Emptying of the heavy pellets conformed to a single linear function, whereas the lighter pellets showed a two-phase pattern. At early times the emptying rate of the heavy pellets was greater than that for the light pellets, which tended to float towards the fundus of the stomach. At later times the light pellets were images in the lower part of the stomach and then were generally emptied more quickly from the stomach than the heavy pellets. Since the density of the light pellets used in the study was only 0.94, this may not represent gastric retention of true low-density devices. However, this study points to the same problem for all dosage forms, i.e., dosage forms are emptied from the stomach in the fasted state regardless of density differences.

The effectiveness of floating devices is in large part determined by the presence of enough liquid in the stomach, which requires frequent drinking of a large quantity of water. Another limitation is that gas-generation does not guarantee subsequent floating of the device on top of the gastric juice. As described, above, the results of many studies did not support the efficacy of the buoyant systems. While these particular studies should not be used to disprove the entire concept, they indicate that improvements have to be made before the buoyancy truly prolongs gastric residence time. In many situations, there may just not be enough water in the stomach to make the devices float. Even with truly floating devices, housekeeper waves tend to remove these devices from the stomach.

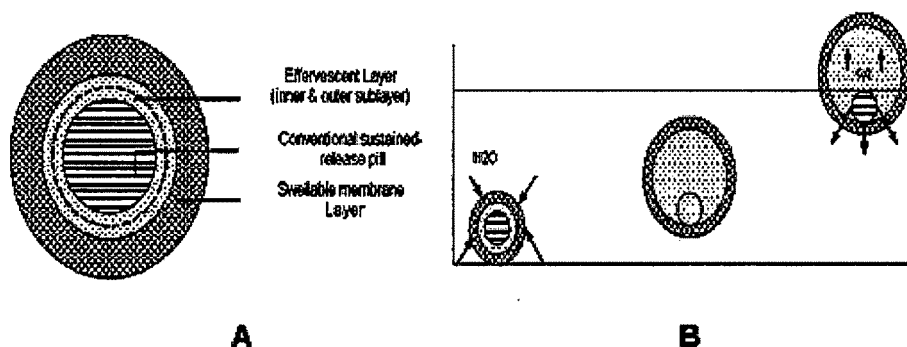
Although extension of gastric residence time of low-density devices may not be easy to achieve under fasted conditions, such devices may offer an advantage over other devices in that they may prevent direct contact of undissolved drug with the stomach lining. This may be a substantial advantage in using drugs that are known to damage the stomach surface.

#### **Work Done**

- **Effervescent Floating Dosage Forms**

Ichikawa et al (1991) developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid

viscosity and the drug (para-amino benzoic acid) released in a sustained manner (Figure II.18, A and B).



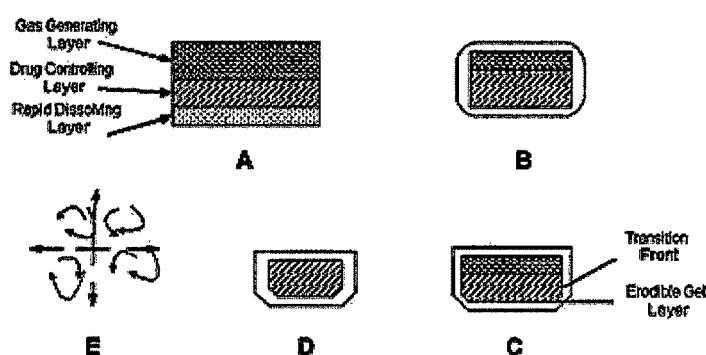
**Figure II. 18 (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.**

Ichikawa et al. (1989) developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas-generating agents. This layer was further divided into 2 sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours ( $FP_{5h}$ ). It was observed that both the TPF and  $FP_{5h}$  increased as the percentage of swellable membrane layer coated on pills having a effervescent layer increased. As the percentage of swellable layer was increased from 13% to 25% (wt/wt), the release rate was decreased and the lag time for dissolution also increased. The percentage of swellable layer was fixed at 13% wt/wt and the optimized system showed excellent floating ability in vitro (TPF ~10 minutes and  $FP_{5h}$  ~80%) independent of pH and viscosity of the medium.

Yang et al. (1999) developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in *Helicobacter pylori*-associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the



polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high-localized concentration of tetracycline and metronidazole (Figure II.19).



**Figure II. 19** Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.

Ozdemir et al. (2000) developed floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with  $\beta$  cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, ie, when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Choi et al. (2002) prepared floating alginate beads using gas-forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of  $\text{CO}_2$  generation on the physical properties, morphology, and release rates. The study revealed that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less-effective gas-forming agent than sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates. In vitro floating studies revealed that the beads free of gas-forming agents

sank uniformly in the media while the beads containing gas-forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%).

Li et al. (2002, 2001) evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived using taguchi design. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force values of the different grades of HPMC were in the order K4 M~ E4 M~K100 LV> E5 LV but different polymers with same viscosity, ie, HPMC K4M, HPMC E4M did not show any significant effect on floating property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior.

Penners et al. 1997) developed an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus reside in stomach over an extended period of time. In addition to this, gas-forming agents were incorporated. As the gas formed, the density of the system was reduced and thus the system tended to float on the gastric contents.

Fassihi and Yang (1998) developed a zero-order controlled release multilayer tablet composed of at least 2 barrier layers and 1 drug layer. All the layers were made of swellable, erodible polymers and the tablet was found to swell on contact with aqueous medium. As the tablet dissolved, the barrier layers eroded away to expose more of the drug. Gas-evolving agent was added in either of the barrier layers, which caused the tablet to float and increased the retention of tablet in a patient's stomach.

Talwar et al. (2001) developed a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The viscolysing agent initially and the gel-forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporal delivery).

Two patents granted to Alza Corporation revealed a device having a hollow deformable unit that was convertible from a collapsed to expandable form and vice versa. The deformable unit was supported by a housing that was internally divided into 2 chambers separated by a pressure-sensitive movable bladder. The first chamber contained the therapeutic agent and the second contained a volatile liquid (cyclopentane, ether) that vaporized at body temperature and imparted buoyancy to the system. The system contained a bioerodible plug to aid in exit of the unit from the body (Michaels et al., 1975; Michaels, 1974).

Baumgartner et al. (2000) developed a matrix-floating tablet incorporating a high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101, and a gas-generating agent gave the best results. It took 30 seconds to become buoyant. In vivo experiments with fasted state beagle dogs revealed prolonged gastric residence time. On radiographic images made after 30 minutes of administration, the tablet was observed in animal's stomach and the next image taken at 1 hour showed that the tablet had altered its position and turned around. This was the evidence that the tablet did not adhere to the gastric mucosa. The MMC (phase during which large nondisintegrating particles or dosage forms are emptied from stomach to small intestine) of the gastric emptying cycle occurs approximately every 2 hours in humans and every 1 hour in dogs but the results showed that the mean gastric residence time of the tablets was  $240 \pm 60$  minutes ( $n = 4$ ) in dogs. The comparison of gastric motility and stomach emptying between humans and dogs showed no big difference and therefore it was speculated that the experimentally proven increased gastric residence time in beagle dogs could be compared with known literature for humans, where this time is less than 2 hours.

Moursy et al. (2003) developed sustained release floating capsules of nicardipine HCl. For floating, hydrocolloids of high viscosity grades were used and to aid in buoyancy sodium bicarbonate was added to allow evolution of  $\text{CO}_2$ . In vitro analysis of a commercially available 20-mg capsule of Nicardipine HCl (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. The optimized sustained release floating capsule formulation was evaluated in vivo and compared with MICARD capsules using rabbits at a dose equivalent to a human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded that of the MICARD capsules. In the latter case the drug was traced for 8 hours compared with 16 hours in former case.

Atyabi et al., (1996) developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of  $\text{CO}_2$ . Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in  $\text{CO}_2$  generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads (Figure II.20). The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).

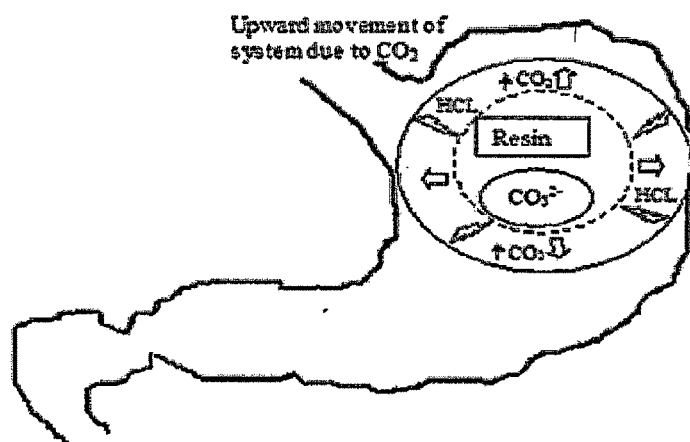


Figure II. 20 Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin.

- **Non-Effervescent Floating Dosage Forms**

Thanoo et al. (1993) developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to-polymer ratio increased both their mean particle size and release rate of drug.

Nur and Zhang (2000) developed floating tablets of captopril using HPMC (4000 and 15000 cps) and carbopol 934P. In vitro buoyancy studies revealed that tablets of 2 kg/cm<sup>2</sup> hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm<sup>2</sup> sank for 3 to 4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm<sup>2</sup> hardness showed no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.

Bulgarelli et al. (2000) studied the effect of matrix composition and process conditions on casein gelatin beads prepared by emulsification extraction method. Casein by virtue of its emulsifying properties causes incorporation of air bubbles and formation of large holes in the beads that act as air reservoirs in floating systems and serve as a simple and inexpensive material used in controlled oral drug delivery systems. It was observed that the percentage of casein in matrix increases the drug loading of both low and high porous matrices, although the loading efficiency of high porous matrices is lower than that of low porous matrices.

Whitehead et al. (2000) prepared floating alginate beads incorporating amoxycillin. The beads were produced by dropwise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved.

Streubel et al. (2003) prepared single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% wt/wt foam powder (based on mass of tablet) was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

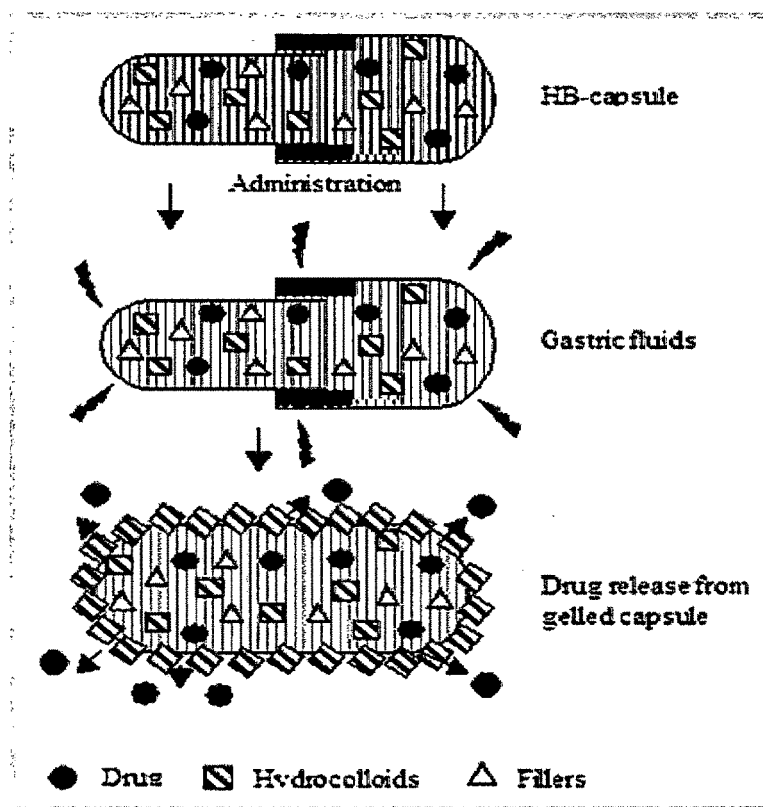
Asmussen et al. (2001) invented a device for the controlled release of active compounds in the gastrointestinal tract with delayed pyloric passage, which expanded in contact with gastric fluids and the active agent was released from a multiparticulate preparation. It was claimed that the release of the active compound was better controlled when compared with conventional dosage forms with delayed pyloric passage.

El-Kamel et al. (2001) prepared floating microparticles of ketoprofen, by emulsion solvent diffusion technique. Four different ratios of Eudragit S 100 with Eudragit RL were used. The formulation containing 1:1 ratio of the 2 above-mentioned polymers exhibited high percentage of floating particles in all the examined media as evidenced by the percentage of particles floated at different time intervals. This can be attributed to the low bulk density, high packing velocity, and high packing factor.

Illum and Ping (2001) developed microspheres that released the active agent in the stomach environment over a prolonged period of time. The active agent was encased in the inner core of microspheres along with the rate-controlling membrane of a water-insoluble polymer. The outer layer was composed of bioadhesive (chitosan). The microspheres were prepared by spray drying an oil/water or water/oil emulsion of the active agent, the water-insoluble polymer, and the cationic polymer.

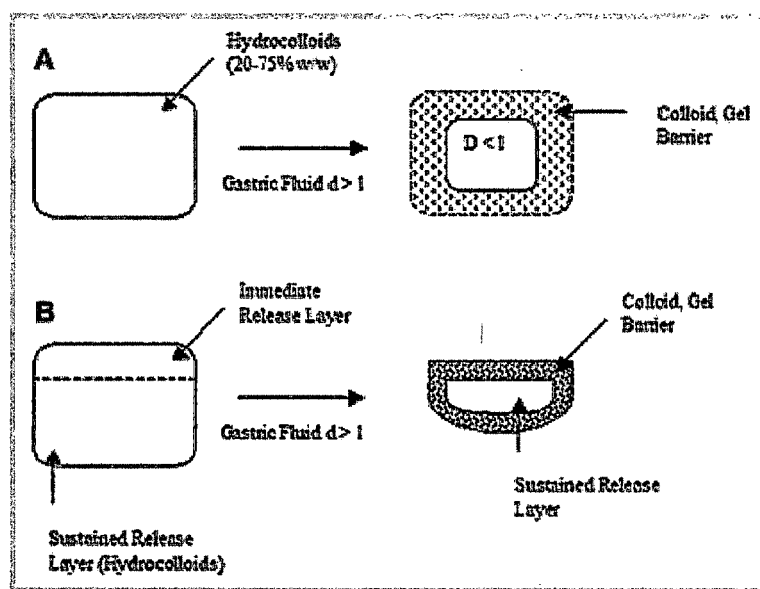
Streubel et al. (2002) developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethyl methacrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S. This could be attributed to the different permeabilities of the drug in these polymers and the drug distribution within the system.

Sheth and Tossounian (1978) developed an HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released (Figure II.21).



**Figure II. 21 Working principle of hydrodynamically balanced system**

Sheth and Tossounian (1979) developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids (Figure II.22, A and B).



**Figure II. 22 Intragastric floating tablets. (A) Sheth and Tossounion, 1979. (B) Sheth and Tossounion, 1979**

Ushomaru et al. (1987) developed sustained release composition for a capsule containing mixture of cellulose derivative or a starch derivative that formed a gel in water and higher fatty acid glyceride and/or higher alcohol, which was solid at room temperature. The capsules were filled with the above mixture and heated to a temperature above the melting point of the fat components and then cooled and solidified.

Bolton and Desai (1989) developed a noncompressed sustained release tablet that remained afloat on gastric fluids. The tablet formulation comprised 75 % of drug and 2% to 6.5 % of gelling agent and water. The noncompressed tablet had a density of less than 1 and sufficient mechanical stability for production and handling.

Kawashima et al. (1991) prepared multiple-unit hollow microspheres by emulsion solvent diffusion technique. Drug and acrylic polymer were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer-to-drug ratio. Microballoons were floatable in vitro for 12 hours when immersed in aqueous media. Radiographical studies proved that microballoons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hours against peristaltic movements.

Dennis et al. (1992) invented a buoyant controlled release pharmaceutical powder formulation filled into capsules. It released a drug of a basic character at a controlled rate regardless of the pH of the environment. pH-dependent polymer is a salt of a polyuronic acid such as alginic acid and a pH-independent hydrocarbon gelling agent, hydroxypropylmethyl cellulose.

Spickett et al. (1993) invented an antacid preparation having a prolonged gastric residence time. It comprised 2 phases. The internal phase consisted of a solid antacid and the external phase consisted of hydrophobic organic compounds (mono-, di-, and triglycerides) for floating and a non-ionic emulsifier.

Franz and Oth (1993) described a sustained release dosage form adapted to release of the drug over an extended period of time. It comprised a bilayer formulation in which one layer consisted of drug misoprostal and the other had a floating layer. The uncompressed bilayer formulation was kept in a capsule and was shown to be buoyant in the stomach for 13 hours. The dosage form was designed in such a way that the entire drug was released in the stomach itself.

Wu et al. (1997) developed floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content a decline in in vitro release of nimodipine occurred.

Wong et al. (2000) developed a prolonged release dosage form adapted for gastric retention using swellable polymers. It consisted of a band of insoluble material that prevented the covered portion of the polymer matrix from swelling and provided a segment of a dosage form that was of sufficient rigidity to withstand the contractions of the stomach and delayed the expulsion of the dosage form from the stomach.

Mitra (1984) developed a sustained release multilayered sheet-like medicament device. It was buoyant on the gastric contents and consisted of at least 1 dry, self-supporting carrier film of water-insoluble polymer. The drug was dispersed or dissolved in this layer and a barrier film overlaid the carrier film. The barrier film was composed of 1 water-insoluble layer and another water-soluble and drug-permeable polymer or copolymer layer. The 2 layers were sealed together in such a way that plurality of small air pockets were entrapped that gave buoyancy to the formulation.

Harrigan (1977) developed an intragastric floating drug delivery system that was composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. However, the peripheral walls were sealed to prevent any physical contact of the drug in the reservoir with the stomach walls

Joseph et al. (2002) developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. In vivo studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration vs time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period.



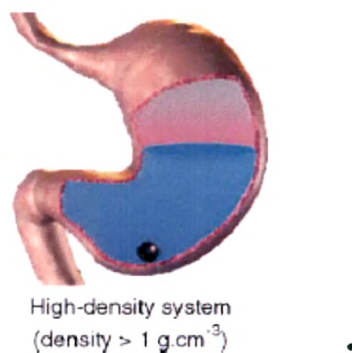
**Figure II. 23 Schematic illustration of the barrier formed by a raft-forming system**

**Jorgen et al., (1991)** described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. The system also contained a buffer, which contributed to the prolongation of acid neutralizing effect. Floating formulations with similar mechanism were described in the literature (Washington et al., 1986; Degtiavera et al., 1994; Fabregas et al., 1994).

### II.18.3 High-Density Systems

#### Concept

High-Density devices utilize weight as a retention mechanism. As the density of the device is larger than that of gastric juice, the device settles down to the bottom of the stomach. For veterinary applications, the high density devices are made of heavy materials such as steel cylinders or steel balls (Cardinal, 1985). Such devices work well in ruminants, but obviously can not be applied to humans. There are limits to the density of oral dosage forms for humans, as well as to the size of oral dosage forms based on a high-density mechanism.



**Figure II. 24 Schematic localization of a high density system in the stomach.**

#### Improvements to be Made

Since an early observation that the GI transit time of multiple-unit formulations was increased dramatically from 7 h to 25 h by increasing the density from 1 to 1.6 (Bechgaard and Ladefoged, 1978, 1981; Bechgaard, 1982), many studies have been conducted to exploit this approach for increasing gastric retention time. Unfortunately, however, subsequent studies found that, under their experimental conditions, higher density single-unit devices did not really extend gastric residence time (Gupta and Robinson, 1995).

In many experiments, specific gravity was shown to have only a minor effect on gastric emptying (Miiller-Lissner and Blum, 1981; Bechgaard et al., 1985; Kaus, 1987). It should be noticed, however, that the density of the particles used in most experiments was less than 2, and the size of the particles was small, i.e., much less than 10 mm. It may be necessary to use particles of a density much higher than 2 and large sized devices to really observe the desired effect of high-density devices. Until then, it may not be fair to conclude that high-density devices are not effective in gastric retention.

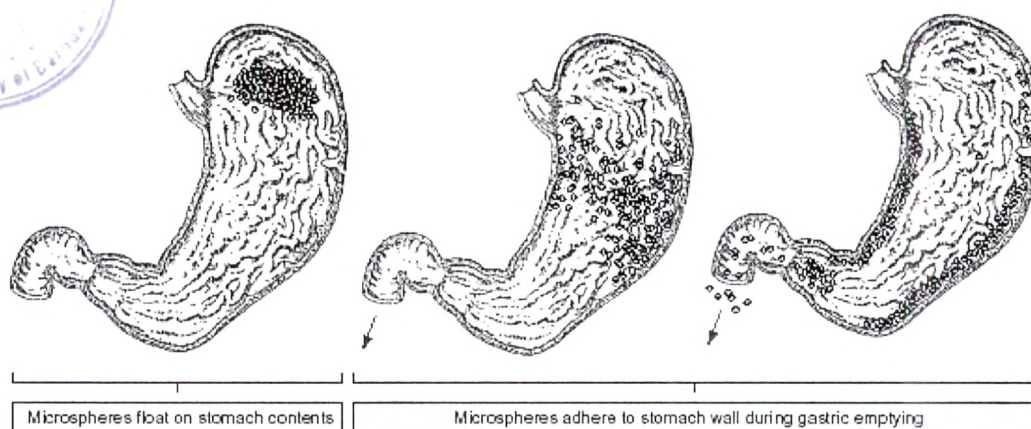
A dog was brought to a small animal clinic at Purdue University (Blevins, 1997). It has swallowed a stone a few centimeters in diameter. According to x-ray imaging, the stone remained in the stomach for a few days and then emptied. It thus appears that high-density systems should work, if the density and size of the devices are optimized, but gastric emptying would depend on the position of the high-density device in the stomach at the time of the housekeeper wave.

Obviously more work is necessary, but the high-density approach should not be considered invalid.

#### **II.18.4 Mucoadhesive Systems**

##### **Concept**

The concept of mucoadhesives (or bioadhesives) is that an oral dosage form in the stomach can stick to the mucosal surface of gastric tissue. Once the dosage form firmly sticks to the mucosal surface, its residence time is expected to be prolonged until it is removed by turn over of mucins. The study on mucoadhesive was initiated by a paper by Park and Robinson in 1984 (Park and Robinson, 1984). Professor Gilbert Banker, then at Purdue University, also studied mucoadhesive oral dosage forms at about the same time. Since then, numerous investigators have been involved in studying fundamental aspects and potential applications of mucoadhesive dosage forms (Peppas and Buri, 1985; Achar and Peppas, 1994; Akiyama et al., 1995; Borechard et al., 1996; De Ascentiis et al., 1995; Jimenez Castellanos et al., 1993; Lee and Chien, 1995; Lehr et al., 1992; Mortazavi and Smart, 1995; Tobyn et al., 1996). Of all the studies done in this area, the best mucoadhesive still remains slightly crosslinked poly (acrylic acid), which is commercially available as polycarbophil and Carbopol. Polycarbophil and Carbopol are poly (acrylic acid) loosely cross-linked with divinyl glycol and allyl sucrose, respectively. Due to differences in crosslinking density, polycarbophil is water-insoluble, while Carbopol picks up so much water that it appears to be water-soluble. Polycarbophil is a granular substance that swells to 1 mm-3mm in diameter (Russel and Bass, 1985).



**Figure II. 25** Mechanism for retention of bioadhesive microspheres in the human stomach. A capsule containing the bioadhesive microspheres is administered with water and the released microspheres float on the fluid in the stomach. During the process of gastric emptying, a proportion of the bioadhesive microspheres adheres to the stomach wall to provide gastrorretention.

### Improvements to be Made

Despite the excellent mucoadhesive properties of polycarbophil and Carbopol, gastric emptying studies using these products in animals and in humans have shown rather disappointing results. In a typical study on mucoadhesives by Harris et al. (1990), 50 $\mu$ l of suspension or liquid in capsule formulation containing bioadhesive polymers was orally administered to rats. Polycarbophil and Carbopol showed the delayed gastric emptying in rats with T50% over 3 h in the fasted condition; T50% for a control group was 1h -1.5 h. In man, however, different results were obtained when polycarbophil or Carbopol was mixed with radioactive resins for Gama – Scintigraphy observation. The T50% values in fasted stomachs were 36 min, 82 min, and 25 min for polycarbophil, Carbopol, and control formulations, respectively. Other researchers who mixed Polycarbophil with radioactive pellets in human testing also observed similar results (Khosla and Davis, 1987). The data from many laboratories suggest that gastric residence time of mucoadhesive formulations in human is not substantially longer than with control formulations.

The main problem with Carbopol and Polycarbophil is that they are good adhesives that tick to almost everything they come in contact with. For this reason, they also interact with gelatin released from gelatin capsules or with soluble proteins and mucins present in the stomach. Any such interactions would easily deactivate an ability to stick to the mucus layer (Khosla and Davis, 1987).

In studying mucoadhesives, specially cross-linked Poly (acrylic acid), one needs to understand the mechanism of their bioadhesiveness. Poly (acrylic acid) interacts with mucins and other biomolecules through numerous hydrogen bondings provided by carboxyl groups of poly (acrylic acid). For this reason, poly (acrylic acid) is only bioadhesive when it exists in a protonated form, i.e., only when the pH is lower than the

pKa of the polymer. This means that polycarbophil and all poly (acrylic acid) – based mucoadhesives are adhesives only at pHs lower than 5. Polycarbophil is most mucoadhesive at pH 4 and below. At physiological pH poly (acrylic acid) exists in an ionized form and it is not bioadhesive. This information has been available in the literature since 1985 (Park and Robinson, 1985; Kamath and Park, 1993), but not many researchers appear to be aware of it.

To further develop mucoadhesive gastric retention devices, it is necessary to find polymers with a specific mucoadhesive property, i.e., polymers that are adhesive only to the mucus layer and to nothing else. Currently known mucoadhesives, however, do not show any specificity toward mucin – they bind to other small substrates as well. This non specificity makes it difficult to formulate practical dosage forms. If a mucoadhesive, e.g., polycarbophil, is applied to conventional dosage forms such as tablets or capsules, the delivery of these mucoadhesive – coated dosage forms to the stomach will be difficult, since they will bind to fingers, tongues, and the esophagus surface. It may be suggested that mucoadhesive dosage forms be contained in gelatin capsules, but gelatin upon dissolution will interact with polycarbophil and the mucoadhesiveness of polycarbophil will be lost as mentioned above.

Even if the polycarbophil is delivered to the stomach intact, soluble mucin will interact with polycarbophil before it has a chance to interact with the mucus layer. For a mucoadhesive dosage form to be practical, mucus layer-specific bioadhesives have to be found.

## Work Done

Ch'ng et al., (1985) reported that a marked delay in gastric emptying of particles in rats was due to the presence of the mucoadhesive polymer Polycarbophil. This was associated with an increased bioavailability of chlorothiazide delivered from such a dosage form (Longer et al., 1985), this drug being absorbed preferentially in the upper part of the GI tract.

A pronounced gastric retention of small particles coated with carbomer (Carbopol 934P) also has been observed in mice by Smart and Kellaway (1989), but they did not attribute the observed effects exclusively to bioadhesion.

Khosla and Davis (1987), using the technique of gamma scintigraphy, could not detect any delaying effect of Polycarbophil on the gastric emptying of pellets in human volunteers.

Harris et al. (1989, 1990) studied a number of mucoadhesive formulations both in rats and humans. For polymers of the acrylic acid type, a 25% delay in orocecal transit time was observed in rats, but the oral bioavailability of hydrochlorthiazide was the same as for a nonadhesive hydroxyethylcellulose formulation. In a scintigraphic study in man (Harris et al. (1990), only small differences in orocecal transit was seen with certain combinations, but no dramatic effects on the GI transit were observed. The two formulations studied in this study consisted of 100 mg Amberlite resin, labeled with 50 microns CI 99 m tc, and 250 mg bioadhesive or non adhesive diluent, contained in a sized



0 hard gelatin capsule. Formulation 1 contained radio labeled ion exchange resin beads, 710-1000 micro meter, comparable in size to the beads found in many sustained release formulation. Formulation 2 contain radio labeled resin of a smaller particle size (20 micro meter), with the same adhesive and non adhesive diluents, and was thus more representative of a capsule formulation containing a fine powder mix. For each of the two formulations, two bioadhesive forms (Polycarbophil and Carbopol 934P) were compared with a control form, in which the adhesive was replaced with an equal weight of lactose. Gastric emptying of these forms was assessed by the time taken for 50%(T50%) or 90%(T90%) of the activity to leave the stomach. Similarly, the time taken for 50%(T50%) or 90 % ( T90%) of the activity to reach the ascending colon was considered as the time of arrival at the colon. The difference between the T values for gastric emptying and colon arrival was taken to be the small intestine transit time of the formulation. From the T values of formulation 1 and 2, the authors concluded that the proposed bioadhesives Polycarbophil and Carbopol 934P did not greatly effect the transit of either these formulations types. They certainly did not show the effects that might have been expected from the reports of Robinson and co-workers (Ch'ng et al., 1985; Longer et al., 1985) working with the rat. According to Harris et al. (1990), the most likely reason for this disagreement lies in the amounts of polymer administered in the respective studies: 70 to 150 mg Polycarbophil in the rat studies (300 to 600 mg/kg), compared with the 250 mg in man ( $\pm 4$  mg/kg). The doses administered to rat were probably able to slow GI transit by virtually blocking the tract with their bulk.

Using the chronically isolated intestinal loop method described by Poelma and Tukker (1987), Lehr et al, (1991) was able to estimate the turnover time of the intestinal mucus gel layer in the rat. This estimate varies in a range between 47 and 270 min. This time scale is similar to the mean residence time found for mucoadhesive microspheres in earlier experiments using the same animal model (Lehr et al., 1990). It was concluded that the permanent renewal of the mucus gel layer probably is a crucial physiological factor that has to be taken into consideration when evaluating the concept of mucoadhesive dosage forms. In his Ph.D thesis, Lehr (1991) states in a more general manner that the concept of mucoadhesion as a means to control or delay in the GI transit of drug delivery systems to be substantially limited by this physiological factor.

Some the most promising data on gastro retentive delivery systems using bio adhesion have resulted from the use of acrylate-based as well as chitosan – based polymers. Poly (acrylates) have been shown to have significant mucoadhesive properties in contact with intestinal mucosal tissues (Ch'ng, 1985; Leung and Robinson, 1988; Gu et al., 1988). Longer et al. (1985) demonstrated successful reduction in the gastric emptying rate of chlorthiazide using loosely cross linked polymers of acrylic acid (polycarbophil) as bioadhesives. The formulations were in the form of microparticles (mean diameter of 505 micrometer) of polycarpobhil (Ch'ng, 1985) mixed with sustained release albumin beads (3:7 w/w ratio of albumin to polycarpophil) loaded into gelatin capsules. Their results showed that 90% of the albumin-polycarbophil beads remained in the stomach after 6 hours and that polycarbophil was bound to the gastric mucin –epithelial cell surface (Longer et al., 1985).

Among the natural polymers, chitosan and derivatives have shown pronounced mucoadhesive in contact with GI mucosa (Lehr et al., 1992; Fiebrig et al., 1994; Bernkop-Schnurch and Krajicek, 1998; Takayama, 1990; Borchard et al., 1996; Bogataj and Mrhar, 1997; He et al., 1998, 1999). Intestinal absorption of insulin loaded in chitosan – coated liposomes was demonstrated (Takeuchi et al., 1996). Blood glucose levels were reduced significantly after the administration of a single dose of these liposomes in rats. Microspheres of chitosan, prepared by a novel w/o/w emulsion spray drying technique, provided rapid release of model H<sub>2</sub>-antagonist drugs (cimetidine, famotidine and nizatidine) (He et al., 1999). The microspheres displayed significant mucoadhesive properties, as determined by turbidimetric measurements (He et al., 1998). Bioadhesion studies using rat small intestine have shown prominent retention of chitosan microspheres as compared with ethylcellulose microspheres as controls, where more than 50% of the chitosan microspheres were absorbed on the small intestine (Harding, 1999). In vivo Phase I clinical studies were initiated to evaluate bioadhesive performance of chitosan microspheres in human subjects by Gama scintigraphy (Harding, 1999).

Microspheres (10 to 200 micrometer in diameter of poly (fumaric acid-co-sebacic acid) anhydride (20:80) (P (FA: SA)) were shown to exhibit very strong and pronounced mucoadhesive properties both in vitro and in vivo (Jacob et al., 1995; Mathiowitz et al., 1997, 1999). The microspheres were tested for their effect on GI transit of low molecular weight drugs salicylic acid and dicumarol. As compared with the control (drug-loaded alginate microspheres of similar size), the (P (FA: SA)) microspheres significantly delayed the GI transit of these drugs in rats (Mathiowitz et al., 1999).

## II.18.5 Magnetic Systems

### Concept

Magnetic dosage forms are usually constructed from a hydrophilic matrix tablet and from osmotic systems containing a small internal magnet (Groning et al., 1994, 1996; Fujimori et al., 1994; Ito et al., 1990). In one system, a permanent magnet (e.g., magnesium ferrite) 5 mm in diameter and 2 mm thick was placed in the centre of the tablet. The final dimensions were 10 mm in diameter and 5.5 mm in height. An extracorporeal magnet (6x4x2 cm) was placed and fixed over the position of the stomach to control gastrointestinal transit of the dosage form (Fujimori et al., 1994). Drugs delivered by magnetic dosage forms, e.g., cinnarizine (Fujimori et al., 1994), acetaminophen (Fujimori et al., 1995), and riboflavin (Groning et al., 1996), showed improved bioavailability. It was suggested from absorption rate-time profiles that the variation in pharmacokinetics was caused by a 3 h delay in gastric emptying time. The data in their study showed that a 3 h delay in gastric emptying increased the AUC two fold (Fujimori et al., 1995).

In a separate study, gastric retention of a magnetic dosage form was monitored by use of a pH –sensitive radiotelemetric capsule, also known as the Heidelberg capsule (Groning and Berntgen, 1996). Small magnets were attached to the Heidelberg capsule and this model dosage form was administered to humans. The dosage forms transited to the

alkaline area (i.e., intestine) within 2.5 h after administration in all subjects without an external magnetic source. On the other hand, gastric residence time of model dosage forms were longer than 6 h in most of the test subjects with the external magnets positioned on the stomach level. Fujimari et al. (1994, 1995) reported similar results. In their studies, double-layered magnetic tablets were prepared. Drug-acetaminophen or theophylline- and magnetic component- fine ferrite ( $\gamma$ -FeCO<sub>3</sub>) particles- were contained in separate layers. Two layers were bonded together by cyanoacrylate -type adhesives. After administration of the magnetic tablet, a magnetic field or a permanent magnet was externally applied at the stomach level of dogs for 8 h. Results showed that bioavailability of the drugs was significantly increased (near 90% increase) when external magnetic control mean were applied.

**Improvements to be made**

While the concept of this approach is clean and obviously works, its practical application is rather difficult. The exact positioning of the extracorporeal magnet to the magnetic dosage forms in the stomach by each individual may not be easy. The benefit of the magnetic dosage form would be all-or-none depending on whether the external magnet is in the right place for the duration of drug delivery. Asking patients to pay attention to the exact position of the magnet is not any better than asking them to eat something every two hours to maintain the fed state. For this approach to be useful, better and easier systems for applying the magnetic field need to be developed.

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