Chapter 5

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Novel Drug Delivery Systems

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Note: It is better to study the ion-exchange systems, osmotically Controlled, Floating Drug Delivery System in detail Make your own short notes.

ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Introduction

During the last two decades, there has been remarkable increase in interest in controlled release drug delivery system. This has been due to various factors, viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems.

Modified release dosage forms: The term 'modified release dosage forms' is used to denote the dosage forms for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic objectives not offered by the conventional dosage forms. Two types of modified release dosage forms are recognized.

1. Extended release dosage forms: It is defined as the one that allows at least a twofold reduction in the dosing frequency as compared to that of conventional dosage form.
2. Delayed release dosage forms: It is defined as one that releases the drug at a time other than "immediately" after administration.

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Rationale of controlled drug delivery

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration.

Terminology

The general consensus is that controlled release denotes systems, which can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body. In other words, the systems attempt to control drug concentration in the target tissue or cells. Thus, prolonged release or sustained release systems, which only prolong therapeutic blood or tissue levels of the drug for an extended period of time, cannot be considered as controlled release systems by this definition. They are distinguished from rate-controlled drug delivery systems, which are able to specify the release rate and duration in vivo precisely, on the basis of simple in vitro tests. Drug targeting, on the other hand, can be considered as a form of controlled release in that exercises spatial control of drug release within the body.

In general, controlled delivery attempts to:

- Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.
- Localize drug action by spatial placement of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ.
- Target drug action by using carriers or chemical derivatization to deliver drug to a particular "target" cell type.

In practice, very few of the applied systems embrace all of these actions. In most cases, the release systems create constant concentration of drug within the body over an extended period of time. The assumption is that there is steady state drug levels in plasma and in target tissue or cells are correlated. Ideally, it is desirable to place the drug at the target, be it a tissue, a population of cells or receptors, leaving the rest of body drug free. Obviously this would be quite difficult, specially if the target is sheltered from systemic circulation by various barriers. For example, drug targeting to the brain via systemic administration is severely limited by selectivity of the blood brain barrier. Figure 5.1 shows comparative blood level profiles obtained from administration of conventional, controlled and sustained release dosage forms. The conventional tablet or capsule provides only a single and

transient burst of drug. A pharmacological effect is seen as long as the amount of drug is within the therapeutic range. Problems occur when the peak concentration is above or below this range, specially for drugs with narrow therapeutic windows. Indeed, prolonged release dosage forms reduce fluctuations in plasma drug levels by slowing down the absorption rate due to slower drug release rate.

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

The term "controlled release", on the other hand, has a meaning that goes beyond the scope of sustained drug action. It also implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug from controlled release drug delivery system proceeds at a rate profile that is not predictable kinetically, but also reproducible from one unit to another.

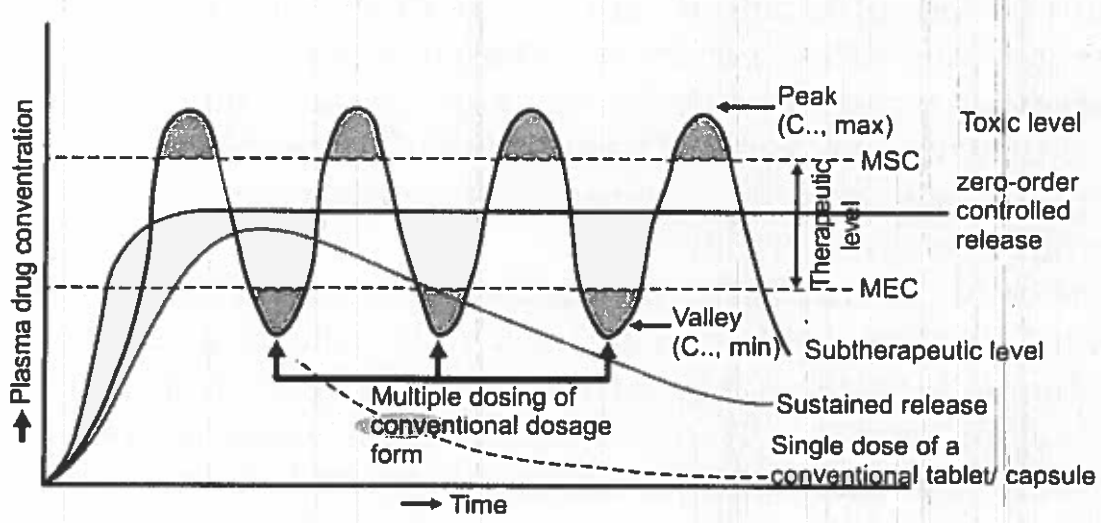

FIGURE 5.1: Comparative blood level profiles obtained from administration of conventional, controlled and sustained release dosage forms

Theoretical overview

The basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for extended period of time. Modified-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting.

Delayed release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dose form. For example, delayed release system include repeat action tablets, capsules and enteric coated tablet where timely release is achieved by barrier coating.

Sustained release system includes any drug delivery system that achieves slow release of drug over an extended period of time. If the system provides some control, whether this is of temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

Site-specific targeting refers to targeting of drug directly to a certain biological locations. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue.

Receptor targeting refers to the target in particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspects of drug delivery and are also considered to be controlled-drug delivery systems.

Basically, controlled-drug delivery forms, rather than conventional dosages forms, are used in the following instances:

1. When less frequent administration is desired for drugs that are eliminated rapidly from the body. These prolonged release products initially make available to the body a quantity of drug comparable to that delivered from a single dose of the drug in a conventional dosages form, but contain additional quantities of the drug which are slowly made available to the body so as to prolong the clinical effect beyond that attainable with a single dose. The prolonged-release dosage forms should be most useful for drugs that are used chronically but that have relatively short half lives and must be administered several times a day.
2. When high peak blood levels due to rapid drug absorption from conventional dosages forms are associated with adverse side effects. Thus, the use of certain drugs with relatively long

half lives in slow release dosages forms may also be rational and advantageous if there is question regarding the safety of giving the entire daily dose in a single administration of conventional dosages forms.

Ideally with sustained and controlled drug delivery forms, the drug absorption into the body should be determined by dosages form factors rather than by physiological factors. Basically, the drugs delivered into the systemic circulation are a function of the rate of drug release from the dosages form and the rate of drug passage through biological membranes. The slower of the two processes will be rate determining. In conventional dosages forms the physiologic factors are often rate controlling. But in controlled drug delivery forms the dosages formulation is rate controlling.

It is important to understand physiologic factors while designing controlled drug delivery systems. For example, the most used route of drug administration is oral, yet the gastrointestinal tract presents a very challenging variety of physiologic factors that affect dosages form performance, e.g. gastric acidity and more neutral intestinal fluids, thick membranes with small surface area and poor blood supply (gastric) and thinner membranes with large surface area and good blood supply (duodenal), highly liquid environments and semisolid environments, etc. these variations are made even more challenging by changing transit times and the probability of first pass metabolism. To render these physiologic factors less important to the rate of drug absorption than the dosages form factors is sometimes not possible, e.g. for drugs that are not absorbed throughout the gastrointestinal tract or for some drugs that undergo extensive first pass metabolism. The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a controlled release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion.

Potential advantages and disadvantages of sustained and controlled release dosage forms

Advantages

1. **Patient compliance**: Lack of compliance is generally observed with long-term treatment of chronic disease, as

success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule and also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system.

2. **Reduced 'see-saw' fluctuation**: Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see-saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well-designed controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a steadier drug concentration in blood circulation and target tissue cells.
3. **Reduced total dose**: Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.
4. **Improved efficiency in treatment**: Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in nontarget tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.
5. **Economy**:
   a. In comparison with conventional dosage forms the average cost of treatment over an extended period may be less.

b. Economy also may result from a decrease in nursing time and hospitalization.

6. **Improved therapy:**
   a. *Sustained blood level*: The dosage form provides uniform drug availability/blood levels unlike peak and valley pattern obtained by intermittent administration.
   b. *Attenuation of adverse effects*: The incidence and intensity of undesirable effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced.
   c. It is seldom that a dose is missed because of non-compliance by the patient.

Disadvantages

1. **Dose dumping**: Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which has a narrow therapeutic index, e.g. phenobarbital.
2. **Less flexibility in accurate dose adjustment**: In conventional dosage forms, dose adjustments are much simpler, e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.
3. **Poor in vitro–in vivo correlation**: In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in vitro release characteristics.
4. **Patient variation**: The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Factors considered in designing of sustained/controlled release dosage forms

The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

Biopharmaceutical factors

1. **Dose size**: For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5–1.0 gm is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another consideration is the margin of safety involved in administration of large amounts of a drug with narrow therapeutic range.
2. **Dissociation constant "pKa"**: A drug to be absorbed, it first must dissolve in the aqueous phase surrounding the site of administration and then partition in the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behavior are its aqueous solubility and if it is a weak acid or base it is pKa. These properties pay an influential role in the performance of controlled release systems.
3. **Partition coefficient**: When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic, therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility.

4. **Drug stability**: The stability of the drugs at the site of its release and exposure bio milieu is one more drug property that can influence the design of oral controlled drug delivery. Drugs that are unstable in gastric pH can be developed as slow release dosage form and drug release can be delayed till the dosage form reaches the intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for controlled drug delivery systems.
5. **Protein binding**: It is well-known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are for the most part recirculated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, specially if high degree of drug binding occurs. There are, however, other drug-protein interaction that has bearing on drug performance.

Pharmacokinetic factors

1. **Absorption**: The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a controlled-release system. Since, the rate limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the system is to be successful.
2. **Distribution**: The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue to that in plasma at the steady state is called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence the need to employ a controlled-system.
3. **Metabolism**: Drugs that are significantly metabolized before absorption either in the lumen or tissue of the intestine can show decreased bioavailability from slower-releasing dosage forms. Formulation of these enzymatically susceptible compounds as prodrug is another viable solution.

4. **Elimination half-life:** Smaller the $t_{1/2}$, larger the amount of drug to be incorporated in the controlled release dosages forms. For drugs with $t_{1/2}$ less than 2 hours, a very large dose may be required to maintain the high release rate. Drugs with half- life in the range of 2–4 hours make good candidates for such a system, e.g. propranolot. Drugs with long half-life need not be presented in such a formulation, e.g. amlodipine.

Criteria to be met by drug proposed to be formulated in sustained/controlled release dosage forms

1. Desirable half-life

The half-life of a drug is an index of its residence time in the body. If the drug has a short half-life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drugs with elimination half-life of 8 hours or more are sufficiently sustained in the body, when administered in conventional dosage form, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3–4 hours.

2. High therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities, e.g. digitoxin.

3. Small dose

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled-release is seriously undetermined. This is chiefly because the size of a unit dose controlled-release formulation would become too big, to administer without difficulty.

4. Desirable absorption and solubility characteristics

Absorption of poorly water-soluble drug is often dissolution rate limited. Incorporating such compounds into controlled-release formulations is, therefore, unrealistic and may reduce overall absorption efficiency.

5. Desirable absorption window

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as

the absorption window. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled-release dosage form, are unsuitable.

Design and formulation of oral controlled release drug delivery system

Advances in oral controlled-release technology are attributed to the development of novel biocompatible polymers and machineries that allow preparation of novel design dosage forms in a reproducible manner. The main oral drug-delivery approaches that have survived through the ages are as follows:

1. Diffusion controlled systems
    i. Reservoir type
    ii. Matrix type
2. Dissolution controlled systems
    i. Reservoir type
    ii. Matrix type
3. Methods using ion-exchange
4. Methods using osmotic pressure
5. pH independent formulations
6. Altered density formulations
7. Mucoadhesive systems
8. Intestinal release systems
9. Colonic release systems.

1. Diffusion controlled systems

Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized reservoir devices and matrix devices.

i. Reservoir devices

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system (Fig. 5.2). It is also possible to use polymer coatings to achieve sustained release. For this purpose the polymer itself should not dissolve, but rather should allow the drug to diffusion through the polymer membrane to the outside, in the case of oral drug delivery, into the gastrointestinal tract.

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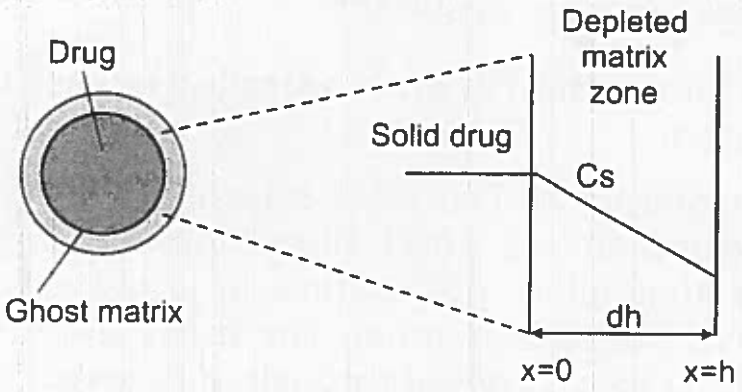

FIGURE 5.2: Schematic representation of a reservoir diffusional device

ii. Matrix devices (Fig. 5.3)

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix (Fig. 5.3). This process continues with the interface between the bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

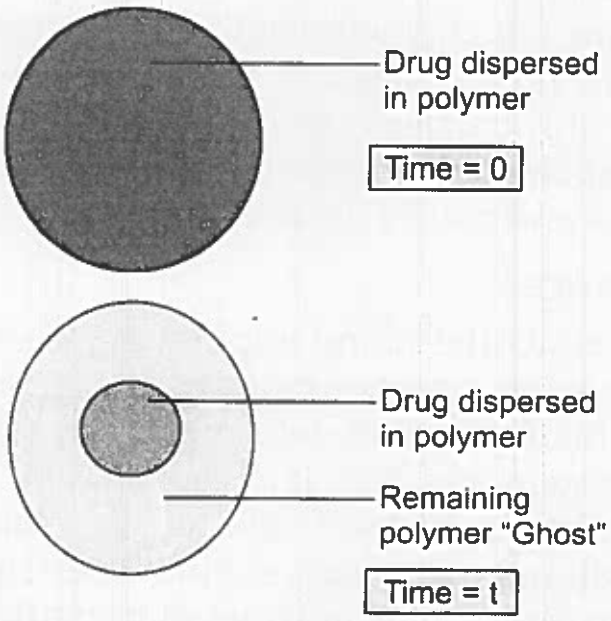

FIGURE 5.3: Matrix diffusional system before drug release (time = 0) and after partial drug release (time = t)

Matrix systems

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant materials and additives to form a tablet in which drug is embedded in matrix core of the retardant. Alternately, retardant drug blends may be granulated prior to compression.

Types of matrix

a. Hydrophobic matrices

These matrices are mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided into two broad groups:

i. *Cellulose derivatives*: Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropyl methylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxy methylcellulose.
ii. *Noncellulose natural or semisynthetic polymers*: Agar-Agar, alginates, polysaccharides of mannose and galactose, chitosan and modified starches.

b. Lipid matrices

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are, therefore, more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized as retardant base for many sustained release formulation.

2. Dissolution controlled systems

It seems inherently obvious that a drug with a slow dissolution rate will demonstrate sustaining properties, since the release of drug will be limited by the rate of dissolution. This being true, sustained-release preparation of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier (Figs 5.4A and B).

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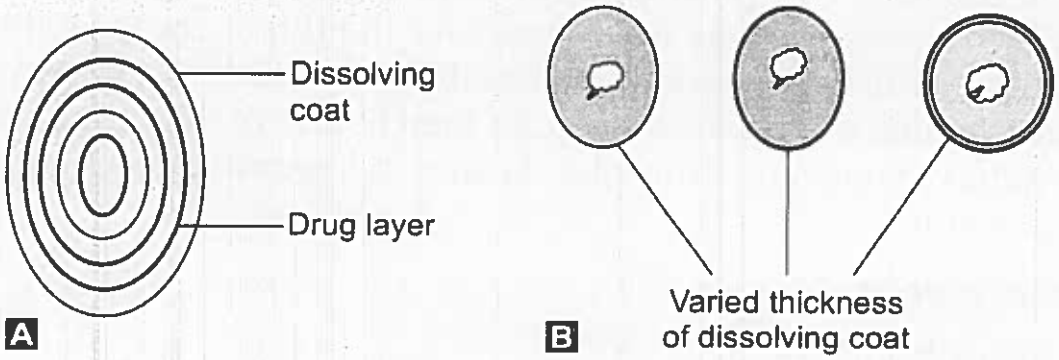


FIGURES 5.4A and B: Two types of dissolution-controlled delivery system (A) Single bead type device with alternating drug and rate controlling layer, (B) Beads containing drug with differing thickness of dissolving coats

3. *Osmotic controlled systems*

Osmotic pressure is employed as the driving force to generate a constant release of drug. Consider semipermeable membrane that is permeable to water, but not to drug. When this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference. These systems generally appear in two different forms. The first contains the drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference. The second system contains the drug in solution in an impermeable membrane within the device (Fig. 5.5).

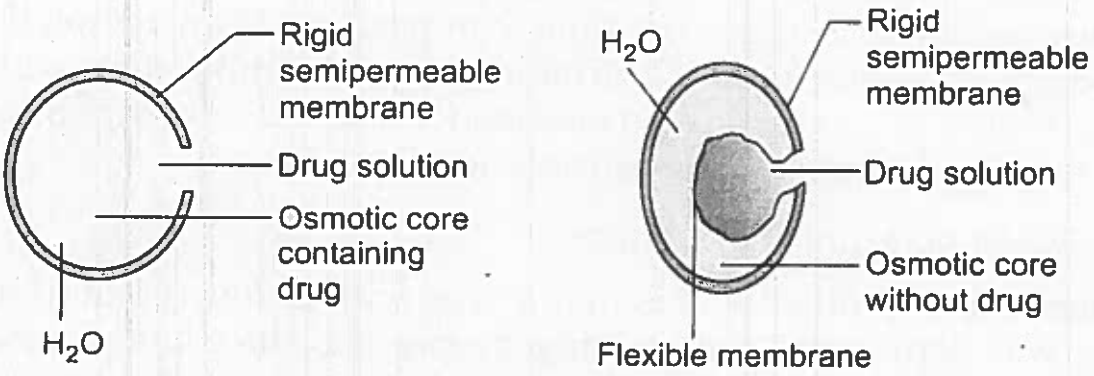


FIGURE 5.5: Diagrammatic representation of two types of osmotically controlled system

4. *Ion-exchange systems*

Ion-exchange systems generally use resins composed of water-insoluble cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer

chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$$Resin^{+} - drug^{-} + X^{-}\ resin^{+} = X^{-} + drug^{-}$$

Conversely,

$$Resin^{-} - drug^{+} + Y^{+}\ resin^{-} = Y^{+} + drug^{+}$$

The free drug diffuses out of the resin. The drug-resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column, or by prolonged contact in solution.

5. *Swelling and expansion systems (hydrogels)*

Conventional hydrogels swell slowly upon contact with water due to their small pore size, which usually ranges in the nanometers and low-micrometer scale. However, if the hydrogel has a pore size of more than 100 µm, swelling is much faster and may lead to a large increase in size. Swelling ratios of over 100 can be achieved. These swollen systems become too large to pass through the pylorus and thus may be retained in the stomach even after housekeeper wave, provided they have a sufficiently high mechanical strength to withstand the peristaltic movement in the antrum of the stomach.

6. *Muco (Bio) adhesive drug delivery systems*

Mucosal drug delivery technologies are expanding exponentially with applications in every imaginable route of administration. Because of the indisputable therapeutic benefit this delivery system brings benefits include site-specific targeting, less frequent dosing and maintaining effective plasma concentration without increased consumption.

Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extended period of time by interfacial forces. For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissues, or the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred as mucoadhesion (Fig. 5.6).

The mucosal layer lines a number of the body including the gastrointestinal tract, urogenital tract, ear, nose and eye. These

represent potential sites for the attachment of any bioadhesive system and hence, the mucoadhesive drug delivery system includes the following:

a. Buccal delivery system
b. Oral delivery system
c. Vaginal delivery system
d. Rectal delivery system
e. Nasal delivery system
f. Ocular delivery system.

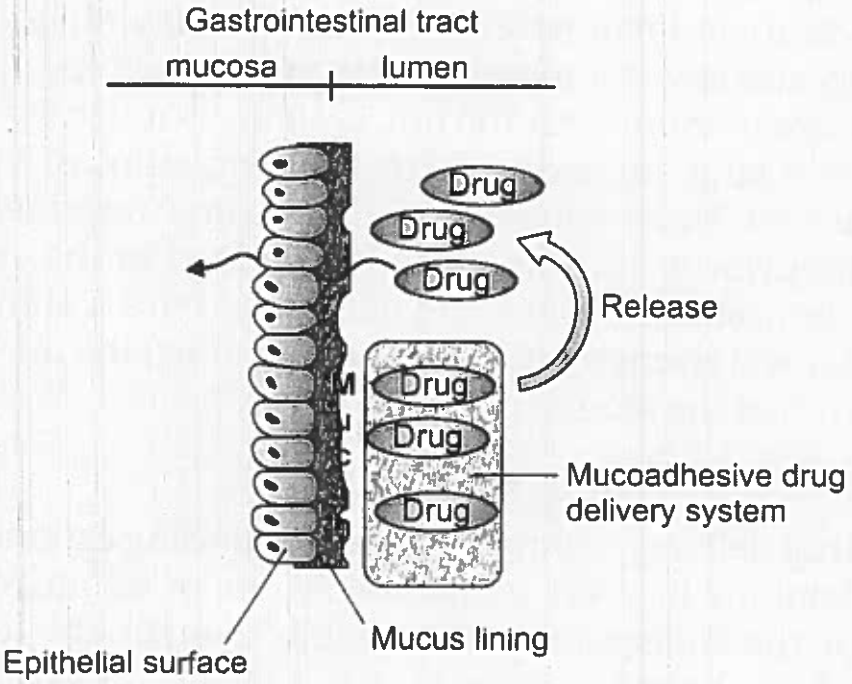


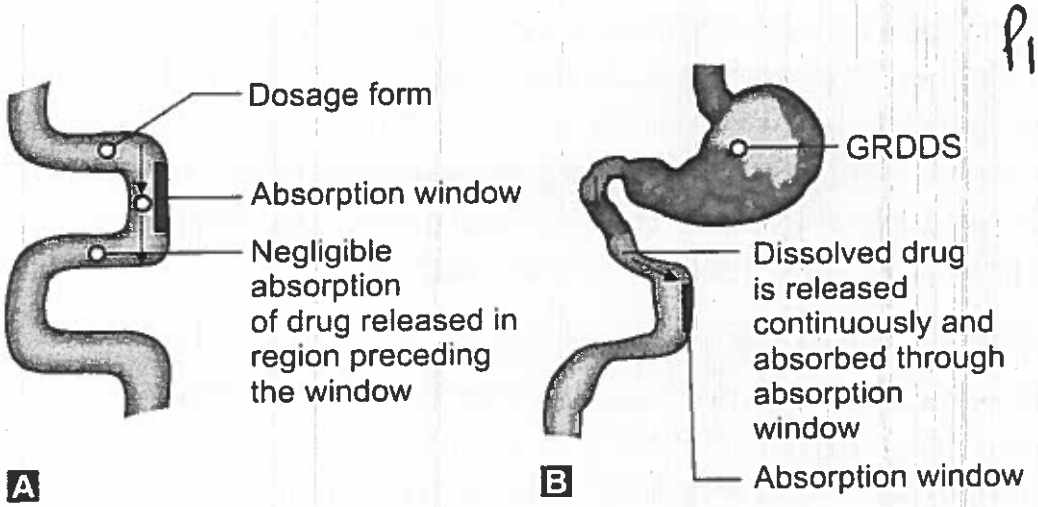
FIGURE 5.6: Diagrammatic representation of bioadhesive or mucoadhesive systems

7. *Gastroretentive drug delivery systems*

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To overcome these limitations, various approaches which have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract, includes floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, modified-shape systems, high-density

system and other delayed gastric emptying devices. Among these systems, FDDS has been most commonly used.

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site (Figs 5.7A and B), thus ensuring its optimal bioavailability. GRDDS provides a rational approach to enhanced bioavailability and improve pharmacokinetic and pharmacodynamic profile is to retain the drug reservoir above its absorption area, i.e. in the stomach and to release the drug in a controlled manner, so as to achieve a zero order kinetic (i.e. oral infusion) for a prolong period of time. Another group of drugs that can benefit from retained and controlled release in the stomach are those which are meant for the treatment of pathologies located in the stomach, the duodenum or the small intestine. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro-retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.



FIGURES 5.7A and B: Drug absorption in the case of (A) Conventional dosage forms (B) Gastroretentive drug delivery systems

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract:

- **High density approach**: In this approach, the density of the pellets must exceed that of normal stomach content and should, therefore, be at least 1–4 gm/cm.
- **Low density approach**: Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

8. Colon specific drug delivery systems

The colon is advisable site where both local or systemic drug delivery can be achieved. The topical treatment of inflammatory bowel disease (IBD) includes ulcerative colitis or Crohn's disease, irritable bowel syndrome, etc. Colon specific drug delivery is having capability to protect the drug from the acidic environment and the release of drug is only possible at the colonic environment. The use of hydrophilic gums which degrade in the colon helps in release of drug from the formulation. The colon is believed to be an absorption site for proteins and peptide drugs and protects them from the enzymatic degradation in duodenum and jejunum. Among all the routes being used, oral route is preferable route for colon specific drug delivery. The colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.

To achieve the successful colon drug delivery a drug need to be protected from the environment of upper GIT. Colon drug delivery requires longer release periods and slower release rates, which can be achieved by the application of conventional enteric coating and by use of slow release matrices.

Approaches for CDDS

1. pH sensitive polymer coated drug delivery to colon
2. Time-release drug delivery to colon
3. Microbially triggered drug delivery to colon
4. Pressure controlled drug delivery systems.

1. **pH- and time-dependent systems**: A multiparticulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug

release properties. Enteric coating has traditionally been used to prevent drug release in the upper GI tract.

2. **Microbially controlled systems:** Natural hydrophilic polymer includes chondroitin sulfate, guar gum, pectin and dextran are commonly useful in this system, all of which undergo microbial degradation at colonic environment where the site is rich of microbial load.
3. **Pressure controlled drug delivery systems:** Such systems develop pressure controlled drug delivery, where the release of drug takes place as a result of peristalsis. It is the pressure difference which makes the release of the drug only at the site of colon, as low pressure existing in the small intestine prevents the drug release. Here, the drug is placed in the form of liquid into the ethylcellulose capsules, whose thickness is the major factor for the disintegration.

PARENTERAL CONTROLLED DRUG DELIVERY SYSTEMS

Introduction

The parenteral administration route is the most effective and common form of delivery for active drug substances with poor bioavailability and the drugs with a narrow therapeutic index. Drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in terms of compliance, but also to improve the quality of the therapy and also may reduce the dosage frequency. Such reduction in frequency of drug dosing is achieved by the use of specific formulation technologies that guarantee the release of the active drug substance in a slow and predictable manner.

A number of technological advances have been made in the area of parenteral drug delivery, leading to the development of sophisticated systems that allow drug targeting and the sustained or controlled release of parenteral medicines. Parenteral formulations, particularly intravascular ones, offer a unique opportunity for direct access to the bloodstream and rapid onset of drug action as well as target to specific organ and tissue sites.

Ideal properties of parenteral controlled drug delivery system:

a. Safe from accidental release
b. Simple to administer and remove

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copolymers and poly(lactic acid) and poly(glycolic acid) copolymers also exhibit thermo-responsiveness. These polymers are useful in developing thermogelling systems.

5. **Other drug delivery systems:** There are many other drug delivery systems that are currently being investigated such as *polyelectrolyte complex* and *polymeric micelle systems*, have gained emerging popularity and valuable potential in the field of gene therapy and drug delivery.

ION-EXCHANGE SYSTEMS

Ion-exchange resins may be defined as high molecular weight water insoluble polymers containing fixed positively or negatively charged functional groups in their matrix, which have an affinity for oppositely charged counter ions. Ion exchange systems use resin composed of water-insoluble cross-linked polymers **(Table 10.1)**.

Since the majority of drugs possess an ionic site in their molecule, the charge of the resins provides a means to loosely attach such drugs to insoluble polymers. The ion-exchange phenomenon is driven by electrostatic interactions between the resins and oppositely charges drugs. The driving force behind this exchange is due to the electronic differences between the ions. The reversibility of this interaction is exploited in oral drug delivery in which the resins may carry the drug and release the payload in a certain region of the gastrointestinal tract (GIT) due to a pH change or presence of competing ion. The drug molecules attached to the resins are released by appropriate charged ions in the GIT, followed by diffusion of free drug molecules out of the resin as shown below.

$$Resin^{+} - Drug^{-} + X^{-} \longrightarrow Resin^{+}\ X^{-} + Drug$$

$$Resin^{-} - Drug^{+} + Y^{+} \longrightarrow Resin^{-}\ Y^{+} + Drug$$

where X and Y are ions in the gastrointestinal tract.

Table 10.1: Examples of ion exchange resins

Type	*Exchange species*	*Polymeric backbone*	*Examples*
Strong cation	$-SO_3H$	Polystyrene-DVB	INDION-244, 254, 284
Weak cation	-COOH	Methacrylic acid -DVB	Amberlite IRC-50
Strong anion	N^+R_3	Polystyrene-DVB	Dowex-1, Amberlite IR 400
Weak anion	N^+R_2	Polystyrene-DVB	Dowex-2, Amberlite

Applications

Various studies have revealed that ion exchange resins are equally suitable for drug delivery technology. Ion exchange resins offer better drug retaining properties and prevention of dose dumping. The physical and chemical properties of ion exchange resin will release the drugs more uniformly than that of simple matrices. Resinates used provides simplest form of controlled or sustained release delivery system. Resinates can be filled directly in a capsule, suspended in liquids, suspended in matrices or compressed into tablets **(Figure 10.9)**.

Microencapsulation of resinates provides better control over the drug release because of presence of rate controlling membrane. The absorption of the drug from coated resinates is a consequence of the entry of the counter ions into the coated resinates and release of drug ions from drug resin complex by the ion-exchange process and diffusion

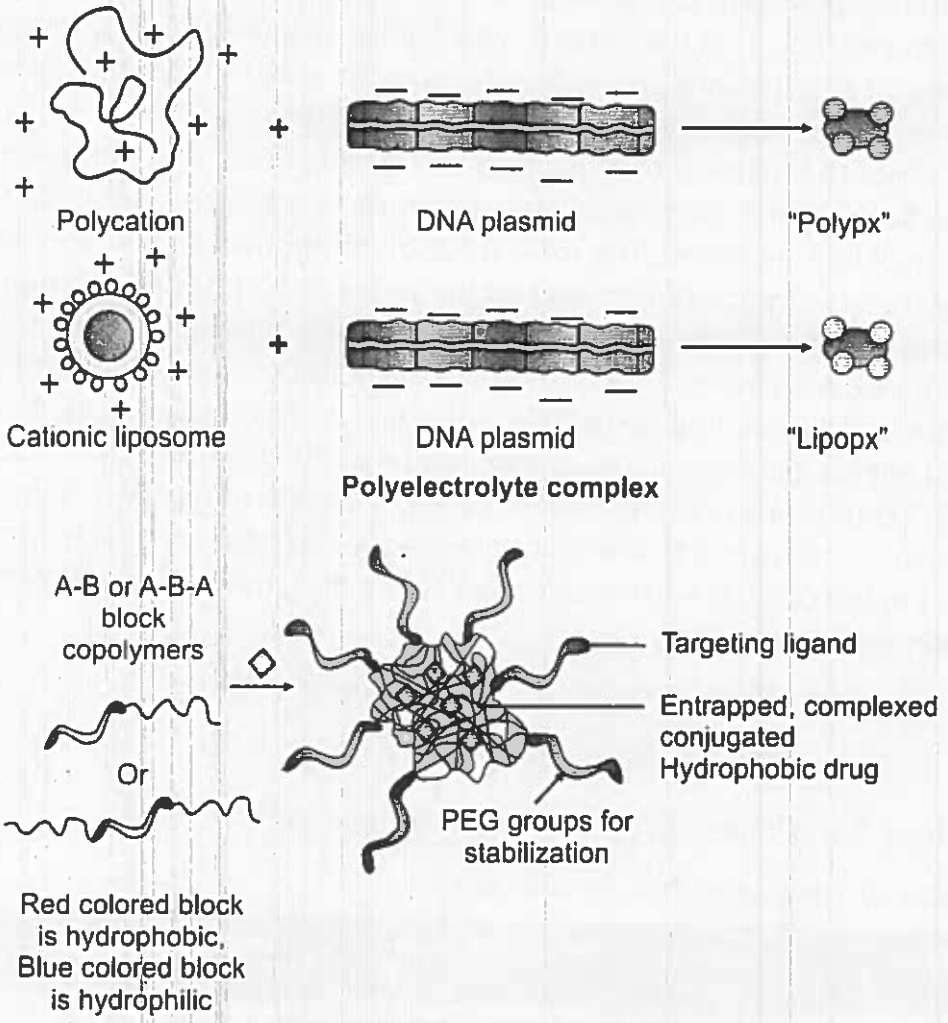

Figure 10.9: Examples of newer drug delivery systems

of drug ions through the membrane into the dissolution medium. Ion exchange resins may be useful mucoadhesive systems for treatment of stomach such as in *H. pylori* infection for prolonging the gastric residence of amoxicillin and cimetidine.

Entrapment of anticancer drugs in the form of microspheres or microcapsules is used to treat cancer. Attempts have been made to deliver some of these drugs in a controlled release fashion to anticancer cells with help of ion-exchange resin. Eudragit RS an anion exchange resin with limited quaternary ammonium groups is coated over beads with a sugar core surrounded by organic acid and drug mixture. The ionic environment induced by addition of an organic acid to the system, was found be responsible for pulsatile release.

In a study which employed resinates of cationic drugs ambroxal and chlorpheniramine, the amount of drug released from the resinate prepared by simultaneous loading of (dual resinate) ambroxal and chlorpheniramine was not significantly different from that from the classical ambroxal resinate or chlorpheniramine resinate, but was considerably higher than that from the concurrent administration of two classical resinates. These results indicated that the concurrent administration of resinates affected drug release and the dual-drug resinate can be used as an alternative carrier for an ion-exchange delivery system.

Many therapeutically useful drugs are quite bitter, limiting their utility in chewable tablets designed for pediatric or geriatric use. Bitter tasting drugs like ciprofloxacin, azithromycin, chloroquine phosphate, norfloxacin, dextromethorphan hydrobromide can be adsorbed onto ion exchange resins, thus effectively removing them from solution during the transit through the mouth, at salivary pH, remains in intact form, making the drugs unavailable for the taste sensation.

OSMOTICALLY CONTROLLED SYSTEMS

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.

Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. A major advantage of drug release from these systems is that it is largely independent of pH and other physiological parameters, and it is possible to modulate the release characteristics by optimizing

the properties of the drug and system. Thus a constant osmotic pressure, and thereby a constant influx of water, can be achieved by an osmotic delivery system that results in a constant release rate of drug. Therefore, zero-order release, which is important for a controlled release delivery system when indicated, is possible to achieve using these platforms.

Osmotic pressure is used as driving force for these systems to release the drug in controlled manner. Osmotic drug delivery technique is the most interesting and widely acceptable among all other technologies used for the same. Intensive research has been carried out on osmotic systems and several patents are also published. Development of osmotic drug delivery systems was pioneered by Alza and it holds major number of the patents analyzed and also markets several products based on osmotic principle. These systems can be used for both route of administration i.e. oral and parenterals. Oral osmotic systems are known as gastro-intestinal therapeutic systems (GITS). Parenteral osmotic drug delivery includes implantable pumps.

The following advantages have contributed to the popularity of osmotic drug delivery systems:

- The delivery rate of zero-order is achievable with osmotic systems.
- Delivery may be delayed or pulsed, if desired.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
- For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- A high degree of in vivo-in vitro correlation (IVIVC) is obtained in osmotic systems.

Many forms of osmotic pumps are reported; in general they can be divided into two classes- oral and implantable systems **(Table 10.2)**.

Table 10.2: Types of osmotic drug delivery systems

Oral Osmotic Systems	*Implantable Osmotic Systems*
• Elementary osmotic pump	• Duros osmotic pump
• Controlled porosity osmotic pump	• Alzet osmotic pump
• Push-pull osmotic pump	
• OROS-CT	
• Asymmetric membrane capsule	

Principle of Osmotic Drug Delivery

First, osmotic pressure arises from the fundamental law that the chemical potential of solvent in a solution and a pure liquid must be the same, if they are in contact through a semi-permeable membrane at the same pressure. In other words, the solute lowers the chemical potential on the solution side of the membrane and results in water moving across the membrane to the solution side. This continues until equilibrium is reached. At equilibrium, the hydrostatic pressure, ρgh, is equal to the osmotic pressure. The equation for osmotic pressure for this system is reduced to:

$$\Pi = RTc_B$$

Where Π is the osmotic pressure, R is the gas constant, T is temperature and c_B is the concentration of the solute in g/liter.

The osmotic pump comprises three concentric layers: An innermost drug reservoir contained within an impermeable membrane, an osmotic solution, and a rigid outer layer of a rate-controlling semi-permeable membrane. As water from the body permeates through the outermost membrane and into the osmotic "sleeve", the sleeve expands and compresses the innermost drug reservoir. This squeezes the drug out of the reservoir through a delivery portal. The rate of drug release is proportional to the rate at which water flows into the "osmotic sleeve" due to an osmotic imbalance $\Delta\pi$:

$$\frac{dV}{dt} = \frac{Ak}{h}(\Delta\pi)$$

Where A, k and h are the membrane area, permeability and thickness, respectively.

Theeuwes first tested the elementary osmotic pump for drug delivery using potassium chloride to serve as both the osmotic agent and the drug model. In a later report, Theeuwes et al. designed a therapeutic system based on the principle of the osmotic pump to deliver indomethacin at a constant zero-order rate. For zero-order delivery rate, these workers used the equation:

$$\left(\frac{dM}{dt}\right)_2 = \frac{S}{h}k'\pi_s C_s$$

Where $(dm/dt)_z$ is the rate of delivery of solute under zero-order conditions, S is semipermeable membrane area, h is membrane thickness, k' is permeability coefficient, π_s is osmotic pressure of the

formulation under zero-order conditions (saturated solution) and C_s is the concentration of saturated solution.

Some of the drug is released from the device by simple diffusion through the membrane. The above equation therefore should be modified as follows:

$$\left(\frac{dM}{dt}\right)_2 = \frac{S}{h}k'\pi_s C_s + \frac{S}{h}PC_s$$

or

$$\left(\frac{dM}{dt}\right)_2 = \frac{S}{h}(k'\pi_s + P)C_s$$

where P is permeability coefficient for passage of KCl across semipermeable membrane.

Basic Components of Osmotic Systems

It includes the following:

Drug

Drugs which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems. Drugs with high and low water solubility do not form a good candidate for osmotic delivery. Solubility of drug in the core is modulated by incorporating suitable solubility modulators to control the release of drug from the osmotic system. Excipients like cyclodextrin, sodium chloride, effervescent mixtures, surfactants, etc. have been used to modulate solubility of drugs for formulating into osmotic system. Drugs selected as candidate for osmotic system should possess osmotic pressure. If a drug does not possess sufficient osmotic pressure an osmogent is to be added in the core formulation to control release of drug from osmotyic system. Various drug candidates such as diltiazem hydrochloride, carbamazepine, metoprolol, oxprenolol, nifedipine, glipizide, etc. have been investigated for osmotic delivery.

Osmotic Agent

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Different type of osmogents can be used for such systems are categorized as water-soluble salts of inorganic acids like magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate; water-soluble salts of organic acids like sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium

ascorbate; carbohydrates like mannose, sucrose, maltose lactose; water-soluble amino acids and organic polymeric osmogents.

Semipermeable Membrane

An important part of the osmotic drug delivery system is the semi-permeable membrane housing. Therefore, the polymeric membrane selection is key to osmotic delivery formulation. The membrane must possess certain performance criteria such as:

- Sufficient wet strength and water permeability
- Should be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices, e.g. cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose are widely used.

Plasticizers

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are:

- Polyethylene glycols.
- Ethylene glycol monoacetate; and diacetate- for low permeability.
- Triethyl citrate.
- Diethyl tartarate or diacetin—for more permeable films.

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Classification of Osmotic Systems

Oral osmotic systems are known as gastrointestinal therapeutic systems (GITS). Parenteral osmotic drug delivery includes implantable pumps. Oral osmotic pumps are classified as in **Table 10.3, Figure 10.10 and Flowchart 10.1**.

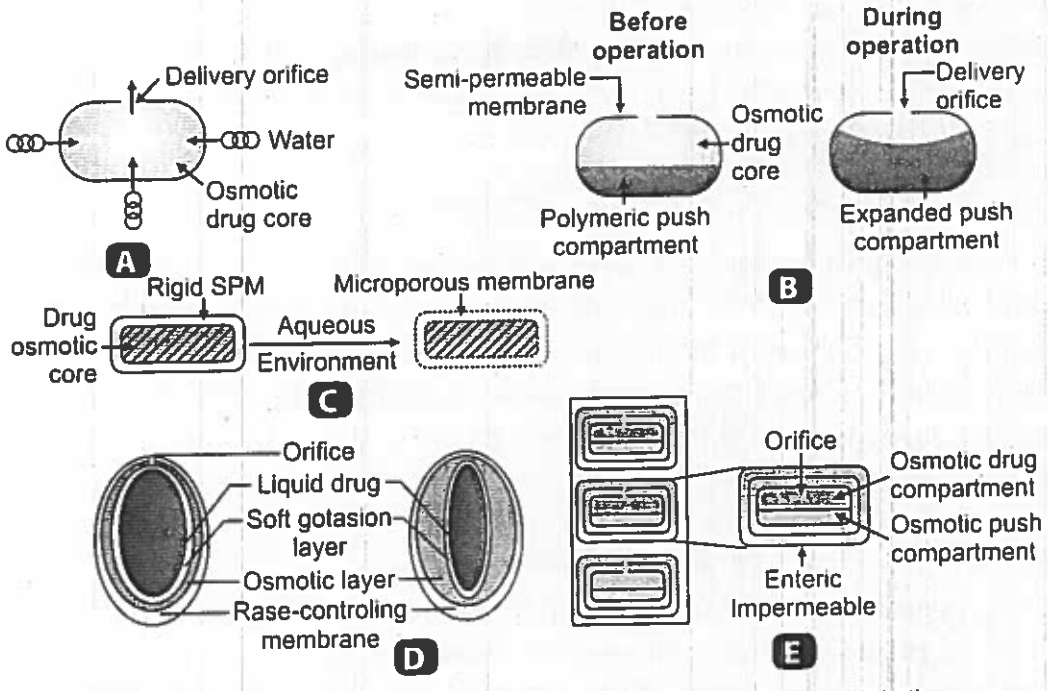
Elementary Osmotic Pump (EOP)

In the OROS elementary osmotic pump, a tablet core of drug is surrounded by a semi-permeable membrane that has one or more openings. After ingestion, the core draws water through the semi-permeable membrane from the gastrointestinal (GI) surroundings.

Table 10.3: Examples of different types of osmotic systems

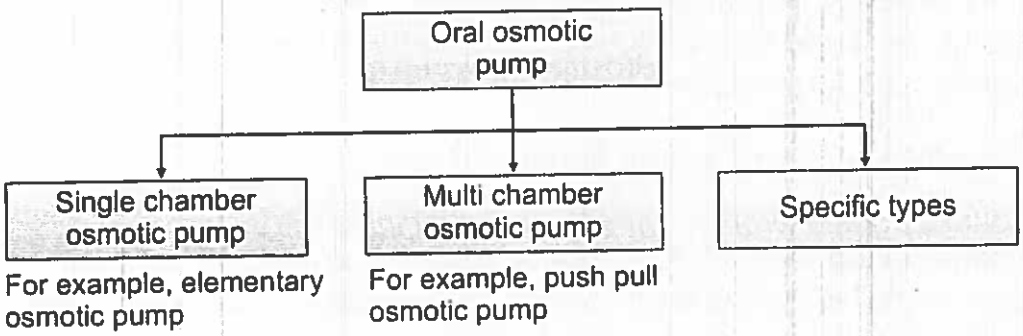
Osmotic System	*Characteristics of Release*
Elementary osmotic pump (EOP)	The water penetrates inside the dosage form at the rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. This will result in formation of saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane
Controlled porosity osmotic pump (CPOP)	Water-soluble additives dissolve after coming in contact with water, resulting in an in situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release is found to be osmotic
Push-pull osmotic pump (PPOP)	After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, and thus releasing drug in the form of fine dispersion via the orifice
OROS-CT	OROS-CT is used as a once or twice a day formulation for targeted delivery of drugs to the colon. Gelatin capsule shell dissolves after coming in contact with GI fluids. Enteric coating on the system prevents entry of fluid from stomach to the system and it dissolves after entering into intestine. The water imbibes into the core and push compartment will swell. At the same time, the flowable gel is formed which is pushed out via delivery orifice at predetermined rate
Asymmetric membrane capsule	Imbibition of water through the capsule wall and dissolving soluble components within it and releasing from same wall
Duros osmotic pump	Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by osmotic agent residing in the engine compartment, which expands the osmotic agent and displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice
Alzet osmotic pump	Water enters into the salt chamber through semi-permeable membrane and causes compression of flexible reservoir and delivery of drug solution

The imbibed water dissolves the drug, which is expelled through the orifice in a zero-order fashion. The semi-permeable membrane for OROS typically is composed of cellulose acetate. The membrane is non-extendable and preserves the physical dimensions of the dosage



Figures 10.10A to E: Examples of osmotic drug delivery systems: (A) Elementary osmotic pump, (B) Push-pull osmotic pump; (C) Controlled porosity osmotic pump; (D) Liquid oral osmotic system and (E) OROS-CT

Flow chart 10.1: Types of oral osmotic pump



form. Drug delivery is zero-order until the solid portion of the core is exhausted. The driving force that draws water into the system is the osmotic pressure difference between the outside environment and the saturated drug solution. Therefore, the osmotic pressure of the drug solution must be greater than the GI osmotic pressure.

Push-pull Osmotic Pump (PPOP)

The PPOP is a bilayered tablet coated with a semi-permeable membrane. Drug-osmogent mixture is present in the upper compartment forming 60–80% of tablet weight and lower compartment consists of polymeric osmotic agent forming 20–40% of tablet weight. A delivery orifice is drilled through the coat on the drug side of tablet. When the system

comes in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer thereby delivering the drug in the form of a fine dispersion via the orifice. Push-pull system is available in a number of modifications such as delayed push-pull system, multilayer push-pull system and push-stick system.

Controlled Porosity Osmotic Pump (CPOP)

The CPOP contains water-soluble additives in the coating membrane, which after coming in contact with aqueous environment dissolves and results in formation of in situ microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes. Such system is independent of pH and has shown to follow zero-order kinetics.

Liquid Oral Osmotic System (L-OROS)

In this system liquid API formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate-controlling membrane. A delivery orifice is formed through these three layers. When the system comes in contact with aqueous environment, water permeates across the rate controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice.

Colon Targeted Oral Osmotic System (CT-OROS)

It is single osmotic unit containing as many as five to six PPOP filled in hard gelatin capsule. The osmotic system is enteric coated. Gelatin capsule shell dissolves after coming in contact with GI fluids. Enteric coating on the system prevents entry of fluid from stomach to the system and it dissolves after entering into intestine. The water imbibes into the core and push compartment will swell. At the same time, the flowable gel is formed which is pushed out via delivery orifice at predetermined rate.

Sandwiched Osmotic Tablets (SOTS)

It consist of a middle push layer in the core, attached to two drug layer coated with a semi-permeable membrane having two delivery orifice, one on each side of the drug layer. When in contact with aqueous environment the middle push layer swells and drug is released from delivery orifices.

Characterization

The important characterization parameters related to osmotic delivery systems (capsules/tablets) includes osmotic release study, size of delivery orifice, release rate study, porosity of semipermeable membrane, determination of osmotic pressure, etc.

Osmotic Behavior

Osmotic release behavior is studied by conducting a dye-test. For this purpose, capsules are filled with the water-soluble dye amaranth, mixture of dye with osmogent and solubilizing agent SLS. The capsules are then suspended separately in 50 mL water and 50 mL sodium chloride solution (10%). The capsules are observed visually for release of any colored dye.

Release Rate Study

The in vitro study of drug release from osmotic system is studied as the function of the increasing amount of added osmogent and solubilizing agent in each system. The formulations are subjected to a release rate study using a USP dissolution apparatus II.

Porosity of Semipermeable Membrane

Influence of pore forming agent on osmotic delivery is generally studied by surface morphology using scanning electron microscopy (SEM).

Other Parameters

The effects of pH, temperature and hydrodynamic conditions on drug release and the floating behavior of floating osmotic pump system is also studied. In vivo bioavailability studies in beagle dogs is performed to estimate pharmacokinetic parameters like C_{max}, t_{max}, AUC, K_{el}, etc.

Applications

Most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

Controlled- or modified-release of drugs is possible through the use of osmotic pumps. Osmosis offers several advantages as a driving force for constant pumping of drugs, including accurate mass transfer. The development of osmotic pumps was pioneered with the commercialization of the ALZET® osmotic pump for animal studies in the mid-1970s. More recently, osmotic principles have been applied to human therapy, resulting in the development of drug delivery systems such as the DUROS® system, OROS Push-Pull™, L-OROS™, and EnSoTrol® that can release drugs continuously for up to 1 year. Recently, osmotic pumps have been studied as regulated systems for the acquisition, metering, buffering, delivery, and assay of fluid biological samples.

Many drug products using various osmotic principles have been introduced into the market. OROS designs have been used in more than 10 marketed products. The first OROS product introduced to the US market in 1983 was Acutrim®, a 16-hour appetite suppressant marketed by Ciba-Geigy. Volmax®, a twice-a-day controlled release dosage form for Glaxo's antiasthma drug albuterol, was marketed in 30 countries, including the United States, starting in 1987. Minipress XL®, a once-a-day system for Pfizer's antihypertensive drug prazosin, was launched in 1989. Efidac/24®, the first over-the-counter osmotically driven controlled release cold medication marketed by Ciba Consumer Pharmaceuticals, was introduced in 1992. Glucotrol XL®, a once-a-day orally active hypoglycemic drug delivery system for glipizide, was launched in 1994. Procardia XL, which is marketed by Pfizer, is a billion-dollar product employing Push-Pull technology. The preparation contains the calcium channel blocker nifedipine.

The OROS technologies have been used successfully to deliver pharmacotherapy in a controlled manner, usually once-daily, in a number of therapeutic areas. These technologies are based on the osmotic pressure as the driving force for highly predictable and reliable controlled drug release. They have evolved over the last 30 years, from the elementary osmotic pump to the osmotic push-pull tablet, which can sustain water insoluble drugs, to the latest advanced LCT multilayer formulation, which represents an increased sophistication in the ability to control drug release. The L-OROS technology is now also being applied to deliver drugs as a liquid for those drugs that have poor aqueous solubility.

The OROS delivery system has been developed for two calcium channel blockers; nifedipine and verapamil (Covera-HS; Pfizer, Inc., New York, USA). Both of these agents employ the osmotic

push-pull technology. In the field of endocrinology, the OROS push-pull technology is employed with sulfonylurea glipizide (Glucotrol XL; Pfizer, Inc., New York, USA). Glipizide was formulated as an ER preparation using the OROS technology to provide once-daily administration. In urology, two important OROS products are available: doxazosin (Cardura XL; Pfizer, Inc., New York, USA) for the treatment of the symptoms of benign prostatic hyperplasia (BPH), and oxybutynin for the treatment of overactive bladder. The OROS formulation of doxazosin was developed to provide more stable drug concentrations and reduce the need for dose titration. OROS doxazosin has a prolonged absorption profile compared to that of the standard IR formulation.

The most recent developments with OROS technologies are with drugs that affect the CNS. Approved for use in 2000, the stimulant methylphenidate, combined with the advanced LCT multilayer delivery formulation, represents one of the most current commercialized products that incorporate OROS technology. Two new agents are currently under development. Paliperidone ER is a new psychotropic drug that utilizes the advanced LCT multilayer formulation, and has been shown to be efficacious and generally well-tolerated in the treatment of patients with schizophrenia. OROS hydromorphone has been designed with the push-pull osmotic delivery system for the treatment of chronic pain.

FLOATING DRUG DELIVERY SYSTEMS

Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration.

Stomach specific floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as hydrodynamically balanced systems (HBS), since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3–4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcellulose (HPMC).

Advantages of FDDS are:

- Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site
- Delivery of drugs for local action in the stomach
- Minimizing the mucosal irritation due to drugs, by drug releasing slowly at a controlled rate
- Protecting the drug from degradation in colon
- Protecting the degradation of normal GI flora by restricting the dosage form in stomach and upper part of GI tract.

Classification of FDDS

Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastrointestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. Based on the mechanism of buoyancy FDDS can be classified into:

Effervescent Floating Systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Non-effervescent Floating Systems

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming

polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Characterization of FDDS

Various parameters that need to be evaluated in gastroretentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry, particle size analysis, flow properties, surface morphology, and mechanical properties are also performed **(Table 10.4)**.

Table 10.4: Evaluation of floating drug delivery systems

Parameter	*Method*
In vitro floating behavior	The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 M HCl maintained at 37°C. It is commonly determined by using USP dissolution apparatus containing 900 mL of 0.1M HCl with 0.02% v/v Tween 80 surfactant. The use of Tween 80 is to account for the wetting effect of the natural surface active agents such as phospholipids in the GIT. The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT)
In vivo flotability	X-ray and Gamma scintigraphy is popular evaluation parameter for floating dosage form and is carried out in beagle dogs or human subjects. The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner
Drug release study	Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution

Contd...

Contd...

Parameter	Method
Pharmacokinetic studies	Pharmacokinetic studies are the integral part of the in vivo studies. The parameters estimated are C_{max}, T_{max}, K_{el} and $t_{1/2}$ values. C_{max} and T_{max} can be read directly from the observed mean drug-plasma concentration against time profile. K_{el} and $T_{1/2}$ are usually computed from observed mean drug-plasma concentration against time profile. The extent of absorption from the test formulation relative to marketed one can be calculated as relative bioavailability
Stability studies	With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, subtropical and temperate. Stability studies are carried out as per ICH guidelines
Other parameters	Tablets: content uniformity, hardness, friability. Microspheres: entrapment efficiency, particle size, flow properties, surface characterization by SEM

Applications

Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of intestine, and drugs with an absorption which can be modified by changes in gastric emptying time. Such gastroretentive dosage forms are also useful for local as well as sustained drug delivery for certain conditions, like *H. pylori* infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (penicillins and cephalosporins).

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability **(Table 10.5)**.

The currently available polymer-mediated noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of it **(Table 10.6)**.

Table 10.5: Applications of floating drug delivery systems

Purpose	*Characteristics*	*Example of Drugs Investigated*
Sustained drug delivery	The problem of short gastric residence time encountered with an oral CR formulation can be overcome with these systems. These systems have a bulk density of G1 as a result of which they can float on the gastric contents. These systems are relatively large in size and assign from the pyloric opening is prohibited	Nicardipine hydrochloride, Madopar
Site-specific drug delivery	These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine	Riboflavin, furosemide, Misoprostol
Absorption enhancement	Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as FDDS	Indomethacin, p-aminobenzoic acid, bromocriptine, atenolol, tetracycline, metronidazole, clarithromycin, melatonin

Table 10.6: Marketed products of floating drug delivery system

Name	*Type*	*Drug*	*Uses*
Madopar HBS® (ProlopaHBS®)	Floating capsule	Levodopa, benserazide	Peripheral dopa decarboxylase inhibitor
Valrelease®	Floating capsule	Diazepam	Tranquilizer
Topalkan®	Floating antacid	Aluminium-magnesium mixture	Antacid, antiseptic and protective
Almagate Float coat®	Floating antacid	Aluminium-magnesium mixture	Antacid
Liquid Gaviscon®	Floating gel	Mixture of alginate	Suppress gastroesophageal reflux, alleviate heart burn

NANOPARTICLES

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm can be either spherical or vesicular. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. This general category can be divided into nanospheres, which consist of a polymeric matrix with drugs dispersed