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# *Chapter I*

## *Introduction*

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## ***1.1 INTRODUCTION***

Faced with soaring R&D costs, an impending onslaught of patent expirations, mega-merger mania, a declining number of new drug approvals in the U.S. and abroad and increasing consumer demands for improved medications, pharmaceutical companies are relying more heavily on advanced drug delivery technologies to help sustain the high growth and profit margins they have been experiencing since the 90s.

Against this background, pharmaceutical companies are recognizing that drug delivery technologies are a powerful strategic marketing tool to differentiate products and extend product life cycles, thereby overcoming many marketplace challenges. They are pursuing stronger alliances with drug delivery companies, including acquisitions, to enable them to develop superior drugs and remain competitive. The market for advanced drug delivery systems is expected to mushroom from \$16.28 billion in 2000 (according to a report from Business Communications Company) to \$27.35 billion in 2005 (Baichwal et al,2001).

The application of drug delivery is a valuable, cost-effective life-cycle management resource. By infusing drugs with new and innovative therapeutic benefits, drug delivery systems extend products' profitable life cycle, giving pharmaceutical companies competitive and financial advantages and providing patients with improved medications.

### ***HOW DRUG DELIVERY SYSTEMS BENEFIT PHARMACEUTICAL COMPANIES AND PATIENTS***

Advanced drug delivery technologies can improve a product's clinical and commercial value, differentiate a product, and serve as an effective resource to outdo competitors. Clinically, they improve the pharmacoeconomics of drugs by reducing adverse effects, identifying new indications, and improving therapy, safety, efficacy, convenience, and compliance.

Drug delivery technologies make medicines more convenient and acceptable to patients by simplifying the dosing regimen and improving administration. These improvements, in turn, bolster compliance, which helps improve patient outcomes and quality of life and reduce costs.

By reducing dosing frequency, these improved medications reduce the frequency of caregiver interactions. Fewer visits from doctors and nurses save administration costs and time and reduce inconvenience for patients and caregivers.

With medications for chronic diseases that display time-dependent symptoms, such as ulcers or asthma, drug delivery systems can control the formulation release according to the timing of symptoms. For example, they can enable a drug to release when asthma attacks occur, generally in the middle of the night. This chronotherapeutic technology can provide valuable and clinically proven therapeutic benefits and another means for marketers to differentiate their product.

Commercially, delivery technologies give new life to drugs, repositioning them with a new or improved therapeutic benefit and a competitive edge. By extending the product's life cycle with a line extension, they sustain the drug's market value.

### ***USING DRUG DELIVERY SYSTEMS TO EXTEND PRODUCT LIFE CYCLE***

#### ***To give a product a competitive edge***

When a competitor is introducing a new drug with superior benefits that threatens to erode your drug's market share, drug delivery technology can be an effective defensive marketing strategy. By adding a relevant new benefit, such as reduced side effects, it can boost your drug's value and revive its marketplace position. In the same way, these systems can jump-start products in a mature life-cycle stage (see following page, patent expiration).

#### ***To enable or accelerate market entry***

Drug delivery systems reduce the attrition rates and development time for new active substances. Each year, more companies assess and dismiss thousands of active substances for reasons such as insolubility or unacceptable toxicity. Ten percent are terminated because of adverse effects. Others never come to market because of high dosing frequency or the inability to formulate the drug. Drug delivery systems can overcome these issues, enabling more active substances to proceed to clinical trials and more products to reach the market.

#### ***When patents expire***

Novel drug delivery systems can protect or prolong a product's patent exclusivity. When patents are expiring, the originating drug company and companies seeking to benefit from the patent expiration can use drug development technologies to seize this market opportunity. Below are some commonly used strategies.

#### ***Develop a generic***

Developing a generic requires use of sophisticated drug delivery technologies that must not only match the pharmacokinetic profile of the reference drug, but must also avoid the innovators' patents. Technologies known for ease, flexibility, and rapid development time will increase the chances of being first to market. For example, in 1994, Penwest partnered with Mylan Laboratories to develop a generic equivalent of Pfizer's 30-mg Procardia, XL, joining the industry race to produce a controlled-release nifedipine tablet. The speed and flexibility of Penwest's TIMERx controlled-release technology enabled the two companies to develop a generic and Mylan to gain the first-to-file status.

***Develop an improved product***

Drug delivery technologies give formulators a value-added opportunity to develop innovative, therapeutically enhanced alternatives to compete against generics and branded products. They enable the originating drug company to extend exclusivity by developing an enhanced version with therapeutic benefits, such as improved efficacy or dosing frequency, or new therapeutic indications. For example, when Cardizem, a three-times-daily cardiovascular drug, achieved revenues of \$260 million in 1988, Hoechst Marion Roussel and Elan extended the product's life cycle by introducing Cardizem SR (diltiazem, twice-daily). Revenues peaked in 1989 at \$400 million, remaining steady until 1991, when Cardizem CD was introduced for once-daily dosage. By 1996, revenues for Cardizem CD soared to almost \$900 million (Figure 1).

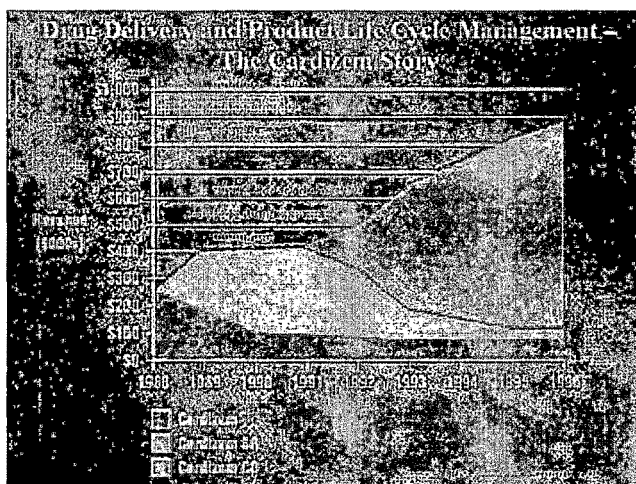


Figure I. 1 Drug Delivery and Product Life Cycle Management – The Cardizem Story

***Introduce a new product***

To replace sales of a product with an expiring patent, drug delivery technologies can be used to develop a new product with a different chemical entity and brand name. Or transfer value from the branded drug to a successor product by switching the ethical drug to an over-the-counter product.

***Extend exclusivity***

From the earliest stage of development of an NCE, speed to market should be a key consideration. A product that is first to market may soon lose that advantage as similar products with improved formulations erode its market share. Using drug delivery technology to introduce a novel new drug with enhanced benefits, such as optimal dosing, can deter competition and lengthen the period of product exclusivity.

For mature products, a drug delivery system can extend patent life only if it provides a significant enough benefit to warrant the inevitable price premium that can occur following patent expiration. Another strategy to extend exclusivity is to expand the overall market for the original patented compound, such as developing a palatable antibiotic for children, a smaller tablet size for elderly patients or children, or determining new therapeutic indications.

The biggest challenge industry faces today is selecting the right delivery solution. A molecule works best with technology if the relation between two is symbiotic. Some technology work wonders with a molecule, but we are not magicians and can only work with what we have. Exciting technological developments have been seen over the past few decades and the next few promise the introduction of even more fantastic ideas into our everyday lives. In general, technologies can be classified as being either 'sustaining' or 'disruptive'; those that are built on incremental improvements to existing technologies, or those that represent a departure from the conventional path, respectively.

Drugs that have absorption limited to the upper gastrointestinal tract coupled with poor absorption in the distal small intestine, large intestine and colon are usually regarded as inappropriate candidates for formulation into oral controlled delivery systems. This limitation on absorption is referred to as the "*absorption window*".

The gastrointestinal tract functions to propel ingested material from the stomach into the small intestine and on to the large intestine.

Conventional oral controlled release delivery systems function by releasing their payload of drug over an extended period of time following administration. Thus, conventional controlled release dosage forms may only spend a relatively short period in the regions of the gastrointestinal tract where good absorption of certain drugs can occur. The dosage form will pass on to regions of the intestine where absorption of certain drugs is poor or non-existent, still releasing its contained drug albeit with a significant percentage of its payload still to be delivered. Drug when released from the dosage form in the circumstances described will not be absorbed. Thus, administration of a drug subject to a window of absorption in a conventional controlled release delivery system can lead to sub therapeutic blood levels and ineffective treatment of the disease state for which the drug was intended.

Improvements in the therapeutic regimes employing drugs having absorption limited to the upper gastrointestinal tract might be achieved by increasing the residence time of dosage form into the stomach so that released drug is available for longer duration at the site of absorption window. This could be achieved either by co-administering a drug that reduces gastrointestinal motility or applying specific dosage form technology.

The co-administered drug may have other undesirable pharmacological effects or side effects deleterious to the patients well being and furthermore, it may be difficult or impossible to appropriately co-formulate the two agents due to chemical compatibility issues or solubility differences, the latter preventing the required release rate of agent

influencing residence time in the upper GI tract. Thus, the patient could be required to take separate, multiple medications to achieve the desired effect. The timing of taking the two medications would be critical to effective delivery of the drug with the limited window of absorption and many patients may thus fail to take their medication correctly resulting in ineffective treatment.

Therefore it is more desirable to provide a dosage form that inherently has the property of extended gastric residence, possessing some resistance to the pattern of waves of motility present in the gastrointestinal tract that serve to propel material through it. Such systems are known as *gastro retentive systems*.

*Various Gastro-Retentive Systems available in the literature are:*

- ***Floating or buoyant systems:***  
These are designed to have a low density by generating gas, which is entrapped into the gel layer of the dosage form and thus float on gastric contents after administration.
- ***Bioadhesive systems:***  
These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa / mucus layer.
- ***Swelling and expanding systems:***  
These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult. On ingestion they rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree.
- ***High Density systems:***  
These are designed by using high-density materials that sink in the stomach and because of the anatomy of stomach (pylorus well above the body of the stomach) are retained in the stomach for longer period of time.

*Disadvantages associated with the above systems:*

- ***Floating or buoyant systems:***
  - Besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required.
  - Cannot exit through pylorus or with difficulty especially floating balloons or gas chambers inserted to achieve the buoyancy.
  - Possibility of being expelled out during the lag time.

➤ **Bioadhesive systems:**

- Adheres to mucous that slough off readily.
- With increase in hydration, mucoadhesive strength decreases and may be suitable for only short duration of time.
- Intrinsic difficulty to cause bioadhesive phenomena in a dynamic system subject to outstanding propulsive forces (gastric walls).

➤ **High Density systems:**

- Most of the high-density materials cannot be used in pharmaceutical compositions.
- High variability.

*Therefore, there is a need for new Gastro Retentive Systems with following properties:*

- Suitable for low dose drugs.
- Suitable for low dose and high solubility drugs.
- Floats independent of gas generating system or a floating chamber.
- Has a prolonged gastric residence time.

## 1.2 AIM AND OBJECTIVES

The objective of the present invention is to develop an efficient, safe, reliable and stable means of drug delivery that allows an optimal therapeutic concentration of a drug to be absorbed through upper gastrointestinal tract. The research work is aimed at development of novel gastro retentive drug delivery system containing effective amount of drug for the treatment of Benign Prostatic Hyperplasia like Alfuzosin, which should prolong the residence time of the drug in the stomach, so that the drug is slowly absorbed through the upper gastrointestinal tract.

- Characterization of Alfuzosin Hydrochloride for solubility at different pH, in various solvents, hygroscopicity studies, XRD, FTIR, DSC, TGS, microscopy, bulk density, tap density, compressibility index, particle size compatibility with different excipients.
- Evaluation of marketed preparation for release profile in different media.
- Permeability study in rat intestine by Single-pass Intestinal Perfusion (SPIP) Technique and segmental absorption by Closed-Loop method.
- Formulation development with different gastro-retentive techniques (size exclusion non –swelling and swelling technique and floating drug delivery) and in-vitro characterization by optimizing dissolution.
- Gastric residence time of all the three technologies in healthy human volunteers in fasted and fed state.
- Bioequivalence studies in healthy human volunteers in fasted and fed state.
- Process optimization and Stability studies in different packaging according to ICH guidelines.
- Development of IVIVC.