INTRODUCTION AND OBJECTIVES OF THE INVESTIGATION

Controlled drug delivery is a topic of current interest in pharmacy and biotechnology. In recent years considerable attention has been focused on the development of controlled release drug delivery systems. Controlled release drug delivery systems are designed to release one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ. Drug release from these systems should be at a desired, predictable and reproducible rate. The primary objectives of controlled release drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Controlled release drug delivery systems have been designed for oral, parenteral, implantation and transdermal routes. Oral route is the most convenient and common mode of administration of controlled release systems. Controlled release systems for oral use include systems in the form of coated pellets, matrix tablets, microcapsules, poorly soluble drug complexes, ion exchange resin complexes, osmotic pumps etc. designed to release the drug over an extended period of time, either in a continuous manner (sustained release) or as a series of pulses (timed release).

Though oral controlled drug delivery is the most widely utilized route of administration it suffers with a major limitation of short residence time of the drug delivery system in the g.i.tract. Among the various approaches developed to prolong the residence time of the dosage form in the g.i.tract, the principle of mucoadhesion was very successful\(^1\). Mucoadhesion is a topic of current interest
in the design of drug delivery systems. Drug delivery systems formulated employing mucoadhesive polymers prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underlying absorption surface and thus contribute to improved or better bioavailability and therapeutic performance of drugs. Design of mucoadhesive tablets for oral controlled release is envisaged in the present investigation.

The major objective of the investigation is to design mucoadhesive tablets for oral controlled release of selected medicaments which require controlled release formulation and are having different physico-chemical properties and to develop technology for this type of new drug delivery systems.

Diltiazem is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has a short biological half-life of about 3.5 h and is rapidly eliminated. The oral bioavailability of diltiazem is 40% in humans. Because of its low bioavailability and short biological half-life, attempts have been made to develop sustained release products with extended clinical effects and a reduced dosing frequency. As diltiazem hydrochloride is a highly water-soluble drug, its formulation into SR products is rather difficult. There are a few reports on the formulation of oral controlled release products of diltiazem employing coated beads, pan coating, microencapsulation and complexation techniques.
Glipizide is widely used in the treatment of type II diabetes. It has a short biological half-life\(^1\) of 3.4±0.7 h. Because of its short biological half-life and problems associated with gastrointestinal disturbances attempts have been made to develop sustained release products with prolonged clinical efficacy, reduced side effects and dosing frequency. There are few reports on the formulation of oral controlled release products of glipizide by encapsulation\(^1\) and marumerizer\(^2\) techniques. A few sustained release formulations of glipizide (10 mg) are also available commercially.

Diclofenac is an effective analgesic and anti-inflammatory drug used mainly in the treatment of rheumatoid arthritis and other rheumatic disorders. It is used at a dose of 25 mg, three or four times a day. It has a short biological half-life\(^3\) of 2 h. It is reported\(^4, 5\) that the drug causes gastrointestinal disturbances, peptic ulcer and bleeding if present in larger concentration in the g.i. tract. Hence it would be advantageous to slow down its release in the g.i. tract not only to prolong its therapeutic action but also to minimize its g.i. side effects. Though several sustained release formulations of diclofenac are available presently in the market, their quality, particularly the release character, is not satisfactory\(^6\). Diclofenac release was complete with in 5-7 h from many commercial sustained release formulations.

Indomethacin is an effective analgesic and anti-inflammatory drug. It is used at a dose of 25-50 mg three or four times a day. Indomethacin has a short biological half-life\(^3\) of 2.4±0.4 h and also it causes gastrointestinal disturbances such as gastric irritation, abdominal pain, peptic ulceration in
g.i. tract. Hence it would be advantageous to slow down its release in the g.i. tract not only to prolong its therapeutic action but also to minimize its g.i. side effects.

The medicaments selected belong to different pharmacological categories and exhibit different physico-chemical properties. A physical property of importance in the design of controlled release products is drug solubility. Diclofenac sodium is an acidic drug with pH-dependent solubility and diltiazem hydrochloride is a basic drug soluble at both acidic and alkaline pHs. Glipizide and Indomethacin are poorly soluble in water and aqueous fluids.

Polymer used as release-retarding material plays a vital role in controlling drug delivery from controlled release systems. A wide range of polymeric materials have been employed as release-retardants. These polymers are broadly classified on the basis of their interaction with water into (i) non-biodegradable hydrophobic polymers (e.g., ethyl cellulose, cellulose acetate) (ii) hydrogel (e.g., crosslinked polyvinyl alcohol, polyhydroxy ethyl methyl acrylate), (iii) soluble polymers (e.g., hydroxypropyl methyl cellulose, polyethylene glycols, polyvinyl pyrrolidone) and (iv) biodegradable (e.g., polylactic acid, polyglycolic acid). Several polymers in the hydrogel and soluble category exhibit mucoadhesive property. Hydrophilic polymers which are reported to have mucoadhesive property are tried in the design of controlled release tablets. Hydroxypropyl methyl cellulose (HPMC, 50 and 500 cps), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (sodium
CMC), carbopol 934 P, polyvinyl pyrrolidone, (PVP) with and without other added excipients such as ethyl cellulose and mannitol were evaluated for their application in the design of oral controlled release products. The specific objectives of the investigation are as follows:

1. To design and evaluate mucoadhesive tablets of diltiazem, glipizide, diclofenac and indomethacin for oral controlled release.

2. To make a comparative evaluation of HPMC (50 cps and 500 cps), HPC, sodium CMC and carbopol 934 P for this application in the design of oral controlled release products.

3. To evaluate the kinetics and mechanisms of drug release from mucoadhesive tablets.

4. To evaluate the desired sustained release rate needed for the selected medicaments based on their pharmacokinetics.

5. To evaluate the release kinetics of commercial SR products of the selected drugs.

6. To evaluate the pharmacokinetics and Bioavailability of diclofenac from the mucoadhesive tablets designed for once a day administration.

7. To evaluate the stability of the drug release rates of the mucoadhesive tablets designed.

8. To evaluate the mucoadhesive property of the matrix tablets designed.
Extensive *in vitro* and *in vivo* experimentation has been done to fulfill the above objectives of the investigation and the studies carried out and the results obtained are described in the subsequent chapters.
REFERENCES


CHAPTER – I

LITERATURE REVIEW ON CONTROLLED RELEASE DRUG DELIVERY SYSTEMS
LITERATURE REVIEW ON

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

In recent years considerable attention has been focused on the development of new drug delivery systems known as controlled release drug delivery systems. Controlled release drug delivery systems\(^1\) are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate, predictable and reproducible.

Fig. 1: Shows plasma drug concentration profiles for conventional tablet or capsule formulation, a sustained releases formulation and a zero order controlled release formulation.
Advantages of controlled release drug delivery systems:

1. Improved patient convenience and compliance due to less frequent drug administration.

2. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.

3. Increased safety margin of high potency drugs due to better control of plasma levels.


5. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

Limitations of controlled release dosage forms:

1. Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH-dependent solubility, etc.

3. Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

4. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

5. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

ORAL CONTROLLED RELEASE SYSTEMS

Oral route has been the most popular and successfully used for controlled delivery of drugs because of (1) Convenience and ease of administration. (2) Greater flexibility in dosage form design (possible because of versatility of g.i. anatomy and physiology). (3) Ease of production (4) Low cost of such system.

In the exploration of oral controlled release drug administration, one encounters three areas of potential challenges.

(i) Development of a Drug Delivery System:

To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for a duration required for optimal treatment.

(ii) Modulation of g.i. Transit time:

To modulate the g.i. transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

(iii) Minimization of Hepatic first-pass Elimination:

If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.
The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified\textsuperscript{2-4} as follows.

I. Continuous Release Systems:

These systems release the drug for a prolonged period of time along the entire length of g.i.t (especially up to the terminal region of small intestine) with normal transit of the dosage form. The various systems under this category are

1. Dissolution controlled release systems.
2. Diffusion controlled release systems.
3. Dissolution and diffusion controlled release systems.
5. Slow dissolving salts and complexes.
6. pH dependent formulations.
7. Osmotic pressure controlled systems.
8. Hydrodynamic pressure controlled systems.

II. Delayed Transit and Continuous Release Systems:

These systems are designed to prolong their residence in the g.i.t along with their release. Often the dosage form is fabricated to retain in the stomach
and hence the drug present therein should be stable to gastric pH. Systems included in this category are:

1. Altered density systems.
2. Mucoadhesive systems.
3. Size-based systems.

III. Delayed Release Systems:

The design of such systems involves release of drug only at a specific site in the g.i.t. The drug contained in such a system are those that are:

1. Destroyed in the stomach or by intestinal enzymes.
2. Known to cause gastric distress
3. Absorbed from a specific intestinal site.
4. Meant to exert local effect at a specific g.i. site.

The two types of delayed release systems are:

1. Intestinal release systems.
2. Colonic release systems.

1. Dissolution Controlled Release Systems:

The drug present in such system may be the one:

1) With inherently slow dissolution rate.

e.g., Griseofulvin and Digoxin; such drugs act as natural prolonged release products.
2) That produce slow dissolving forms when it comes in contact with g.i. fluids e.g., Ferrous sulfate.

3) Having high aqueous solubility and dissolution rate e.g., Pentoxifylline. Drugs in this category present challenge in controlling their dissolution rate. The techniques employed are:

   a) Embedment in slowly dissolving or erodible matrix

   b) Encapsulation or coating with slowly dissolving or erodible substances.

a) **Matrix (or Monolith) Dissolution controlled Systems:**

   (i) Matrix systems are also called as Monoliths since the drug is and homogeneously dispersed throughout a rate-controlling medium. They are very common and employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, etc.

   (ii) These waxes, which control drug dissolution by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate.

   (iii) The wax embedded drug is generally prepared by dispersing the drug in molten wax and congealing and granulating the same. The drug release is often first-order from such matrices.
b) Encapsulation / Coating Dissolution Controlled Systems (Reservoir Devices):

In these systems drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes etc. The resulting pellets may be filled as such in hard gelatin capsules (spansules) or compressed into tablets.

The dissolution rate of coat depends upon the solubility & thickness of the coating, which may range from 1 to 200 microns.

2. Diffusion Controlled Release Systems:

i. In these types of systems, the rate-controlling step is not the dissolution rate but the diffusion of dissolved drug through a polymeric barrier.

ii. The drug release rate is never zero-order since diffusional path length increases with time as the insoluble matrix is gradually depleted of drug.

iii. The two types of diffusion controlled systems are

a) Matrix Diffusion Controlled Systems

b) Reservoir Devices (or) Laminated Matrix Devices
a) **Matrix Diffusion Controlled Systems:**

1) Here, the drug is dispersed in an insoluble matrix of rigid nonswellable hydrophobic materials or swellable hydrophilic substances.

2) Materials used for rigid matrix are insoluble plastics such as PVC and fatty materials like stearic acid, beeswax, etc. With plastic materials, and the drug is generally kneaded with the solution of PVC in an organic solvent and granulated.

3) Waxy matrix is prepared by dispersing the drug in molten fat followed by congealing. The granules are then compressed into tablets.

4) Swellable matrix – systems are popular for sustaining the release of highly water-soluble drugs. The materials for such matrices are generally hydrophilic gums and may be of natural origin (guar gum, tragacanth), semi synthetic (HPMC, CMC, xanthan gum) or synthetic (polyacrylamides.) The drug and the gum are granulated together with a solvent such as alcohol and compressed into tablets. The release of drug from such initially dehydrated hydrogels involves simultaneous absorption of water (resulting is hydration, gelling & swelling of gum) and desorption of drug via a swelling controlled diffusion mechanism. As the gum swells and the drug diffuses out of it, the swollen mass, devoid of drug appears transparent or glasslike and therefore the system is sometimes called as glassy hydrogel. The drug release follows Fickian
first-order diffusion under equilibrium conditions. However, during the swelling process, such an equilibrium may not exist and the diffusion may be non-Fickian or anomalous diffusion.

b) **Reservoir Devices (or Laminated Matrix Devices):**

These systems are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane. The polymer can be applied by coating or micro-encapsulation techniques.

The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are HPC, ethyl cellulose and polyvinyl acetate. A disadvantage of all such microencapsulated drug release systems is a chance of sudden drug dumping which is not common with matrix devices.

3. **Dissolution and Diffusion Controlled Release Systems:**

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which:

i) Permit entry of aqueous medium into the core and hence drug dissolution.

ii) Allow diffusion of dissolved drug out of the system.
E.g., Using a mixture of ethyl cellulose with PVP or methyl cellulose; the latter dissolves in water and creates pores in the insoluble ethyl cellulose membrane.

4. **Ion-Exchange Resin – Drug Complexes:**

Controlled delivery of ionizable acidic and basic drugs can be obtained by complexing them with insoluble nontoxic anion exchange and cation exchange resins respectively. The drug is released slowly by diffusion through the resin particle structure. E.g., A number of basic drugs like noscapine, phenyl-propanolamine and phentermine have been retarded by such an approach.

5. **Slow Dissolving Salts and Complexes:**

Salts or complexes of drugs, which are slowly soluble in g.i. fluids can be used for controlled release of the active principle.

Eg., Amine drugs can be reacted with tannic acid to form poorly soluble complexes that can be formulated as long acting tablets.

Eg.: Penicillin G has been complexed with N, N'- dibenzyl ethylene diamine to give benzathine penicillin G that can be formulated as oral suspension.
6. pH Independent Formulations:

Such systems are designed to eliminate the influence of changing g.i. pH on dissolution and absorption of drugs by formulating them with sufficient amount of buffering agents (salts of Phosphoric, citric or tartaric acids), that adjust the pH to the desired value as the dosage form passes along the g.i.t. and permit drug dissolution and release at a constant rate independent of g.i. pH. The dosage form containing drug and buffer is coated with a permeable substance that allows entry of aqueous medium but prevents dispersion of tablet.

7. Osmotic Pressure Controlled Systems:

An oral osmotic pump popularly called as oros works on the principle of osmotic pressure to release the drug at a constant zero-order rate. A core comprising of drug and an osmotically active substance (osmogen) such as potassium chloride or mannitol is surrounded by a rigid semipermeable membrane coating such as cellulose ester or cellulose ether having an orifice of 0.4 mm diameter produced by laser beam for drug exit. When exposed to g.i. fluids, water follows through the semipermeable membrane into the tablet due to osmotic pressure difference which dissolves the drug and pumps it out through the orifice by the osmotic force.

8. Hydrodynamic Pressure Controlled Systems:

The hydrodynamic pressure generated by swelling of a hydrophilic gum can also be used to activate the delivery of drugs. The device comprises of a
rigid, shape retaining housing enclosing a collapsible impermeable compartment containing liquid drug.

The space between the external housing and the drug compartment contains a layer of swellable, hydrophilic gum such as polyhydroxyalkyl methacrylate. In the g.i.t., the gum imbibes water through the opening present at the lower side of external housing and swells creating a hydrodynamic pressure. The pressure thus created squeezes the collapsible drug reservoir to release the medicament through the delivery orifice at zero-order rate. Such systems are also called as push-pull osmotic pumps.

II. **Delayed Transit and Continuous Release Systems:**

(1) **Altered Density Systems:**

The transit time of g.i. contents is usually less than 24 h. This is the major limiting factor in the design of oral controlled release formulations, which can reduce the frequency of dosing to a time period little more than the residence time of drug.

However if the residence time of drug in the stomach and/or intestine is prolonged in some way, the frequency of dosing can be further reduced. There are three ways by which this can be achieved. Altering the density of the drug particles, use of mucoadhesive polymers and altering the size of the dosage form.
Limitations of Oral Controlled Release Products:

1. Short residence time.

2. Lower bioavailability.

1. **Short Residence Time:** The transit time of g.i. contents usually less than 24 h. This is the major limiting factor in the design of oral controlled release formulations. There are new approaches to overcome the potential problems associated with oral drug administration.

Methods of Overcoming Limitations in Oral CR Products:

Delayed Transit and Continuous Release Systems:

These systems are designed to prolong their residence in the g.i.t. along with their release. Often, the dosage form is fabricated to retain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are:

1. Altered density systems

2. Mucoadhesive systems

3. Size-based systems

1. Altered density systems involves use of either high or low density pellets

i) **High Density Pellets:**

The density of g.i. fluids is around 1.4 g/cc. Use of drug pellets having density greater than this value. Preferably above 1.6 g/c.c. results
in prolonged g.i. residence that is unaffected by food. Iron oxide, titanium dioxide and barium sulfate have been used to increase the density of drug pellets. The drug is coated on the heavy core and then covered by a diffusion-controlled membrane.

ii) Low Density Pellets:

Also called as hydrodynamically balanced systems. Such pellets, having density less than that of g.i. fluids, float on the gastric juice for an extended period of time while slowly releasing the drug.

Globular shells such as that of poprice and celluloses have been used to lower the density of system. A swellable gum like HPMC can be used for a similar purpose.

iii) Floating or Buoyant Tablets / Capsules:

These can be formulated by granulating a drug with 20 to 80% of hydrogel such as HPMC, HEC, & HPC. On contact with G.I. fluids, the tablet swells and forms a diffusible gel barrier that lowers the density of system to less than one allowing it to float. Lipophilic polymers such as silicone elastomer can also be modified to have swelling properties. This is achieved by impregnating a water miscible liquid such as glycerol or a water-soluble salt such as sodium chloride in the lipophilic matrix. On contact with aqueous medium, the modified lipophilic polymer swells due to absorption of water by the hydrophilic additives in the matrix.
Alternatively, a gas filled flotation chamber can be attached to a membrane-coated tablet for making it buoyant.

2. **Mucoadhesive Systems:**

   A bioadhesive polymer such as cross-linked polyacrylic acid, when incorporated in a tablet, allows it to adhere to the gastric mucosa or epithelium. Such a system continuously releases a fraction of drug into the intestine over prolonged periods of time.

3. **Size-Based Systems:**

   Gastric emptying of a dosage form can be delayed in the fed state if its size is greater than 2 mm. Dosage form of size 2.5 cm or larger is often required to delay emptying long enough to allow once daily dosing. Such forms are however difficult to swallow.
MATRIX DEVICES

A matrix device as the name implies, consists of drug dispersed homogeneously throughout a polymer matrix as represented in Fig. 2.

In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and solid drug moving toward 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.

Fig. 2: Matrix diffusional system before drug release (time=0) and after partial drug release (time=1)

Derivation of the mathematical model to describe this system involves the following assumptions.

1. A pseudo-steady state is maintained during drug release.
2. The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

3. The bathing solution provides sink conditions at all times.

4. The diffusion coefficient of drug in the matrix remains constant (i.e. no change occurs in the characteristics of the polymer matrix).

The next equations, which describe the rate of release of drugs dispersed in an inert matrix system have been derived by Higuchi. The following equation can be written

\[
\frac{dm}{dh} = dC_0 \frac{dh}{C_0} - \frac{Cs}{2} \quad \text{.... (1)}
\]

where:

- \(dm\) = change in the amount of drug released per unit area.
- \(dh\) = change in the thickness of the Zone of matrix that has been depleted of drug.
- \(C_0\) = total amount of drug in a unit volume of the matrix.
- \(Cs\) = saturated concentration of the drug within the matrix.

From the diffusion theory:

\[
\frac{dm}{dh} = \frac{Dm Cs}{h} \quad \text{dt} \quad \text{.... (2)}
\]

where:

- \(Dm\) is the diffusion coefficient in the matrix.

Equating equations (1) and (2), integrating and solving for \(h\) gives

\[
M = [Cs Dm (2C_0 - Cs) t]^{1/2} \quad \text{.... (3)}
\]
When the amount of drug is in excess of the saturation concentration, that is

\[ C_0 > > C_s \]

\[ M = (2C_s D_m C_o t)^{1/2} \] \hspace{1cm} \ldots (4)

Which indicates that the amount of drug released is a function of the square root of time.

In a similar manner, the drug release from a porous or granular matrix can be described by

\[ M = [D_{s2} p / t (2c^o - p c^2)]^{1/2} \] \hspace{1cm} \ldots (5)

Where

\[ p \] = porosity of the matrix

\[ t \] = tortuosity

\[ C_2 \] = solubility of the drug in the release medium.

\[ C_s \] = diffusion coefficient in the release medium.

This system is slightly different from the previous matrix system. In that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly.

For purposes of data treatment, equation (4) or (5) can be reduced to

\[ M = K t^{1/2} \]

Where \( K \) is a constant
So that a plot of amount of drug release versus the square root of time will be linear, if the release of drug from the matrix is diffusion controlled. If this is the case, then, by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying the following parameters.

1. Initial concentration of drug in the matrix.
2. Porosity
3. Tortuosity
4. Polymer system forming the matrix and
5. Solubility of the drug.

**Advantages of Matrix System:**

Matrix system offers several advantages. They are, in general, easy to make and can be made to release high-molecular weight compounds. Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although, occasionally, cracking of the matrix material can cause unwanted release.

**Disadvantages:**

The primary disadvantages of this system are the remaining matrix "ghost" must be removed after the drug has been released. Also, the release rates generated are not zero-order, since the rate varies with the square root of time. A substantial sustained effect, however, can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.
TYPES OF MATRIX DEVICES

1. Matrix Diffusion Controlled Systems (Matrix Tablets):

Here the drug is dispersed in an insoluble matrix of rigid nonswellable hydrophobic materials or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as PVC, and fatty materials stearic acid, beeswax etc. With plastic materials the drug is generally kneaded with the solution of PVC in an organic solvent and granulated. Waxy matrix is prepared by dispersing the drug in molten fat followed by congealing. The granules are then compressed into tablets.

Swellable matrix systems are popular for sustaining release of highly water soluble drugs. The materials for such matrices are generally hydrophilic gums and may be of natural origin (guar gum, tragacanth). Semisynthetic (HPMC, CMC, xanthan gum) or synthetic (polyacryl amides). The drug and the gum are granulated together with a solvent such as alcohol and compressed into tablets. The release of drug from such initially dehydrated hydrogels involves simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug via a swelling controlled diffusion mechanism. As the gum swells and the drug diffuses out of it, the swollen mass, devoid of drug appears transparent or glasslike and therefore the system is sometimes called as glassy hydrogel. The drug release follows Fickian first-order diffusion under equilibrium conditions. However during the swelling
process, such an equilibrium may not exist and the diffusion may be non-Fickian or anomalous diffusion.

2. **Matrix Reservoir Devices (Microcapsules and Coated Beads)**

These systems are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane. The polymer can be applied by coating or micro-encapsulation techniques.

The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are HPC, ethyl cellulose and polyvinyl acetate. A disadvantage of all such microencapsulated drug release systems is a chance of sudden drug dumping which is not common with matrix devices.

**Characteristics of Drugs Suitable for Controlled Release:**

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the g.i. tract.
3. Administered in relatively small doses.
4. Possess a good margin of safety.
5. For the treatment of chronic therapy.

**Characteristics of Drugs Unsuitable for Controlled Release:**

1. Not effectively absorbed in the lower intestine (riboflavin)
2. Absorbed and excreted rapidly, short biological half lives, <1h (Penicillin G, furosemide).
3. Long biological half-lives > 12 h (diazepam, Phenytoin.)
4. Large doses required, 1g (sulfonamides).
5. Drugs with low therapeutic index (Phenobarbital, digoxin).
6. Precise dosage titrated to individuals required (anticoagulants, cardiac glycosides).
7. No clear advantage for sustained release formulation (griseofulvin).

Factors Influencing The Design and Performance of Controlled Release Products:

To establish criteria for the design of controlled release products, a number of variables must be considered.

1. Drug Properties:

The physicochemical properties of a drug, including stability, solubility, partitioning characteristics, charge and protein binding property, play a dominant role in the design and performance of controlled release systems.

2. Route of Drug Delivery:

The area of the body in which drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable controlled release mechanism or device. Performance of the controlled release systems may also be influenced by physiological constraints imposed by the particular route, such as first-pass metabolism, g.i. motility, blood supply, and sequestration of small foreign particles by the liver and spleen.
3. **Target Sites:**

In order to minimize unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue. This can be partially achieved by local administration or by the use of carriers.

4. **Acute or Chronic Therapy:**

Consideration of whether one expects to achieve cure or control of a condition and expected length of drug therapy are important factors in designing controlled release systems. Moreover, long term toxicity of rate controlled drug delivery systems is usually different from that of conventional dosage forms\(^7\).

5. **The Disease:**

Pathological changes during the course of a disease can play a significant role in the design of a suitable drug delivery system.

6. **The Patient:**

Whether the patient is ambulatory or bed ridden, young or old, obese or gaunt, etc., can influence the design of a controlled release product. For example, single unit controlled release products are particularly prone to intra and inter subject variation because of variability’s in individual g.i. motility\(^8\).

**Physicochemical Properties of A Drug Influencing Drug Product Design and Performance:**

The performance of a drug in its release pattern from the dosage form as well as in the body proper is a function of its properties. These properties can at times prohibit / restrict placement of the drug in a sustained / controlled
release form, restrict the route of drug administration, and significantly modify performance for one reason or another.

1. **Aqueous Solubility:**

   Since drugs must be in solution before they can be absorbed, compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undissolved drug particles and limited solubility at the absorption site. The choice of mechanism for oral controlled release systems is limited by aqueous solubility of the drug. Diffusion systems will be poor choices for slightly soluble drugs since the driving force for diffusion, the concentration in aqueous solution, will be low. Aqueous solubility also limits the loading efficiency of drugs into a variety of carriers such as liposomes, erythrocytes, and other microparticles.

2. **Partition Coefficient and Molecular Size:**

   Partition coefficient and molecular size influence not only the permeation of a drug across biological membranes, but also diffusion across or through a rate controlled membrane or matrix. The ability of a drug to diffuse through membranes, its so-called diffusivity, is related to its molecular size by the following equation.

   \[
   \log D = -S_v \log V + K_v = -S_M \log M + K_M
   \]

   Where \(D\) is diffusivity, \(M\) is molecular weight, \(V\) is molecular volume and \(S_v, S_M, K_v\) and \(K_M\) are constants in a particular system.
3. **Drug Stability:**

The stability of a drug in the environment to which it is exposed is another physicochemical factor to be considered in the design of controlled release systems. Drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine.

4. **Protein Binding:**

Blood proteins are for the most part recirculated and not eliminated; drug protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Quaternary ammonium compounds bind to mucin in the g.i. tract. Drugs bound to mucin may increase absorption, if the bound drug acts as a depot.

**Biological Factors Influencing the Design and Performance of Controlled Release Products:**

The design of controlled release product should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing. In the following discussion, it is assumed that the level of drug in blood or body tissue parallels biological activity of the drug.

1) **Absorption:**

To maintain constant blood or tissue level of drug, it must be uniformly released from the controlled release system and then uniformly absorbed. The fraction of drug absorbed from single non controlled dose or drug can
sometimes be quite low for a variety of reasons such as drug degradation due to
solvolysis or metabolism, binding of drugs to proteins, physical loss, or perhaps
site-or dose-dependent absorption. If the drug was erratically absorbed, as
might occur in a route of administration with variable absorptive surface, such
as the g.i. tract, design of a controlled release product would be more difficult
or prohibitive with respect to the oral route. It is well known that the absorptive
character of the different segments of the g.i. tract varies, which in turn can
influence the amount and rate of absorption of certain drugs.

2) Distribution:

The distribution of drugs into tissues can be an important factor in the
overall drug elimination kinetics since it not only lowers the concentration of
circulating drug but it also can be rate limiting in its equilibration with blood
and extra cellular fluids\textsuperscript{10}. In general, the bound portion of the drug can be
considered inactive and unable to cross membranes. At high binding, one sees
prolonged drug action. The apparent volume of distribution of a drug is
frequently used to describe the magnitude of distribution, including binding,
within the body. The total apparent volume of distribution for a drug at steady
state can be calculated from the following equation.

\[ V_{dss} = \left(\frac{K_{12} + K_{21}}{K_{21}}\right) V_b \]

Where \( V_{dss} \) is the apparent volume of distribution at steady state \( K_{12} \) is
the constant for the distribution of drug from the central to peripheral
compartment. \( K_{21} \) is from the peripheral to the central compartment \( V_b \) is the
volume of central compartment.
3) **Metabolism:**

Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active metabolite. Metabolic alteration of a drug can occur in a variety of tissues, some of which are richer in enzymes than others. For example, the organ most responsible for metabolism is the liver and thus the greatest metabolic conversion occurs after a drug has been absorbed into the general circulation. Clearly for optimal bioavailability, the route of drug administration may be dictated by the drug’s metabolic pattern. Metabolism of a drug will be reflected in the elimination constant of a drug or by the appearance of a metabolite. It is possible to incorporate this pharmacokinetic property into the design of controlled release product, provided that the rate and extent of metabolism are predictable and that the rate constant (s) for the process are not too large. Undoubtedly, complex metabolic patterns would make the design much more difficult, particularly when biological activity is wholly or partly due to a metabolite, as is the case in isosorbide 2,5-dinitrate.

4) **Duration of Action:**

The biological half-life and hence duration of action of a drug obviously play a major role in the process of considering a drug for controlled release. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns. Drugs with short half-lives require frequent dosing in order to minimize fluctuations in blood levels accompanying conventional oral dosage regimens. Therefore, controlled release dosage forms would appear very desirable for such drugs. Basic pharmacokinetic principles
suggest that for a given steady state drug concentration, the zero order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus, for a drug with a very short half-life, the desired rate of release will be quite large. This large rate of release in turn will lead to prohibitively large dose, so that the upper limit imposed on the size of the tablet, capsule or other dosage forms may be exceeded. The numerical value of biological half-life (four hours) was quoted to make a drug a good candidate for controlled release.

5. Side effects:

It is believed that for some drugs, the incidence of side effects is a function of plasma concentration. Theoretically, the incidence of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time, and hence controlled release formulations appear to offer a solution to this problem. The technique of controlled release has been more widely used to lower the incidence of g.i. side effects than that of systemic side effects and appears to produce more satisfactory results. It is postulated that by slowing the rate at which the drugs are released, the likelihood of g.i. irritation would be reduced due to a smaller amount of drug exposed to the g.i. mucosa at any given time.

6. Margin of Safety:

Decisions on margin of safety of a drug perhaps can be better made on the basis of its therapeutic index in combination with the range of plasma concentration within which the drug is considered to be therapeutically safe
and effective. This approach has been very valuable as a therapeutic guide in monitoring drug therapy. Especially for drugs with narrow therapeutic indices and a narrow range of therapeutic concentration, such as cardiac glycosides and antiarrhythmics. In designing controlled release systems for drugs with narrow therapeutic indices, it is imperative that the drug release pattern be precise so that the plasma concentration achieved is within the therapeutically safe and effective range.

7. **Total clearance (CL\textsubscript{T})**: 

The CL\textsubscript{T} is that the hypothetical volume of distribution of unmetabolised drug that is cleared per unit of time by any pathway of drug removal. The value of CL\textsubscript{T} can be determined from the dose administered (D), fraction of drug absorbed (F) and absolute bioavailability (AUC).

\[
CL_T = \frac{D \cdot F}{AUC}
\]

The CL\textsubscript{T} is the key to estimate the dose rate R\textsuperscript{0} for controlled release dosage forms and is related to the mean steady state concentration.

8. **Mean residence time (MRT)**:

The MRT is the mean time a drug molecule resides in the body, it is the time corresponding to 63.2% elimination from the body. It is calculated from AUC and AUMC i.e. the area under the first-movement curve\textsuperscript{11}.

9. **Dosage form index (DI)**:

DI is the ratio between the peak (C\textsubscript{ss max}) and trough (C\textsubscript{ss min}) values with in dosing intervals.
REFERENCES


