Chapter 2

Literature review

2.1 INTRODUCTION

Absorption of drugs via the mucous membranes of the oral cavity was noted as early as 1847 by Sobrero, the discover of nitroglycerin[1].William Murell[2] described the effects of oral nitroglycerin in relieving the pain of angina pectoris well over hundred year back; today the drug is still administered by dissolving a tablet sublingually or in buccal puch. The each and convenience of oral mucosa as a means of systemic delivery had led to formulations of a number of therapeutic agents. Although often though under the umbrella term of buccal delivery, drug delivery via the oral cavity is traditionally divided into three categories:

1. Buccal Delivery: which infers drug administration through the lining of the cheek to systemic circulation.

2. Sublingual Delivery: the administration of drug via the membranes of the floor of mouth or underside of the tongue to the systemic circulation.

3. Local Delivery to Mouth: which involves treatment of conditions within the oral cavity by administration to the affected mucosal tissues.

2.2 OVERVIEW OF THE ORAL MUCOSA[1-7]

2.2.1 Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (figure 2.1).

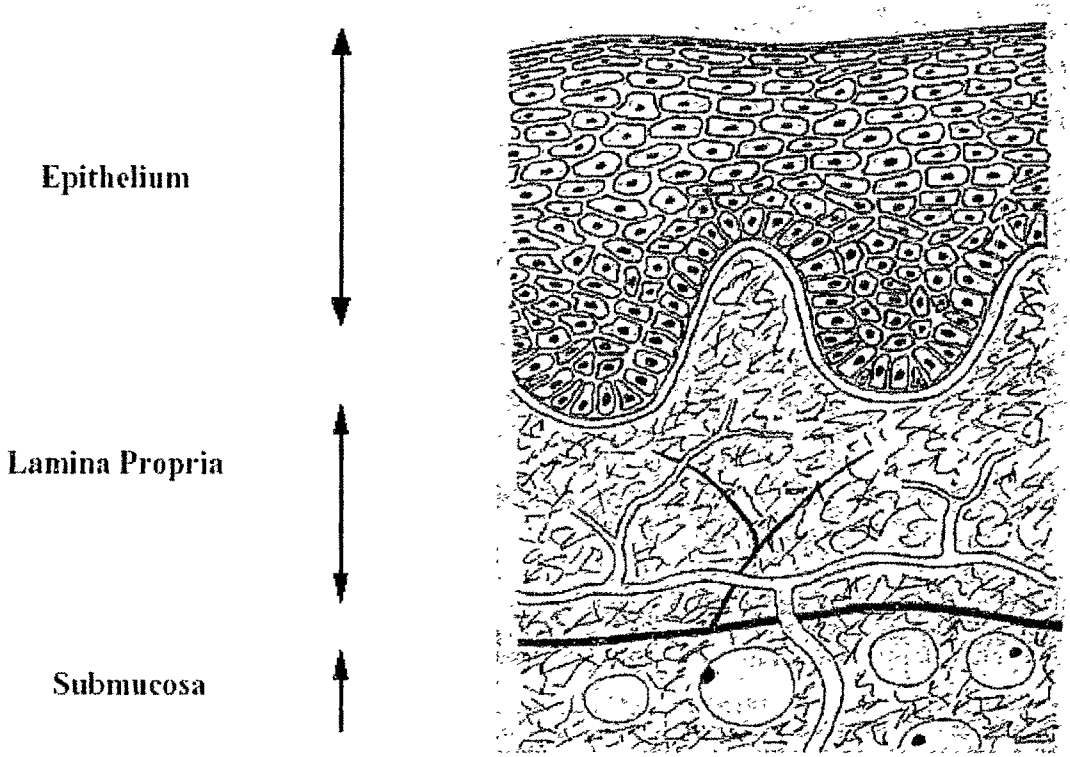

Figure 2.1. Structure of the oral mucosae.

Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium[3]. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days[4] and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas

subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized[4]. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide[5-7]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia[4-6].

2.2.2 Permeability

The oral mucosae in general is a somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4 to 4000 times greater than that of the skin[8]. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal[4]. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG)[9]. When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200μm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase[10] and lanthanum nitrate[11].

2.2.3 Environment[12-14]

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another[12]. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva.

2.3 BUCCAL ROUTES OF DRUG ABSORPTION[15]

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier forhydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve acombination of these two routes. The route that predominates, however, is generally the one thatprovides the least amount of hindrance to passage.

2.4 ORAL MUCOSAL DRUG DELIVERY - OPPORTUNITY FOR NEW DEVELOPMENT[16,17]

The oral mucosa (buccal and sublingual mucosa) has been used as a site for systemic drug delivery for a long time, e.g. nitroglycerin and isosorbide dinitrate. It"s well known that the advantage of oral mucosal drug delivey include:

1. Excellent accessibility.
2. Rapid absorption due to relatively good blood flow.
3. Bypass of enzyme degradation in gastrointestinal tract and "first pass" metabolism in the liver resulting in hogh bioavailabilty.

Despite the above advantages, the number of drugs, which have been developed for buccal or sublingual administration is very limited at present when, compared to the conventional oral intestinal administration.

2.5 SUBLINGUAL (UNDER THE TONGUE) DELIVERY[18,19]

Sublingual delivery traditionally involves systemic administration of drug via membranes of the floor of the mouth or the ventral surfaces of the tongue. The sublingual mucosa is relatively permeable due to the thin membrane and large veins, allows rapid absorption and acceptable bioavailabiiltes of many drugs, and is a convenient and easily accessible location. Fhurthermore, the sublingual mucosa is a smooth surface, not furred like the top of the tongue, and is free of mucus and undigested food, unlike the stomach. Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more efficient. Products passing through the digestive tract are subject to a "first pass" effect, in which many of the ingredients may be broken down by stomach acid or metabolized by the liver. Products absorbed sublingually enter the bloodstream directly and can start working within moments.

2.5.1 Rapid Onset of Action

Sublingual absorption is generally rapid because of the rich vascular supply and the fact that the stratum corneum, the main barrier to drug access transdermally, is not present on mucosal surfaces. This minimal barrier to drug transport results in a rapid rise in blood concentrations. The time in minute required for the onset of action of drug through oral, dermal and sublingual route is given in figure 2.2.

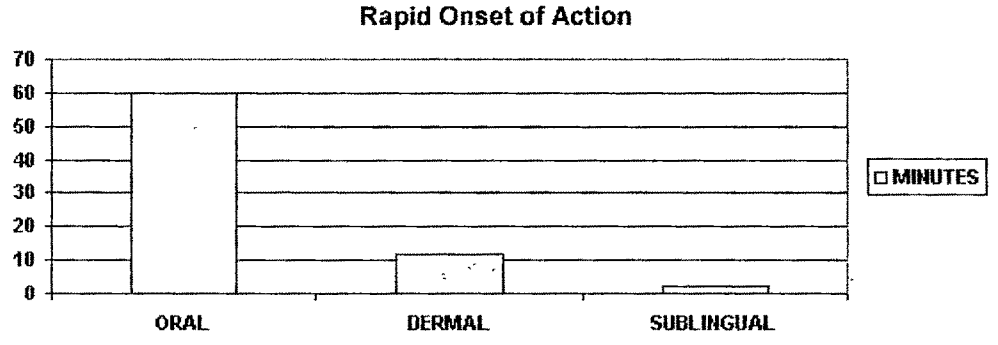

Figure 2.2. Time required for the onset of action through oral, dermal and sublingual route.

2.5.2 Quickly Achieves Peak Plasma Concentration

Peak blood levels of most products administered by sublingually are achieved within 10–15 minutes, which is generally much faster than when those same drugs are ingested orally.

2.5.3 High Percent Absorption

Sublingual absorption is efficient. The percent of each dose absorbed is generally higher than that achieved by means of oral ingestion. The percent absorption of the drug through oral, dermal and sublingual route is given in figure 2.3.

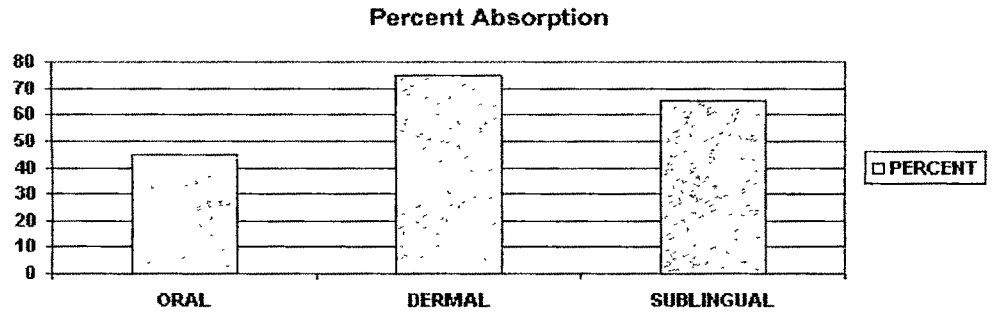

Figure 2.3. The percent absorption of the drug through oral, dermal and sublingual route.

The sublingual administration provides:

- Rapid absorption for **faster action.**
- Greater absorption, so less product is required, possibly resulting in **reduced side effects.**
- A way to avoid direct gastrointestinal exposure, for **less stomach upset.**

2.6 FACTORS INFLUENCING DRUG ABSORPTION FROM THE ORAL CAVITY[18,19,20]

The two main factors that influence the drug absorption from the mouth are the permeability of the oral mucosa to drug and the physiochemical characteristics of drug.

2.6.1 Permeability of the Oral Mucosa to Drugs

The lipid membranes of the oral mucosa are resistant to the passage of large macromolecules; however small unionized molecules tend to cross the memebrane woth relative ease.

2.6.1.1 Mechanisms involved in drug absorption across the oral mucosa

The mechanisms by which drugs cross biological lipid memebranes are passive diffusion, facilitated diffusion, active transport, and pinocytosis. Small, water soluble molecules may pass through small water filled pores. The main mechanism involved in drug transfer across the oral mucosa is passive diffusion. Although facilitzted diffusion has also been shown to take place, primarily with nutrients. It involves the carrier systems and exhibit stereospecificity also. Passive diffusion involves the movement of a solute from a region of high concentration in mouth to a region of low concentration within the buccal tissue.

2.6.1.2 Membrane storage during buccal absorption of drugs

The absorption of a drug mouth is not synonyms with drug entry into the systemic circulation. Instead the drug appears to be stored in the bucal membranes due to drug binding in or on the oral epithelium. Due to this phenomenon, buccal partitioning has been suggested as a more accurate term to describe the diffusion of drugs across the oral mucosa

2.6.1.3 Regional differences in mucosal permeability

In general the permeability of the oral mucosae decrease in the order sublingual> buccal> palatal. Comparative profile of different regions in buccal cavity is given in table 2.1.

Table 2.1. Comparative profile of different regions in buccal cavity.

Tissue	Structure	Epithelial thickness (mm)	Permeability	Residence time	Blood flow (ml/min/cm^2)[a]
Buccal	Non-Keratinized	500-600	+	+	2.4
Sublingual	Non-Keratinized	100-200	++	--	0.97
Gingival	Keratinized	200	--	+	1.47
Palatal	Keratinized	250	--	--	0.89
[a]- blood flow in oral mucosa of the rhesus monkey.					
++ means "very suitable"					
-- means "least suitable"					

2.6.2 Physicoshemical Characteristics of the Drug[19]

Cell membranes are reported to have a large lipid component, and most drugs cross such membranes by simple passive diffusion. In order to cross these lipid membranes, a drug should be in the lipid soluble or unionized form and also in the solution. The various physicochemical characteristics of the drug are therefore of paramount importance in drug transport.

2.6.2.1 Molecular Weight

In general, molecules penetrate the oral mucosa more rapidly that ions, and smaller molecules more rapidly than the larger molecules. However, this rule is not absolute. For hydrophilic substances, the rate of absorption is function of the molecular size. Small molecultes (<75-100Da) appear to cross the mucosa rapidly, but permeability falls off rapidly as molecular size increases. This relationship between size and permeability has

not been demonstrated for lipophilic substances, although common sense suggests that such a relationship must exist.

2.6.2.2 Lipid solubility

Although the undissociated (un-ionized) form of a drug has the larger lipid solubility, the unionized moieties themselves have differing lipid solubiilties. For any series of un-ionizable compounds, their relative permeabilites are functions of their oil-water partition coefficients, with the more lipid soluble compounds having higher permeabilites

2.6.2.3 Ionization

The degree of ionization of permeant is a function of both its pKa and the pH at the mucosal surface. The absorption of many compounds had been shown to be maximal at the pH at which they are mostly unionized. The average pH of saliva is 6.4. The degree of ionization at a specified pH can be calculated using the Henderson-Hasselbalch equation as follows:

For an acid $pH = pKa + \log_{10}$ [ionized species]/[un-ionized species]
For a base $pH = pKa + \log_{10}$ [unionized species]/[ionized species]

The degree of ionization of a drug therefore differes between plasma (pH 7.4) and saliva; hoever, the ionization in plasma is of minor importance to dug absorption from the buccal cavity because circulating blood rapidly remives drug from the plasma side of the absorption barrier. The importance of pH on drug absorption from the mouth has been extensively studied using the buccal absorption model, in which loss of dug buffered drug solutions placed in the mouth is monitered. For example, the rate of disappearance of barbutitates, verampamil, and propanolo has been shown to depend on the concentration of unionized dug in the mouth.

2.7 IMMEDIATE RELEASE FORMULATIONS[21-28]

2.7.1 Challenges in Development of Immediate Release Drug Delivery

2.7.1.1 Taste of the active ingredient

Immediate release formulations dissolve or disintegrate in the patient's mouth in close proximity to the taste bud. Taste masking can be accomplished simply with flavouring agents and sweeteners. For extremely bitter soluble actives, taste masking may be attained through the use of ion exchange resins.

2.7.1.2 Dose

Molecules requiring high doses present the challenges to the development of immediate release formulations. These challenges are not unrelated-because most drugs will require taske masking, the amount of taste masking material used in the diffetent dosage forms will depend on the drug's degree of bitterness relative to its dose, which will result in an increase in the particle size

2.7.1.3 Moisture sensitivity

Most of the immediate release drug delivery technologies are moisture sensitive, hygroscopic and often physically unstable under ambient temperature and humidity conditions. Many immediate release delivery systems require specialized packaging to protect the products from moisture.

2.7.1.4 Friability of the tablets

In order to maximize tablet porosity and minimize oral disintegrating time/dissolution, immediate relese tablets are either very porous and inherentsly soft-moulded matrices to tablets compressed at very low compression forces. These causes immediate release tablets to be soft, friable and/or brittle, often specialized peelable blister packaging.

2.7.2 Desired Criteria for Immediate Release Formulations

- Should not require to swallow, but it should dissolve or disintegrate in the mouth in matter of second.
- Be Compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.

The following two immediate release formulations have been studied.

(1) Fast dissolving sublingual films

(2) Fast dissolving sublingual tablets

2.7.3 Fast Dissolving Film[29-33]

2.7.3.1 Introduction

Many fast-dissolving tablets are soft, friable, and/or brittle (such as the lyophilized dosage forms) and often require specialized and expensive packaging and processing. These tablets are either very porous or inherently soft-molded matrices, or tablets compacted at very low compression forces in order to maximize tablet porosity and minimize oral dissolution/disintegration time. Fast dissolving film however, comprises a tough, solid, soft, flexible film and does not require special packaging. It is thin and can be carried in a patient's pocket, wallet, or pocket book.

The fast dissolving film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The the film can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages[36]. The film alleviates the danger/fear of choking, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture.

Special features of the fast dissolving film:

- Thin elegant film
- Variou sizes and shapes
- Unobstructive
- Mucoadhesion
- Fast disintergrtion
- Quick dissolving
- Rapid release

Advantsages of the fast dissolving film:

- Convenient dosing
- No water needed
- No risk of choking
- Taste masking
- Enhanced stability
- Improved patient compliance
- Life cycle management

Fast dissolving film alleviates the fear of swallowing and the risk of choking commonly associated with a conventional tablet. This fast-dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moisture oral environment. These additional, superior benefits allow patients to take their medication anytime and anyplace under all circumstances. The delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oramucosal absorption or, with formula modifications, will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed.

The thickness of a typical film ranges from 0.1 to 1 mm and its surface area can be 1 to 20 cm^2 for any geometry. Its low dry-tack allows for ease of handling and application. At

the same time, the rapid hydration rate facilitates an almost immediate softening of the film upon application in the oral cavity. The wet-tack and mucoadhesive properties of the system are designed to secure the film to the site of application. The flexibility and strength of the film may be selected/modified to facilitate automatic rewinding, die cutting, and packaging during manufacturing. The flexibility and strength are reflected by the tensile strength, elongation, Young's Modulus, bending length, and tear resistance of the film.

The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the fast dissolving film. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for fast dissolving film. The drug is released from the dosage form upon disintegration and dissolution. The disintegration and dissolving times are prolonged as the film thickness increases as shown in the Figure 2.4. The disintegration and dissolving times may be further influenced, by varying the formulation composition of the film.

2.7.3.2 *In vitro studies*

The physical and mechanical properties of the fast dissolving drug delivery system are primarily controlled by the manufacturing process and are usually measured by in vitro testing methods, such as thickness, dry-tack, tensile strength, percent elongation, tear resistance, and Young's Modulus. Other performance properties, such as wet tack, bending length, disintegration time, dissolving time, and dissolution time, are conducted as quality control tests. The typical release profile of an active ingredient exhibited by a fast dissolving film is 50% released within 30 seconds and 95% within 1 minute.

2.7.3.3 Manufacturing processes

One or a combination of the following processes can be used to manufacture the fast dissolving film: hot-melt extrusion, solid dispersion extrusion, rolling, semi-solid casting, and solvent coating. The current preferred manufacturing process for making this film is solvent casting. Water-soluble hydrocolloids are completely dissolved in water in a

mixing tank to form a homogenous viscous solution. Other ingredients, including active agents, are dissolved in a small portion of aqueous solvent using a high-shear processor. The active mixture is then added to the viscous hydrocolloid solution to form a homogenous viscous solution. This viscous solution is degassed under vacuum. The resulting bubble-free solution is coated on a non-treated casting film with a typical coating thickness of 5 to 20 mm. The coated film is subsequently sent into an aeration-drying oven. The dry film is then cut into the desired shape and size for the intended application.

In order to maintain its fast-dissolving characteristics, the thickness of the film should be carefully controlled. Therefore, its loading capability is limited. Overcoming the unwanted taste of certain active ingredients can be a challenge for fast dissolving films as it is for conventional oral drug delivery devices. The extent of these challenges depends on the size of the dose, the desired release profile, and desired absorption kinetics.

2.7.3.4 Packaging

Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast-dissolving dosage forms. Unlike these other quick-dispersing and/or dissolving oral delivery systems, the fast dissolving film can be packaged using various options, such as single pouch, blister card with multiple units, multiple-unit dispenser, and continuous roll dispenser, depending on the application and marketing objectives.

2.7.3.5 Scale-Up & manufacturing

Provided the desired dose of the active agent is within the loading capacity of a given film having a suitable thickness, there appears to be no significant challenges associated with the scale-up and manufacture of the film using the solvent- coating method. Alternative manufacturing processes, such as cold and hot extrusion may be used to overcome limitations associated with solvent-coating methods.

2.7.4 Fast Dissolving Tablets[21-28,34-40]

Fast dissolving tablets disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few. A major claim of the some fat dissolving tablets is increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those cases where the drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption of the many formulations. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism.

2.7.4.1 Characteristics of fast dissolving tablets

Fast dissolving tablets as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Taste-masking is of critical importance in the formulation of acceptable fast dissolving tablets. Current methods of taste masking in fast dissolving/disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of drug particles. For a tablet to be considered fast-dissolving/disintegrating, it must disintegrate in the saliva, while maintaining a pleasant taste and mouth feel, to allow maximal patient acceptability.

2.7.4.2 Technologies for designing fast dissolving tablets[21]

The oral fast dissolving tablets are also known as fast dispersing and quick disintegrating tablets; however the function and concept of all these dosage forms are similar. Though several technologies are available, a few have reached commercial marketed products such as flash dose, flash tab, oraquick, orasolv, zydis and wowtab.Other techniques are tablet moulding, spray drying, sublimation and disintegration addition,

2.7.4.3 Use of Sugar Based Excipients

Sugar based excipients (e.g. sorbitol, mannitol, dextrose, xylitol, fructose etc.) have been used as bulking agents. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste-masking. But not all sugar-based materials have fast dissolution rate and good compressibility and/or compactability. However technologies are developed to make use of the sugar based excipients in the design of fast dissolving tablets.

2.8 EVALUATION OF FAST DISSOLVING TABLETS[41-44]

Rapidly dissolving tablets can be evaluated for the following characteristics.

2.8.1 Measurement of Tablet Tensile Strength

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction can be measured using a tablet hardness tester. Tensile strength for crushing (T) is calculated using the following equation:

$$T = 2F/(\pi dt)$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

2.8.2 Measurement of Tablet Friability

Tablets can be placed in a Roche friabilator which is rotated for 4 min at 30 rpm.The tablets are weighed and loss I weight (%) can be calculated.

2.8.3 Measurement of Tablet Porosity

A suitable porosimeter like the mercury penetration porosimeer can be used. It should cover a range of pore sizes from 0.06 μm to 360 μm.

2.8.4 Wetting Time and Water Absorption Ratio

A small culture dish can be taken and a piece of paper tissue folded twie is palced, containing 6 ml of water. A tablet is put on it and the time for complete wetting is measured. The wetted tablet is then weighed. Water absorption ratio, R was determined according to the following equation:

$R = 100\ (W_a\text{-}W_b)/W_b$, Where W_b and W_a are the weight before and after water absorption, respectively.

2.8.5 Meaurement of Disintergration Time

Instead of the disintegration apparatus Sunada et al have proposed a modified dissolution apparatus. Figure 2.5 is a chematic representation of the testing apparatus. 900 ml of water maintained at 37 °C and stirred with a paddle at 100 rpm is used as the disintegration fluid. Disintegration time is determined at the point at which the tablet disintegrated completely and passed through the screen of the sinker.

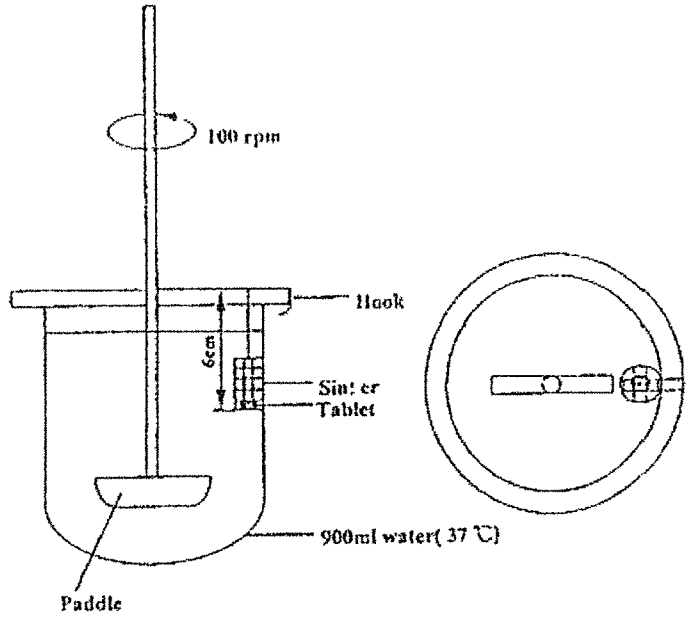

Figure 2.5. Modified disintegration apparatus.

2.8.6 Disitegration in Oral Cavity

The time required for complete disintegration in the oral cavity can be collected from six healthy volunteers.

2.9 IN VITRO AND IN VIVO MODELS FOR ORAL TRANSMUCOSAL DRUG DELIVERY

In the development of an oral mucosal dug delivery system, there is a neeed for experimental methods which allow the release characteristics and permeability of the drug to be determined. A number of in vitro, ex vivo, in vivo and cell culture techniques have been reported for this purpose.

2.9.1 Methods for In Vitro Release

Different workers have used apparatus of varying design and under varying conditions; no standard in vitro method has yet been developed.

2.9.1.1 Beaker method

Dosage form is made to adhere at the bottom of the beaker containing the medium and stired uniformly using overhead stirrer. Volume of the medium varies between 50-500 ml and stirred speed from 60-300 rpm[45].

2.9.1.2 Interface diffusion system

It uses a compartmental container where 1-octanol represents the buccal membrane and partitioning between drug in buffer and octanol is measured[46].

2.9.1.3 Modified Keshary Chein Cell

A specialized apparatus was designed in the laboratory. It comprised of a keshary chien cell containg distilled water 50 ml at 37 °C as dissolution medium. TMDDS was placed in a glass tube fitted with a ≠ 10 mesh at the bottom which reciprocate in the medium at 30 strokes per minute.

2.9.1.4 Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements-paddle and basket. Dissolution medium varied from 100-500 mo and speed of rotation 50-100 rpm.

2.9.2 Methods for Ex Vivo Release

Ex vivo methods enable anatomically well defined areas of mucosa to be studied under controlled conditions, usually by clamping between diffusion cells. Experimental set up is simple and experimental conditions can be easily manipulated. Data correlates well with in vivo studies[47].

2.9.2.1 ***Animal models***[48]

Since human oral mucosa is not widely available, animal mucosa is routinely used for in vitro studies. The main criterion is resemblance of the animal mucosa to the oral mucosa of human beings in both ultra structure and enzyme activity. The most commonly used animals are dogs, pigs, rabbits and rhesus monkey. These animals have non keratinized mucosa like humans. Rats and Hamsters have heavily keratinized oral mucosa. Though it has keratinized mucosa, the hamster cheek pouch model for oral mucosal research is appealing due to economy and convenience. Both dogs and pigs have a large mucosal area that permits multiple simultaneous experiments. The surface area of rabbit buccal mucosa is vey small.

2.9.2.2 *Permeability measurement studies*

Two compartment diffusion cells, with buccal mucosa clamped inside are widely used for the permeation studies. Various types of diffusion cells have been deployed for this purpose: modified using chamber, Franz diffusion cells (figure 2.6), valia chien cells are most commonly used[49]. Apart from these few other modified cells and continuous flow cells have also been reported.

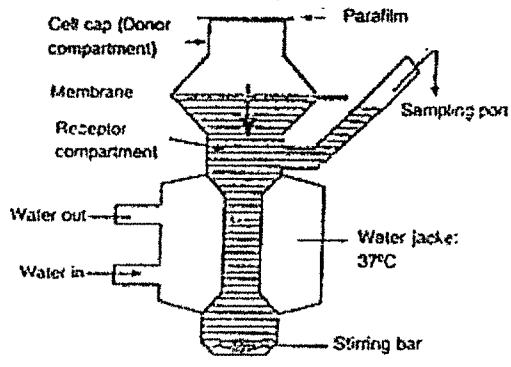

Figure 2.6. Franz diffusion cell.

Ex vivo methods measure the rate at which a compound permeates from one side to membrane to the other and can be used to obtain a first approximation of the expected in vivo absorption rate. Partition coefficient dependency, pH dependency, effect of penetration enhancer etc. can be determined.

2.9.3 In Vivo Methods

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct measurement of uptake or accumulation of penetrants at surface.

2.9.3.1 *Animal models*

A number of animal models have been reported in the literature. However, very few in vivo (animal): in vivo (human) correlation have been reported. Hence selection of an animal model is very important. Animal model such as the dogs, rabbits, pigs and sheep, have been reported[49,50].

2.9.3.2 *Buccal absorption test*[51]

The buccal absorption test developed by Beckett and trig[51] is a simple and reliable method for measuring the extent of drug loss from the human oral for single or multi-component mixtures of drugs. The method involves swirling of a buffered solution of known concentration around the mouth by movement of cheeks and tongue 60 times oe minute. Afer a known period of time the solution is expelled and sbject rinsed their mouth with aliquots of buffer. The dug solution and rinsed are combined, adjusted to volume and analzed for drug content. The difference between the amount of drug contained in the original buffered drug solution and amount recovered was assumed to be the amount of drug lost in the oral cavity mucosa. However, the method does not take into account the amount of drug that may be swallowed and moreover, the method is unsuitable for kinetic studies.

2.9.3.3 *Absorption cells*

Absorption cells involve techniques which restrict known volume of an aqueous solution to a defined area of the oral mucosa. The test solution within the cell is protected from salivary secretions and therefore, does not change in volume and also the test solution is not stirred. The simplest reported absorption cell is a rubber O ring. Kellawey and Warren[52] developed a small cell comprising two concentric sealed chambers of Perspex.

2.9.3.4 *Perfusion Cells*

In a perfusion cell the test solution is well stired and continuously perfuesd across the mucosal surface.

2.9.3.4.1 Perfusion cells for animal studies

A small perfusion chamber made from medical grade silicone polymer was developed by Veillard[53] et al. Polyethylene tubings were used as the input and output lines. Chamber was attached to the mucosa of the upper lip of an anesthetized dog using cynoacrylate adhesive. Blood samples were withdrawn and analyzed.

2.9.3.4.2 Perfusion cells for human studies

Barsuuhn[54] et al constructed a pliable cell made of a hydrophilic vinyl polysiloxane polymer. Cells were maintained in position by the natural suction created by the perfusion circuit and the extended clamp. Samples of drug were removed from stirred reservoir and analysed.

Rathbone[55] reported a buccal perfusion cell design constructed from inflexible material as nylon or Teflon. Drug concentrations were monitored as a function of time by pumping the drug solution through a flow cell in a spectrophotomer.

2.9.4 Cell Culture Methods

- In vitro cell culture models involving monolayers of cells of epithelial origin and grown on permeable support membranes have been increasing used to study transepithelial drug transport and metabolism[56].

2.9.4.1 *Buccal cell cultures*

In first type of tissue culture system, oral keratinocytes derived from human buccal explants have been grown in primary culture. The system is easy to establish but may retain non epithelial cells that may or may not be significant in drug studies[57]. In second type of buccal tissue culture system, hamster pouch buccal cells have been enzymatically dissociated and grown in primary culture. In this respect, the culturesd tissue closely resembles the less differentianted or non keratinized epithelium or man[58]. Neilson[59] et al established the human cell line, TR 146 as an in viro model for studying transport pathways or mechanisms.

2.10 APPLICATIONS IN SUBLINGUAL DELIVERY

The history of sublingual delivery dates back to 1858 when A.G. Field first realized that nitroglycerin dropped on the tongue was readiliy absorbed through the membrane[18].

Research in 1985 by Pimlott and Addy measured the absorption of isosorbide dinitrate (ISDN) into the systemic circulation after application of tablets to the buccal and sublingual sites; maximum plasma levels of ISDN were achieved at 5 minutes, after which fall gradually[18].

Studies evaluating the use of sublingual buprenorphine in patients following surgery and comparing its effects with intramuscularly administered morphine were done by Edge et al in 1979[60]. Each patient received either a tablet of 0.4 mg buprenorphine and an injection of 5 % dextrose in 1 ml or a dummy tablet and an injection of 10 mg morphine in 1 ml.

Goldstein et al[61] reported sublingual administration of glyceryl trinitrate to alleviate the pain of an acute angina attack because of its rapidaction, long-established efficacy and low cost.

Mathur et al[62] published that the difficulties presented in the administration of drugs in the treatment of hypertensive emergencics are largely overcome with the use of nifedipine sublingually. The onsetof action is rapid, and the drug has also been used sublingually for the treatment of acute attacks of angina pectoris.

Tschollar et al[63] have indicated the usefulness of sublingual captopril in the treatment of severe hypertension. The hypertensive patients thus treated showed a marked decrease in systolic and diastolic blood pressure, with the onset of action being 2 to 5 minutes and the peak effect at 10 minutes.

It was reported by Finkler et al[64] that low-dose sublingual methyltestosterone found effective in the treatment of male hypogonadism.

Mouth spraying of fenoterol to both asthmatic patiets and healthy subjects hase been shown to induce a cleacut bronchodilation, probably by absorption of the drug through the oral mucosa[65]

Odou et al[66] developed 5 mg midazolam sublingual tablets to realize a short general anesthesia without intravenous or intramuscular injection. One explanation of this results is that midazolam (pKa=6.1) in presence of 10 mg of citric acid is ionized.

Nappi et al[67] evaluated the efficacy of sublingual administraton of fast dissolving dosage form of 40 mg piroxicam in the acute treatement of migrane. Suglingual administration of piroxiam showed quick onset, long duration and good tolerability.

Seo et al[68] studied sublingual administration of digoxin by gamma-vyclodextrin complexation. The data suggested that sublingual administration of the rapid sissolving form of gamma-cyclodextrin complex may be useful for improving the bioavailabilty of digoxin due to the prevention of acid hydrolysis in stomach and the enhancement of drug absorption rate.

Constantine et al[69] investigated a convenient method for study of the bioavailability of sublingual formulations of pirbuterol in dog and the potential usefulness of a sublingual dosage form of pirbuterol was reported.

Bredenberg et al[70] developed a new tablet system for sublingual administration of fentanyl citrate and rapid drug absorption. The tablet is based on interactive mixtures of components, consisting of carrier particles partially covered by fine dry particles of the drug. The tablets disintegrated rapidly and dissolution tests revealed that fentanyl citrate was dissolved from the formulation almost instantly. Plasma concentrations of fentanyl were obtained within 10 min, with no second peak.

Vaugelade et al[71] developed the progesterone freeze-dried systems in sublingual dosage form. Among the different polymers used, i.e. poly(N-vinylpyrrolidone) (PVP), poly(ethylene oxide) (PEO), Dextran T70 and partially saponified poly(methyl glyoxylate) (PMGz), the latter gives the fastest solubilization rate.

Yoo et al[72] examined the absorption and disposition of clomipramine in rats after sublingual (5 and 50 mg/kg), oral (50 mg/kg), and iv (5 mg/kg) administration. When given sublingually in isotonic saline at a dose of 50 mg/kg, clomipramine was rapidly absorbed, and the mean absolute bioavailability (36.2%) was increased over oral dosing. Sublingual administration (5 mg/kg doses) of clomipramine formulated with a permeation enhancer, 2-hydroxypropyl beta-cyclodextrin, further increased the sublingual bioavailability to 57.1%.

Shephard et al[73] studied the pharmacokinetic behaviour of sublingually administered 8-methoxypsoralen for PUVA therapy. Sublingual PUVA therapy is suitable for patients with skin types I and II, in particular patients who are less suitable candidates for standard PUVA therapy (due to hepatic, renal, or cardiac insufficiency) or who have experienced side effects with standard PUVA.

2.11 SURVEY OF LITERATURE DESCRIBING THE USE OF FILM FOR BUCCAL DELIVERY

Borsadia et al[29] developed quick-dissolving films for oral mucosal delivery that overcomes the shortfalls of conventional fast-dissolving intraoral tablets. The film alleviates the danger/fear of choking, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture.

Peh et al[75] investigated the suitability of an SCMC (sodium carboxymethyl cellulose/polyethylene glycol 400/carbopol 934P) and an HPMC (hydroxypropylmethyl cellulose/polyethylene glycol 400/carbopol 934P) films as drug vehicle for buccal delivery. SCMC films swelled more extensively in distilled water while HPMC films in simulated saliva solution.

Okamoto et al[76] developed the polymer iflm dosage forms of lidocaine for buccal administration. The films of lidocaine with hydroxypropylcellulose as a film base were prepared using the solvent evaporation (SE) method, direct compression physical mixture (DCPM method) and direct compression of the spray dried powder (DCSD method). The drug release rate and penetration rate were affected by the preparation method; that is, DCPM method < DCSD method < SE method. The lidocaine penetration rates through excised hamster oral mucosa were linearly correlated to the release rate of un-ionized lidocaine, which was estimated by the drug release rate multiplied by the un-ionized fraction of lidocaine for the film dosage form.

Das[77] et al developed the of mucoadhesive films of buprenorphine for sublingual drug delivery in the treatment of drug addiction. The formulations include mucoadhesive polymer films, with or without plasticizers. The development of plasticizer-containing mucoadhesive polymer films was feasible; however, these films failed to release their entire drug content within a reasonable period.

Yotaro et al[39] investigated the effect of low-molecular-weight β-cyclodextrin (β-CyD) polymer on *in vitro* release of two drugs with different lipophilicities (*i.e.*, lidocaine and ketoprofen) from mucoadhesive buccal film dosage forms. When β-CyD polymer was added to hydroxypropylcellulose or polyvinylalcohol film dosage forms, the release of lidocaine into artificial saliva (pH 5.7) was reduced by 40% of the control.

Rossi et al[78] investigated the possibility of achieving buccal delivery of a problematic drug, acyclovir, from films based on chitosan hydrochloride (HCS) and polyacrylic acid sodium salt (PAA). Films containing 1 mg/cm^2 of acyclovir and based on pure HCS and on HCS and PAA mixed in different ratios were prepared by casting technique.

Jay et al[79] developed a novel bi-layer mucoadhesive wax-film composite (WFC), and tested the relative bioavailability of testosterone via the buccal route in rabbits. The release rate of testosterone from optimal WFCs (3/8-in. diameter) per unit surface area was 5.6 microg x cm(2) x mL(-1) x min(-1) and was zero-order.

Cui et al[80] developed a novel mucoadhesive bilayer film was developed to test the feasibility of the buccal route of immunization in rabbits. Bilayer films were developed using different ratios of Noveon and Eudragit S-100 as the mucoadhesive layer and a pharmaceutical wax as the impermeable backing layer.

Senel et al[81] developed the formulation containing chitosan for local delivery of Chlorhexidine gluconate to the oral cavity. Gels (at 1 or 2% concentration) or film forms of chitosan were prepared containing 0.1 or 0.2% Chx and their in vitro release properties were studied.

2.12 WORK DONE ON FAST DISSOLVING TABLETS

Lewaschiw et al[82] evaluated the impact of oral administration of ondansetron fast dissolving tablet on the incidence of postoperative nausea and vomiting among patients submitted to general anesthesia. Ondansetron, 16 mg orally, administered before the operation significantly reduced the incidence of postoperative nausea and vomiting.

Bi et al[83] developed the rapidly disintegrating tablets with sufficient mechanical integrity as well as a pleasant taste, microcrystalline cellulose, Tablettose, and crosslinked sodium carboxymethyl cellulose or erythritol using direct compression method. Rapidly disintegrating tablets with durable structure and desirable taste could be prepared.

Ishikawa et al[84] prepared rapidly disintegrating tablet of pirenzepine HCl and oxybutynin HCl containing bitter-taste-masked granules by the compression method. The taste-masked granules were prepared using aminoalkyl methacrylate copolymers (Eudragit E-100) by the extrusion method.

Shu et al[85] prepared the rapid oral disintegration tablets by direct compression using co-ground mixture of D-mannitol and crospovidone. The co-ground mixture was prepared with a vibration rod mill. The tablets were formed by compression using a single punch-tableting machine after addition of the co-ground mixture to non-ground D-mannitol, crospovidone and magnesium stearate..

Ariyoshi et al[86] investigated the inhibitory effects of GG032X tablets,-a new dosage form (fast dispersing tablet) of ondansetron, 5-HT2 receptor antagonist, on nausea and emesis induced by cisplatin along with safety and usefulness. GG032X tablets were evaluated as having the same inhibitory effect as the already-approved ondansetron tablets against cisplatin induced nausea and emesis, and were considered safe and clinically useful.

Valleri et al[87] developed glyburide fast dissolving tablets using solid dispersion technique in polyethylene glycol. Tablets obtained by direct compression, with a hardness of 7-9 Kp, and containing larger sized solid dispersions (20-35 mesh, i.e., 850-500 microm) of micronized glyburide in polyethylene glycol 6000 prepared by the cofusion method gave the best results, with a 135% increase in drug dissolution efficiency at 60 min in comparison with a reference tablet formulation containing the pure micronized drug.

Perissutti et al[88] formulated carbamazepine fast-release tablets by using melt granulation process in high shear mixer. The granules of the drug were prepared using polyethylene

glycol 4000 as a melting binder and lactose monohydrate as a hydrophilic filler. The potential of the intragranular addition of crospovidone as a dissolution enhancer and a disintegrant agent was also evaluated.

Stockli et al[89] studied the use of fast-melt tablet of zolmitriptan in the acute treatment of patients with migraine attacks. With regard to efficacy in headaches, concomitant autonomic symptoms, rapid onset of effect, and acceptance, this fastmelt triptan formulation represents real competition with the other triptans in the usual tablet formulation. It is especially suitable for active migraine patients who would like to have an effective therapeutic agent available for rapid use in all life situations.

Schiermeier et al[90] developed the fast dispersible tablet of ibuprofen using direct compression method. The selected tablet formulation, containing 26% galactomannan and 5% crospovidone, disintegrates before the galactomannan starts to swell. These tablets disperse in water within 40 s and show a crushing strength of 95 N.

Kuno et al[91] evaluated the rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. The tablets were produced by compressing powder containing erythritol (melting point: 122 degrees C) and xylitol (melting point: 93 approximately 95 degrees C), and then heating at about 93 degrees C for 15 min.

Gohel et al[92] developd the mouth dissolve tablets of nimesulide using vacuum drying technique. Granules containing nimesulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum.

Barbanti et al[93] evaluated the effects on functional ability of the new fast isintegrating/rapid release tablet of sumatriptan. Normal functional ability was restored in a significantly ($p < 0.05$) greater percentage of patients treated with sumatriptan than placebo beginning 45 min postdose for sumatriptan 100 mg and 1 h postdose for sumatriptan 50 mg.

Abdelbary et al[94] prepared the orally disintegrating tablets with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder (Superpolystate, PEG-6-stearate). Superpolystate is a waxy material with a melting point of 33-37 degrees C and an HLB value of 9.

Reeves et al[95] developed the orally disintegrating of olanzapine as a possible alternative to injection of antipsychotic drugs. The orally disintegrating formulation of olanzapine dissolved rapidly on contact with saliva. In certain cases, orally disintegrating olanzapine may be administered, instead of injection of an antipsychotic agent. Orally disintegrating olanzapine was intended to deliver a dose analogous to regular olanzapine tablets.

Baldi et al[96] studied the lansoprazole fast disintegrating tablet, an innovative drug delivery system, comprising enteric-coated microgranules of lansoprazole compressed with an inactive, rapidly dispersing matrix to form a tablet. Studies have shown that the its bioavailability was comparable to lansoprazole capsules, at both 15 and 30 mg doses.

Sugimoto et al[97] prepared rapidly disintegrating tablet having both high porosity and practical strength using the amorphous sucrose, which has good compactability. Mannitol-powder with freeze-dried amorphous sucrose was tableted at low compression and stored under certain conditions. The tablet disintegrated rapidly in the mouth, because of its high porosity.

Ito et al[98] prepared the rapidly disintegrating oral tablets using agar as base of rapidly disintegrating oral tablets. The rapid disintegration of the treated agar tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using treated agar.

Bi et al[99] prepared the rapidly disintegrating tablets of ethenzamide and ascorbic acid as poorly and easily water soluble model drugs, respectively. The mixture of microcrystalline cellulose (MCC)and low-substituted hydroxypropylcellulose (L-HPC) was compressed at 100--500 kgf in the absence of an active ingredient. When the

MCC/L-HPC ratio was in the range of 8:2 to 9:1, the shortest disintegration time was observed.

Watanabe et al[100] developed a compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Rapid disintegration (within 30 s) was obtained in vitro using various compounding ratios of crystalline cellulose to L-HPC.

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