CHAPTER - 1

Sustained Release (SR) and Controlled Release (CR)

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Introduction, Basic Concept, Biopharmaceutical Classification System of Drugs, Classification of Sustained Release Products, Factors Influencing, Approaches for SR/CR Formulation, Mechanism of Drug Release From SR/CR Formulation

INTRODUCTION

Pharmaceutical products prepared for oral delivery of a drug which is of immediate release type. These are called conventional drug delivery systems. These are intended for maximum drug release and absorption. But these dosage forms suffer from some limitations such as:

- Frequent administration of drugs with short half-life is required, which can increase the chances of missing dose of drug leading to poor patient compliance.
- The plasma concentration-time profile obtained shows a typical peak-valley; thus, attainment of steady state condition becomes difficult.

To overcome the drawbacks of such conventional delivery systems of drug, various advancements have been made in techniques of preparing drug delivery systems, such as controlled or sustained release delivery systems of drug and multiple dosing could have been avoided in many cases.

Probably in 1938 Lipowski of Israel made a patent in sustained release dosage forms. Coated pallets were prepared for prolonging the release of drug and it was probably the first work for development of the coated particle approach to prepare sustained release tablet that was prepared in the early 1950s[1] by Howard Press, in Hoboken, NJ in his methodology patent were known as "Nitroglyn" which was manufactured under licence by Key Corp. in Florida.

Any delivery system of drug is developed to deliver a therapeutic dose of drugs to the desired location in the body in order to get rapid results and then maintain the desired drug concentration[2]. The novel drug delivery systems (NDDSs) have been developed over a period of time to improve patient

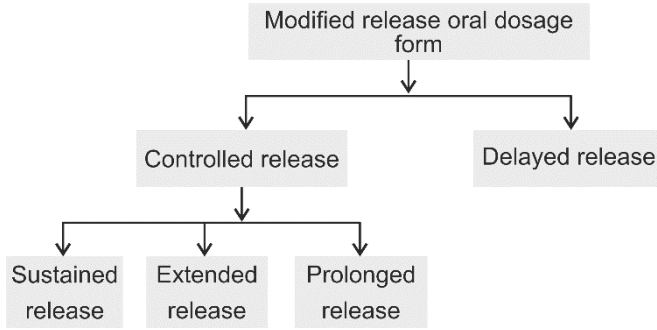
compliance and to optimize the dosage regimen without compromising the therapeutic efficacy. The sustained release dosage forms intended for oral administration have gained greater attention because of more flexibility in dosage form design[3]. Thus, the need for a sustained or controlled release formulation comes out of the following reasons:

- Due to undesirable properties of the drug, such as short biological half-life, local irritation, extensive metabolism, and narrow therapeutic index, etc.
- The nature of the disease state, or
- Patient compliance.

The most important among all these reasons is the need to improve the therapeutic efficacy of the drug and the safety of the patients. Before considering a drug for this type of formulation, the drug must be examined and evaluated for its physicochemical, pharmacokinetic and pharmaco-dynamic characteristics. Each property of a drug there is a range of values those are suitable for making a sustained or controlled-release dosage form. Outside the range, it is really difficult to design such dosage forms; sometimes, in the extreme, it becomes impossible. For example, extremes of aqueous solubility, oil/water partition coefficients, binding, extensive metabolism or degradation of the drug during movement from the site where it is delivered to the site where it is to work (target site), therapeutic index are some of the factors that limit the designing a successful sustained or controlled release product.

However, because of all these limiting factors, a sustained or controlled release product is designed. Theoretically, each of these limiting factors can be overcome by physical, chemical, biological and biomedical engineering methods alone or in combination for the successful design of sustained or controlled release delivery of drug.

The modified release oral dosage forms can be classified as shown below:



Such modified release formulations have been given different names for differences in their design.

- **Repeat action**

  In this type of dosage form, a dose of the drug is initially released just after administration, usually almost equivalent to a single dose of the drug. After a certain period, a second single dose is released[4].

- **Sustained release**

  This is a specific type of modified release dosage form which can reduce at least two-fold in the dosage frequency compared to conventional drug delivery system[5].

- **Controlled release**

  The dosage form in which the drug is released in a predictable manner but slower than conventional dosage form[6,7].

- **Delayed release dosage form**

  This is a specific type of modified release dosage form that releases the drug at a particular time, such as enteric coated tablet[8].

- **Extended release**

  Pharmaceutical dosage forms that release the drug slower than normal manner at a predetermined rate and necessarily reduce the dosage frequency by two folds[9].

- **Prolonged release system**

  These are designed to release the drug slowly and to provide a continuous supply of drugs over an extended period. These prevent very rapid absorption of the drug, which could result in extremely high peak plasma concentration of drug[10].

- **Timed release drug delivery system**

  Timed release drug delivery system is used to achieve the drug release after a lag time of about 4-5 hrs. For example, enteric coated dosage forms using cellulose acetate phthalate are designed to protect the drug from the acids in the stomach. A thick coat delays the drug release in the small intestine and thus, drug release is delayed. The time-controlled drug release maybe retarded up to 5 hrs. This targets the drug to the colon[11].

- **Site-specific release**

  These are designed and developed to target the drug directly to a certain biological location or site. In the case of site-specific release, the drug directly reaches a certain organ or tissue.

Objectives of oral sustained released dosage form

The objectives or purposes of the design and development of sustained release dosage forms intended for oral administration are:

- To maintain the drug concentration at a reasonably constant level for a considerable period.

- To minimize the frequency of doses administrated as compared to conventional dosage form
- To deliver a drug directly to site of action, minimizing or eliminating side effects.
- To deliver the drug directly to specific receptors or to localized cells or to specific areas of the body.
- The safety margins of potent drugs can be increased.
- To reduce both local and systemic adverse side effects in sensitive patient[12, 13].

BASIC CONCEPT

It is understood that duration of action of a drug is more related to the design of a controlled release dosage form. Duration of action is either less or not an inherent kinetic property of the drug molecule itself. Thus, it is necessary to understand the pharmacokinetic and pharmacodynamic properties of the drug molecule. Principal concept behind biopharmaceutical classification system (BCS) is that if two drug products produce the same concentration profile within the gastrointestinal (GI) tract, they should produce the same plasma concentration profile after oral administration. This concept can be summarized by applying the Fick's first law in the following equation

$$J = P_w C_w \qquad \text{.....(1.1)}$$

Where, J is the flux across the gut wall,

P_w is the permeability of the gut wall to the drug, and

C_w is the concentration profile at the gut wall

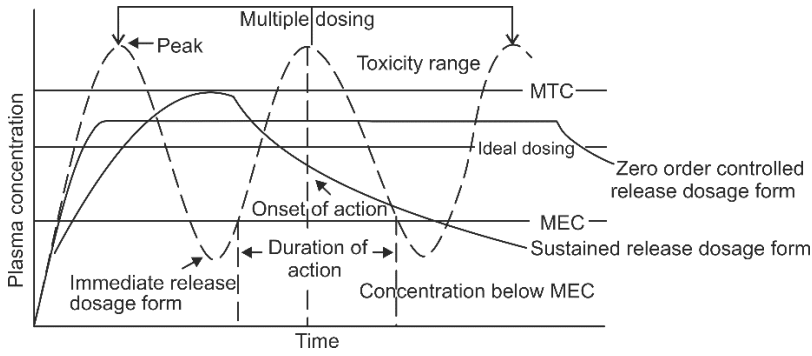


Fig.1.1 Plasma concentation-time profile of a drug.

In terms of bioequivalence, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent. Unless major changes are made to the formulation, dissolution data can be used as a substitute for pharmacokinetic data to demonstrate

bioequivalence of two drug products. This has been mentioned earlier that the basic purpose of developing sustained or controlled release dosage form are safety of the patient and improvement of therapeutic efficacy, and patient's compliance. In case of conventional dosage forms, the dose (D) and dosing interval (τ) can be varied as per therapeutic requirement. As shown in Figure 1.1 each drug has a specific therapeutic window, plasma concentration below the lower limit is not therapeutically effective and the concentration in plasma above the upper limit shows toxic side effects. Therapeutic window can be quantitatively expressed as therapeutic index (TI) can be defined as the ratio of LD_{50} (median lethal dose) to ED_{50} (median effective dose); it can also be defined as the ratio of maximum tolerable drug concentration in the blood (C_{max}) to the minimum concentration of drug in the blood (C_{min}) required to produce an acceptable therapeutic response;

$$\text{Therapeutic index, TI} = \frac{C_{max}}{C_{min}}$$

The drugs which dispose quite linearly, their one compartment characteristics can be expressed as;

$$t_{\frac{1}{2}} \frac{\ln TI}{\ln 2} > \tau$$

Where, $t_{\frac{1}{2}}$ is the half-life of the drug. Since the therapeutic index, TI of most of the drugs is almost 2 and it would necessary to administer the drug at an interval of less than the half-life of the drug. In fact, due to such frequent dosing patient compliance becomes a poor and inadequate treatment result. In general, the dosing interval can be increased either by modifying

(1) The drug molecule to decrease the rate of drug elimination (k_{el}), or

(2) The rate of release of the drug from the dosage form to decrease the rate of absorption (k_a) of the drug.

Both the concepts require to reduce the fluctuation in plasma concentration during multiple dosing, to extend the dosing interval without over-dosing or under-dosing.

The conventional dosage forms release the active ingredients atthe site of absorption immediately. This is demonstrated in the following simple kinetic scheme. The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka and Ke - the first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. For non-immediate release dosage forms, Kr<<<Ka; that is, the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follow the zero-order kinetics, as shown by the following equation:

$$Kr^{\circ} = \text{Rate of incoming of the drug} = \text{Rate of outgoing of the drug}$$

$$= Ke \times C_d \times V_d \quad \text{.....(1.2)}$$

Where,

$Kr°$ is the Zero-order rate constant for drug release-Amount/time

K_e is the First-order rate constant for overall drug elimination-time

C_d is the desired drug level in the body – Amount/volume

V_d is the Volume space in which the drug is distributed in litter

For selecting of the drug, several physicochemical and pharmacokinetic parameters are to be considered for formulation of sustained release dosage form shown in table 1. This mostly includes the knowledge on the absorption mechanism of the drug from the GI tract[14]. Sustained or zero-order drug release has been achieved by following classes of sustained drug delivery system[15].

Table 1.1 Physicochemical and pharmacokinetic parameters for drug selection.

Physicochemical Parameters	
Parameters	***Selection criteria***
Molecular size	>1000 Daltons
Aqueous solubility	More than 0.1mg/ml at pH 1 – 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from GI	Release does not depend on pH and enzyme
Pharmacokinetic Parameters	
Elimination half-life	$(t_{1/2})$2 – 8 hr
Absolute bioavailability	75% or more
Absorption rate constant (K_a)	Must be more than the rate of release
Apparent volume of distribution (V_d)	Larger V_d and MEC, larger would be the required dose
Total clearance	Independent of dose
Elimination rate constant	Depends on the design
Therapeutic concentration (Css)	Lower C_{ss} and smaller V_d, lower amount of drug required
Toxic concentration	Depends on MTC and MEC, safer dose is required

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM OF DRUGS

Based on aqueous solubility and based on aqueous solubility, and intestinal permeability drugs can be classified into four categories – class I, class II, class III, and class IV.

Class* I *drugs: *High Solubility and High Permeability*

The drugs in this class exhibit a high absorption number and a high dissolution number. Bioavailability anddissolution are very rapid. In other words, the drugs of this class have high solubility and high permeability. Bioavailability and bioequivalence studies are unnecessary for such product. These compounds are highly suitable for design of SR and CR formulations. Examples include Propranolol, Metoprolol, Diltiazem, Verapamil etc.

Class* II *drugs: *Low Solubility and High Permeability*

Drugs of this class have a high absorption number but a low dissolution number. Drugs put in class II category have low solubility but high permeability. This drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. For example, Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine, Felodipine, Nicardipine, Nisoldipine, etc

Class* III *drugs: *High Solubility and Low Permeability*

The drugs having high solubility and low permeability are classified as class III. Thus, permeability of these drugs is found to be rate limiting step for their absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability ratherthan the dosage form factors. These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement impermeability. For example, Acyclovir, Alendronate, Captopril, Enalapril, and Neomycin.

Class* IV *drugs: *Low Solubility and Low Permeability*

This class of drugs show poor and variable bioavailability because they have low solubility as well as low permeability. Several factors such asdissolution rate, permeability, and gastric emptying form the rate limiting steps for the drug absorption. These are not suitable for developing controlled release formulation. For example, Chlorothiazide, Furosemide, Tobramycin, Cefuroxime, etc

Difference between sustained release dosage form and conventional dosage form

Therapeutic efficacy and safety of drugs, administered by conventional dosage forms, can be improved by administering the drug through sustained release dosage forms. Therefore, there are differences between sustained release and conventional dosage forms in terms of drug release, therapeutic efficacy, and safety. The major differences are presented in table 1.2.

Table 1.2 Difference between sustained release dosage form and conventional dosage form[16].

Sustained release dosage forms	Conventional dosage form
The total dose of drug and frequency of dosing is reduced by SR dosage form and therefore, it improves the patient compliance and efficiency of a treatment.	Frequency of dosing is more in conventional dosage forms as a result, total amount of drug administered is large, but efficiency of the treatment is also poor.
The plasma concentration of the drug in blood is maintained at steady level and prolonged therapeutic action of the drug is achieved.	In multiple dosing of conventional dosage forms, the plasma concentration of the drug shows variations in blood; hence, prolonged action cannot be achieved.
By using matrix system SR tablet dosedumping can be avoided and toxicity due to overdose can be reduced.	In case of conventional dosage forms, probability of dose dumping is more due to fast release of drug and multiple dosing.
The overall cost of treatment is less because, the number of doses is less, but cost of production of single unit SR dosage formwould bemore due to requirement of costly processes and equipment.	In case of conventional dosage forms, the cost of production is less; but total cost of treatment would increase because of multiple dosing.
The *in-vitro* and *in-vivo* correlations are excellent as compared to the conventional dosage forms.	*In-vitro* and *in-vivo* correlation may be poor.

ADVANTAGES

- It can improve patient compliance and convenience[17].
- Reduces dosing frequency[18].
- Reduces fluctuations in circulating drug levels[19].
- It exerts uniform effect[20].
- Total amount of drug required is less[21].

- It can minimize or eliminate local side effects[22].
- It can minimize or eliminate systemic side effects.
- It can minimize accumulation of drug with chronic dosing[23].
- It obtains less potentiating or reduction in drug activity on chronic use.
- Safety margin of potent drug can be increased by excellent designing the formulation[24].

DISADVANTAGES

- It requires immediate change during the therapy or if any significant adverse effect is noted and immediate termination of therapy is required, sustained release does not permit immediate termination of therapy[25].
- These require more costly process and equipment for manufacturing of the sustained release drug delivery systems (SRDDSs).
- There is less flexibility in adjusting the dosage regimen since the dose is fixed during designing of the dosage form.
- Risk of dose dumping may be there, because the SRDDS contains a drug amounting 3-4 times more than the conventional dosage form. Sometimes this large quantity of drug may get rapidly released and causes toxicity.
- It reduces the absorption of drug that may delays the onset of action. The effect of food can influence the absorption of drug.
- Kinetics may differ markedly from one SR formulations to another.
- SRDDS cannot be formulated with the drug that can be absorbed at specific time in the GIT.
- It can increase the potential for first pass clearance.
- For oral SRDDS, effective drug release is influenced and limited by GI residence time.
- SRDDSs are designed for normal population that is based on the biological half-lives. Since, the disease state alters the drug dispositions as well as inter-patient variability in pharmacokinetic parameters is not accommodated.
- Drugs which are acted upon by enzymes in intestine undergo significant enzymatic breakdown as the drug remains in the body for longer time.
- In case of accidental failure of the product, the effective antidote may be difficult to be used.

CLASSIFICATION OF SUSTAINED RELEASE PRODUCTS

➢ Based on the mechanism of controlling the drug release, the SRs are classified as follows:

1. Chemically controlled systems

2. Biodegradable system
3. Drug polymer conjugates
4. Diffusion-controlled systems
5. Matrix diffusion
6. Polymer erosion
7. Polymer swelling
8. Geometry

Based on drug release from the SRDF is as follows:

(a) Continuous release system: this includes.
   i. Dissolution controlled release systems.
   ii. Diffusion-controlled release systems
   iii. Dissolution and diffusion-controlled release systems
   iv. Ion exchange resin drug complex
   v. Slow dissolving salts and complexes
   vi. pH dependent formulations
   vii. Osmotic pressure-controlled systems
   viii. Hydrodynamic pressure-controlled systems

(b) Delayed transit and continuous release systems
   i. Altered density systems
   ii. Mucoadhesive systems
   iii. Size based systems

(c) Delayed release systems
   i. Intestinal release systems
   ii. Colonic release systems.

FACTORS INFLUENCING

There are number of criteria that must be considered for designing and developing sustained or controlled release dosage forms. The important factors that can influence the rate of release of drug from a sustained release drug delivery system can be classified into two categories:

1) Physicochemical, and
2) Biological

Physicochemical Properties of Drug

These include stability, solubility, partition coefficient, charge, protein binding. All these properties play important role in the design and performance of a sustained or controlled release dosage forms.

1) Aqueous solubility
2) Partition coefficient ($P_{o/w}$)
3) Drug pKa and ionization at physiological pH
4) Drug stability
5) Molecular weight and diffusivity
6) Protein binding
7) Dose size.

1) ***Aqueous solubility***

For absorption, a drug must be present in solution state at the site of absorption. Thus, the drugs having low aqueous solubility and poorly absorbed after oral administration due to less transit time of the undissolved drug in the gastrointestinal tract. This is most surprising that the site of the gastrointestinal tract where the drug is least soluble is its site of absorption. For example, solubility of tetracycline is more in stomach than in intestine, and intestine is the major site of absorption for tetracycline. Such drugs are not suitable for making their SR/CR dosage form. However, such a drug becomes suitable for making SR/CR formulation, if the system can retain the drug in the stomach and gradually release it to the small intestine; or if the solubility of the drug is modified in such a way that the solubility is independent of the external environment (acidic pH) but the drug is gradually released in the intestine.

Since most of the drugs are either weak acids or weak bases; it would be difficult to prepare SR forms of drugs having very low water solubility or greater solubility. Because a drug having greater water solubility and rapid dissolution rate, it is quite difficult to retard its rate of dissolution. A drug with greater water solubility can readily dissolve in water or in gastro-intestinal fluid and its dosage form tends to release the drug from its dosage form at a faster rate. Thus, the drug is absorbed quickly resulting a sharp increase ofits concentration in the blood compared to less soluble drug. Hence, it becomes difficult to incorporate a highly water-soluble drug in the dosage form and retard the drug release, particularly when the dose is high. The pH-dependent solubility, chiefly in the physiological pH range, would be another problem for making SR formulation. Thus, water-solubility of a drug appears as an obstacle and if 10 mg of drug solubilizes perml of water presents difficulties in solubilization of dosage form. In general, highly soluble drugs are undesirable for formulation into an SR product[26].

The most observed that a drug is released from its oral sustained/controlled release dosage form following its aqueous solubility. The delivery systems which follow diffusion mechanism fails to work satisfactorily if it contains a poorly soluble drug; because the driving force for diffusion is the concentration of drug in solution is low. In such cases, bioavailability of the drug would not be consistent and complete. The absorption/ bioavailability of drug shall be dissolution rate limited. If such drugs are formulated as matrix systems, these work satisfactorily.

Therefore, the aqueous solubility of a drug must be considered when suitable polymer is being selected for making SR/CR dosage form by coating. Some antibiotics and drugs of high molecular weight have reasonably good to excellent aqueous solubility, but their dissolution rate is not good. Their slow dissolution rate can be utilized while making their SR/CR dosage form by incorporating the drug in a suitable matrix system.

Moreover, aqueous solubility may become a constraint for efficient drug-loading into various carriers such as liposomes, erythrocytes, and other microparticles. Most observed that many of the water-soluble drugs leak out from such carriers.

2) *Partition coefficient* ($P_{O/W}$)

The partition coefficient is defined as the ratio of the drug soluble in an oil phase to the drug soluble in an adjacent aqueous phase. Permeation of the drug across the biological membranes depends not only on the partition coefficient, but also on the diffusion across the rate controlling membrane when a drug is administered. When the drug is eliminated from the body; it must diffuse through a variety of biological membranes that primarily act as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes; that are its membrane permeability. Its apparent oil and water partition coefficient can be defined as;

$$K = \frac{C_o}{C_w} \qquad \text{.....(1.3)}$$

Where,

K is the partition coefficient,

C_o = Equilibrium concentration of all forms of the drug in an organic phase at equilibrium,

C_w = Equilibrium concentration of all forms in an aqueous phase.

In general, the drugs with an extremely large value of K are very oil soluble and will partition into the membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug is generally defined by

the Hansch correlation, which indicates a parabolic relationship between the logarithms of its partition coefficient as shown in Figure 1. 2[27, 28].

The ability of a drug to diffuse through a membrane (diffusivity) depends on the molecular size of the drug. The relation between the diffusivity and molecular size of a drug can be expressed as;

$$\text{Log } D = -s_V \log V + k_V = -s_M \log M + k_M \quad \text{.....(1.4)}$$

Where,

D = the diffusivity of the drug,

M = molecular weight of the drug,

V = molecular volume of the drug, and

s_V, s_M, k_V and k_M = constants in a particular medium.

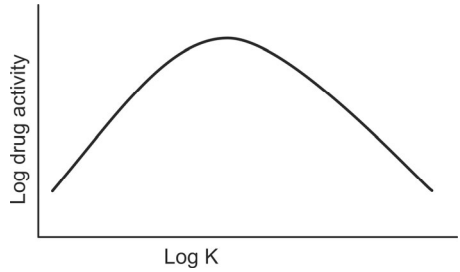


Fig.1.2 Relation between drug action and partition co-efficient.

3) *Drug pKa and ionization at physiological pH*

Drugs which are primarily present in an ionized form are poor candidates for oral SR drug delivery system. Usually, the drugs are well absorbed in their unionized forms; whereas permeation of ionized drug is negligible because the absorption rate of the ionizeddrug is 3-4 times less than that of the unionized drug. The pKa-range for an acidic drug whose ionization is pH sensitive is within 3.0 - 7.5; similarly, the pKa-range for a basic drug whose ionization is pH sensitive is within 7.0-11.0 are ideal for optimum positive absorption. In fact, the drug should remain in unionized form at the site of absorption to an extent 0.1-5.0%[29].

4) *Drug stability*

The stability of a drug in the environment it is placed is another important factor to be considered during development of its sustained/controlled release dosage form. For example, when a drug product is administered orally, gastric and intestinal pH and contents become its environment. A drug hydrolyses both in acid or base medium and drugs also undergo enzymatic degradation when administered orally. Drugs that are unstable in gastric pH can be formulated as slow-release dosage form and the release of drug can be delayed until the dosage form reaches the intestine. Drugs that undergo metabolism in the gut wall and show instability in the small intestine are not suitable for SR system and this could be realized by examining their bioavailability. Their bioavailability will be decreased. However, if the drug is modified chemically to form prodrug, having different physicochemical properties can be administered through different

route of administration[30]. For example, controlled release nitroglycerine. On the other hand, if the drug is metabolized by the enzymes present at the site of administration or along the pathway of the drug, this can be utilized for formulating controlled/sustained release dosage form of the drug for example, prodrug.

5) ***Molecular weight and diffusivity***

Diffusion as such is a concentration gradient phenomenon. Drug diffusivity is the ability of a drug to diffuse through the membrane. Diffusivity depends on size and shape of the cavities of the membrane. The diffusion co-efficient of intermediate drug molecular weight is around 100 – 400 Daltons; through flexible polymer range is 10^{-6}–10^{-9} cm^2/second. Molecular size or weight is indirectly proportional to the diffusibility. Drugs with larger molecular size are not preferred candidate for oral SR system.

6) ***Protein binding***

Protein binding of drugs is a known phenomenon to all. Many drugs bind to plasma proteins and can influence the duration of drug action. The proteins are re-circulated in the blood and not eliminated. If the drug binds with the protein up to a reasonably high degree, the drug-protein complex can be usedas the depot and for prolonged releases of the drug. The literature review suggests this approach. The rate and extent of oral absorption can be influenced if the drug interacts and binds with mucin-like protein[31, 32]. There are other drug-protein interactions that exert effects on the performance of the drug. In 1961, R.R. Levine investigated this and demonstrated that quaternary ammonium compounds bind with mucin present in GI tract. If the bound drug acts as a depot, absorption of the drug will increase. If the drug undergoes degradation and/or washing at the further lower part of the GI tract, binding of the drug to mucin may result in a reduction of availability of free drug for absorption.

7) ***Dose size***

There is an optimum limit of bulk size for the dose that can be given. This is applicable to the formulations intended for oral administration. Usually, a single dose containing 0.5 – 1.0g of drug is considered as maximum strength for a conventional dosage form. This is equally applicable for the sustained-release dose formulations. The drugs that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. In this case, the margin of safety is a point of concern particularly when the drug possesses narrow therapeutic range which is involved in the administration of large amounts of a drug[23].

Biological Properties of Drug

The design of a controlled or sustained release drug-product should be based on complete information about the disposition of the drug. This involves complete characterization and examination of absorption, distribution, metabolism, and elimination (ADME) of the drug following multiple dosing. But most unfortunately, this is available. In general, decisions on the design are taken because of incomplete information. For design of a controlled or sustained release drug-product depends on every pharmacokinetic property and biological response-parameter. The biological factors generally influence the design of a SR/CR dosage forms are:

1) Absorption
2) Distribution
3) Metabolisms
4) Biological half-life/duration of action
5) Margin of safety/therapeutic index
6) Side effect
7) Disease state
8) Route of administration
9) Target sites
10) Acute or chronic therapy
11) Patient

1) Absorption

Almost constant concentration of drug in blood or tissue can be maintained from the orally administered SR dosage form when uniform amount of the drug is released at a consistent rate and equivalent amount of the drug is absorbed. It is desirable that the amount of drug released must be absorbed. In fact, delivery of the drug from a sustained/controlled release system depends on the rate at which the drug is released from dosage form (rate-limiting step). It is expected that the drug once released would be absorbed immediately. But it is not always true, variation in rate and extent of drug absorbed occur commonly, particularly if the dosage form is administered orally. The quality of the sustained release dosage form would be considered as desirable when it could release the drug at predetermined rate and the drug released is completely absorbed. Generally, the release of the drug from the dosage form is the rate limiting step, the rate of drug-absorption (Ka) depends on the rate of release (Kr); that is, $Kr << Ka$. If the transit time of dosage forms in the absorptive areas of GI tract is assumed to be about 8-12 hr, the maximum half-life for absorption should be approximately 3-4 hrs. The drugs with lower absorption rate constants are poor candidates for making SR dosage form. The possible reasons for the lower rate of absorption are

- Poor water solubility,
- Small partition co-efficient,
- Protein binding,
- Acid hydrolysis, and
- Metabolism or site specific or dose-dependent absorption.

Drugs having the high apparent volume of distribution can influence the rate of elimination of the drugs. Such drugs are poor candidates for oral SR drug delivery systems. Similarly, a drug which capable of inducing metabolism, metabolized at the site of absorption is not suitable for SR drug delivery system. A drug capable of inducing first-pass effect is also a poor candidate for SR delivery, as it could be difficult to maintain constant blood level. Drugs that are metabolized before absorption, either in the lumen or in the tissues of the intestine, indicate decreased bioavailability from the sustained release systems[23].

The fraction of the traditional dose of a drug absorbed from a single dose administered orally may be found sometimes quite low due to various reasons such as degradation of drug due to solvolysis, metabolism, binding of drugs with proteins, physical loss, etc. It has been stated earlier that the drug should be completely absorbed, but complete absorption of drug is not essential. Solution of this type of problem can be best explained by development of a controlled release ocular drug delivery system (ocusert). Pilocarpine administered through ocular route is absorbed across the cornea only up to 1% of the delivered dose. The huge loss of drug is mainly due to drainage and absorption of drug into non-target tissues. This low bioavailability problem of the drug can be solved by developing a controlled release formulation and a constant level of drug concentration in target tissues can be maintained for extended period of time.

Significant loss of drug after oral administration occurs mainly due to (1) hydrolytic degradation of the drug in the contents of GI tract, (2) metabolism by intestinal flora, and (3) metabolism during its transit across the GI wall. For all routes of administration, metabolism at the site of administration like hydrolytic degradation is a major problem. However, in all the routes, the quantities of metabolizing enzymes are not same; for example, more in the GI tract and few in precorneal portion of the eye. Both hydrolytic and metabolic degradations are first order reactions with respect to concentration. It is to know that drug only in dissolved state is susceptible to hydrolytic degradation; thus, solid drug or drug present in solid dosage forms is not hydrolytically degraded.

When the drug is absorbed erratically, such as the GI tract, it becomes difficult to design a controlled release product. In case of oral route, different segments of the GI tract have different absorptive properties. Thus, these

segments can influence the rate and extent of absorption of some drugs from GI tract. For example, the rate and extent of absorption of drugs such as dicumarol, and aminoglycosides such as gentamicin, kanamycins are different in different segments of GI tract. Dicumarol, quaternary ammonium compounds such as hexamethonium and decamethonium is an oral anti-coagulant drug. Similarly, there are some drugs which are absorbed in GI tract either by specialized transport mechanism or at special sites of the GI tract. These drugs are not suitable candidate for developing sustained or controlled release dosage form. For example, riboflavin is absorbed by an active transport process and preferentially absorbed at the upper part of the GI tract. However, riboflavin has been formulated in various sustained release multivitamin formulations.

Iron is another drug which is not uniformly absorbed throughout the length of the GI tract. At the upper part of the duodenum, relatively greater absorption of iron takes place, while the lower end of the duodenum has the lower absorptive capacity.

2) Distribution

The distribution of drug molecules into the tissues and cells is one of the primary factors particularly in drug elimination kinetics. The concentration of drug circulating within the system is reduced by this process; simultaneously, the elimination process can also become rate limiting in the attainment of equilibrium drug-concentration with blood and extravascular tissue. The drug-distribution within the body depends on the extent of binding of the drug to the tissues and plasma proteins. The drug molecules bound with proteins are considered as inactive and cannot permeate biological membranes, but a high degree of protein binding can prolong the therapeutic action. In fact, the apparent volume of distribution is one of the important parameters of the drug that can explain the magnitude of distribution as well as the extent of protein binding within the body. The apparent volume of distribution is a proportionality constant of the plasma concentration of the drug to the total drug amount within the body. The driving force behind the rate processes is concentration of the drug, not the amount and it is the quantity which is of interest. Therefore, to design a sustain release formulation, the information about the disposition of drug is very necessary[32]. Interpretation of apparent volume of distribution is difficult not only in one-compartment kinetic system but in multi-compartment kinetics it is more difficult to interpret. Since, definite studies cannot be conducted, it is considered as the proportionality constant or *fudge factor* rather than a specific physiological parameter. Thus, depending on the time course of drug disposition, apparent volume of distribution can accept different values. However, the numerical values of apparent volume of distribution should be carefully interpreted.

The complete information or as much information about drug disposition as possible should be collected before designing a controlled/sustained release formulation; because in most cases, decisions are taken based on the information about apparent volume of distribution. The apparent volume of distribution can influence the concentration and the amount of drug either in circulating blood or in target tissues. It can influence the elimination kinetics of a drug. But the extent of influence cannot be predicted because it is not possible to interpret the apparent volume of distribution completely.

At steady state the total apparent volume of distribution for a drug can be calculated by using the following equations;

$$V_d^{ss} = [(k_{12} + k_{21})/k_{21}]\ Vp \quad \text{.....(1.5)}$$

$$V_d^{extrap} = [(\alpha - \beta)/k_{21} - \beta)]\ Vp \quad \text{.....(1.6)}$$

$$V_d^{area} = V_d^{ss} + [k_{el} - \beta)/k_{21}]\ Vp \quad \text{.....(1.7)}$$

Where,

V_d^{ss} = apparent volume of distribution at steady state,

V_d^{extrap} = apparent volume of distribution, obtained from extrapolation method,

V_d^{area} = apparent volume of distribution, obtained by area method.

V_p = volume of central compartment,

α = fast disposition constant,

β = slow disposition constant,

k_{el} = elimination rate constant (from central compartment),

k_{12} = first order drug distribution constant from central to peripheral compartment,

k_{21} = first order drug distribution constant from peripheral to central compartment.

This has been found that among V_d^{ss}, V_d^{extrap}, and V_d^{area}, the value of V_d^{ss} gives almost correct estimate.

To avoid ambiguity in apparent volume of distribution, it would be better to use T/P ratio as explained below for calculation of the amount of drug in central (P) and peripheral compartments (T) at steady state. If the value of P is known, the value of T can be calculated as indicated below (eqn.1.7);

$$\frac{T}{P} = \frac{k_{12}}{(k_{21} - \beta)} \quad \text{.....(1.8)}$$

It is to be noted that the physical state of the drug (such as the extent of binding) cannot be said from the T/P ratio. The distribution characteristics of a drug can be described by the volume of distribution at steady state and the

T/P ratio. The basic difference between these two parameters: the V_d^{ss} indicates the extent of drug distribution in the body, while T/P ratio indicates the relative distribution of drug between compartments. Prediction of the value of $V_d^{ss}$from T/P ratio and vice versa is not possible. Table 1.3 below shows the values of T/P and V_d^{ss}. This indicates that the two parameters behave independently.

Table 1.3 The values of T/P and V_d^{ss} for some drugs.

Drug	T/P	V_d^{ss} litres	Drug	T/P	V_d^{ss} litres
Amoxicillin	1.04	22	Furosemide	0.96	5
Diazepam	2.85	130	Pentobarbital	1.30	63
Procainamide	14.35	62	Trimethoprim	1.24	12
Tolbutamide	0.27	24	Theophylline	0.97	40
Digoxin	4.31	500	Meperidine	2.04	289

The total body clearance at steady state can be calculated as follows (eqn.1.8):

$$\text{Total body clearance at steady state} = V_d^{ss} \left(0.693 / t_{1/2,\beta}\right) \quad \text{.....(1.9)}$$

Recently, it is recognized that disposition of many drugs follows multi-compartment kinetics; but dose calculation is based primarily on one-compartment kinetics. For a given therapeutic concentration of drug, the dose would be similar for drugs with similar volume of distribution. This assumption is found true only when the relative distribution of the two drugs between compartments is similar. The error which may be reduced by incorporating T/P ratio into sustaining dose considerations for drugs exhibiting multicompartment kinetics.

Finally, this can be said that the parameters, T/P ratio and volume of distribution at steady state, provides the insight aspect of drug disposition.

3) Metabolisms

Metabolism of the drug includes either of the two processes – (1) transformation of active form of drug to its inactive form, (2) conversion of an inactive drug to an active metabolite.

Metabolism of the drug takes place in various tissues containing enzymes. Drugs that are significantly metabolized before absorption are either metabolized in the lumen or inthe tissue of the intestine. As a result, the bioavailability of such drugs is reduced from slower-releasing dosage forms. Most of theenzyme-systems present in the intestinal wall are saturable. If the drug is released at a slower rate at these regions, lesser amount of total drug is

exposed to the enzymatic process during a specific time-period; as a result, relatively more complete conversion of the drug to its metabolites occurs. A better and practical solution to such problem is formulating prodrugs of these enzyme-susceptible compounds. There are some drugs that can either induce or inhibit the enzyme synthesis. These types of drugs are the poor candidates for making SR delivery system because it is difficult to maintain their uniform blood levels. Drugs having variation in bioavailability due to the first-pass effect or intestinal metabolism are not suitable for making SR drug delivery system[30]. When the biological activity of a drug is partly or completely due to a metabolite, the design of SR/CR dosage form becomes more difficult; for example, isosorbide 2, and 5-dinitrate. There are two areas of metabolism that restrict the design of SR/CR dosage form – (1) if a drug induces or inhibits the synthesis of enzymes during its use for a prolonged period, the drug is not suitable for designing of SR/CR dosage form because it becomes difficult to maintain a uniform plasma concentration of the drug, (2) if due to intestinal metabolism or -first-pass effect, the plasma concentration of a drug becomes widely fluctuating, the design of a SR/CR dosage form becomes difficult. Depending on the size (amount) the fraction of the dose would be lost. As a result, the bioavailability of the drug would be reduced significantly, provided the drug is released from its dosage form slowly. For example, hydralazine is metabolized at the intestinal wall and/or the liver during absorption. However, hydralazine is well absorbed. On the other hand, bromocriptine is incompletely absorbed. Its ultimate bioavailability is only 6% due to first pass metabolism at the liver. Similarly, only about 25% of the oral dose of levodopa is absorbed, the loss of drug is mainlydue to first-pass metabolism in the liver and metabolism by gut microbial flora. In fact, studies showed that sustained release dosage form of levodopa is not better than its standard dosage form. Another study showed that about 41% of the oral dose of propoxyphene can reach the systemic circulation due to first-pass effect, if the drug is completely released, absorbed, and not metabolized during its transportation through intestinal wall. The study also showed that the bioavailability of the drug depends on the dose administered. Salicylamide also demonstrated its dose-dependent bioavailability. The drug is metabolized when it passes through the intestinal wall. Maximum of about 60% of the orally administered dose can be observed in blood as glucuronide form, provided the dose is small. The most interesting observation lies with nitroglycerin. Nitroglycerin has been commonlyadministered as sublingual tablet. The purpose of the study was to assess the effectiveness of the oral route of administration as opposed to the sublingual route. The usually the logic in support of the sublingual route was that nitroglycerin is extensively metabolized during its first pass through the liver. In fact, oral doses of 2 mg of nitroglycerin given 4 times a day failed to produce any observable effect in angina pectoris. Other indicated that nitroglycerin was absorbed sufficiently from GI tract to bring about peripheral vasodilatation.

Based on the above discussion, it can not be accepted that it is possible to formulate the controlled release systems for drugs which are extensively metabolized if the rate of metabolism is not too much high nor does the metabolism vary with the oral and other routes. It is logical to accept that a controlled release product can be preparedtill the metabolism remains predictable.

4) Biological half-life/duration of action

The objective of developing an oral sustained-release product is to maintain a constant therapeutic blood levels over an extended period. The duration of action of a drug significantly influences the design of oral SR delivery system. It depends on the biological half-life. The factors influencing the biological half-life of a drug include its

- Elimination,
- Metabolism, and
- Distribution patterns.

To minimize fluctuations in the blood levels, drugs having short half-lives are to be administered frequently. With such drugs, it is desirable to prepare SR dosage forms. For a given steady state plasma-drug concentration, it is necessary that the zero-order rate of release of a drug from its dosage form should be directly proportional to its rate of elimination. Thus, faster rate of release is required for drug having very short half-life, for a moderate duration of time, while the dosage form requires large dosage. Generally, drugs with half-lives less than 2 hr are not good candidates for making sustained-release preparations. Again, drugs having long half-lives, more than 8 hr, are also not suitable for making sustained release dosage forms, because theireffect is already sustained[30].

It should be noted that the duration of action of many drugs, such as monoamine oxidase inhibitors[33] and corticosteroids[34], is longer than that suggested by their biological half-lives. However, corticosteroid for its anti-inflammatory effects is being administered on alternate day which is not related to its biological half-life. Thus, from the standpoint of therapy, it would be justified to say that Sustained release formulation of corticosteroids is not necessary. In fact, sustained release formulation of prednisolone sodium phosphate and methylprednisolone has been found equally effective as their conventional tablets[35]. However, the numerical value of biological half-life which makes a drug a good candidate for controlled release has not been established. In 1961, K.R. Heimlich and his colleagues quoted a value of about 4 hr so that for a drug with such a half-life, the ratio of sustaining dose to immediate release dose becomes approximately 2 if the duration of action of sustained release drug is 12 hr. To extend the release of the drug, having biological half-life of about 4 hr, up to 12 hr, about 1 g of the drug should be the controlled release dose with immediate release dose is of 325 mg.

Sustained release formulations of procainamide are available in the market and have been shown to be capable of either maintaining therapeutic plasma level or minimizing the fluctuations in plasma level over a period of 8-hr. On considering the above discussion, this can be said that a duration of release is extended to 6, 8, or 12 hr for a drug with half-lives between 4 and 6 hr and whose minimum effective dose ranges from 125 mg to 325 mg will enforce little problem as dose size is concerned.

It should be noted that the duration of action of many drugs, such as monoamine oxidase inhibitors and corticosteroids, is longer than that suggested by their biological half-lives. The anti-inflammatory effects of corticosteroids have been considered as the basis for alternate-day dosing schedule and this is not related to the biological half-life. The advantage of this dosage regimen is that it can minimize the adrenal suppression side effects sometimes associated with chronic corticosteroid therapy. Thus, making of sustained release corticosteroid preparation is not justified. In fact, sustained release formulations of prednisolone sodium phosphate and methyl prednisolone have been found to be equally effective as traditional tablets, no benefit is found over the latter.

Similarly, there is hardly any advantage of making sustained release formulations of drugs having long biological half-lives. It has been stated that if there are no appreciable differences in effectiveness when a drug is given as a single large dose per day or in several smaller doses throughout the day, the therapeutic need for a prolonged action dosage form would be doubtful; for example, phenylbutazone is such a drug. The table 4 shows the biological half-lives of various drugs.

Table 1.4 Half-lives of some common drugs.

Drug	Half-life	Drug	Half-life
Ampicillin	1.67 hr	Methylprednisolone	3.3 hr
Cephalexin	0.9 hr	Prednisolone	1.0 hr
Cloxacillin	1.5 hr	Diazepam	20 hr
Furosemide	0.491 hr	Phenytoin	22 hr
Levodopa	0.75 hr	Warfarin	52 hr
Penicillin G	0.75 hr	Meprobamate	11.3 hr
Propylthiouracil	1.05 hr	Guanethidine	9 – 10 days

5) Margin of safety/therapeutic index

Margin of safety of a drug can be described by considering therapeutic index, which is the ratio of median toxic dose and median effective dose.

$$\text{Therapeutic index} = \frac{\text{Median Lethal/Toxic Dose}}{\text{Median Effective Dose}} = \frac{LD_{50}}{ED_{50}}$$

A drug is considered to be relatively safe with therapeutic index more than 10. However; the value of this ratio gives no information about

a) The nature of the distribution of toxicity and effectiveness,

b) The size of the doses producing therapeutic and toxic effects, and

c) Plasma or serum drug concentrations corresponding to toxic and therapeutic levels.

It can only be used as a rough estimate of the relative safety of a drug. The table 5 shows wide variation in the therapeutic index of various drugs. If the ratio is more, the drug is safer. Since the therapeutic index is relative not absolute, the toxic and therapeutic effect must be clearly defined.

Table 1.5 Therapeutic indices of some common drugs.

Drug	Therapeutic Index	Drug	Therapeutic Index
Aprobarbital	5.3	Chlorpheniramine	1400
Digitoxin	1.5 – 2.0	Penicillin	>100
Diphenhydramine	2300	Phenobarbital	2.6
Paracetamol	~10	Tripelennamine	19000

Based on therapeutic index and therapeutically effective and safe range of plasma concentration, the decision on margin of safety of a drug should be determined. It indicates the range of plasma concentration in which the drug is safe and therapeutically effective. The drugs with lesser therapeutic indices, the release pattern becomes more precise to maintain the plasma concentration within the narrow therapeutic and safety range. The unfavorable therapeutic index of a drug can be overcome by suitable use of the SR mechanisms[36].

Based on the properties, drugs can be categorized into two classes. The properties of drugs to be considered before designing a sustained release formulation are tabulated below:

Drugs suitable	Drugs not suitable
Physicochemical properties	1. Large molecular size/weight (proteins and peptides for oral)
1. Compounds with low molecular weight	2. Very low aqueous solubility 0.1 mg/ml) (Nifedipine, Griseofulvin)
2. Good aqueous solubility, pH independent (Penotoxyphylline)	3. Largely in ionized form in the G.I. tract
3. With non-aqueous solubility (for Parenteral; Steroids)	4. Strong bases (pKa> 11.0) such as Guanethidine
4. Unionized (at least 0.1-5%) in GI tract	
5. Very weak bases pKa< 5.0 (Theophylline pKa=0.7, Diazepam pKa = 3.7)	

Table *contd…*

6. Very weak acids pKa> 8.0 (Pentobarbital pKa =8.1) Unionized at all pH, absorb well 7. Moderately weak acids pKa 2.5-7.5 Aspirin (3.5), Ibuprofen (4.4). 8. Moderately weak bases (pKa 5.0-11.0), Codeine (8.2) Ionization depends on pH	5. Strong acids (pKa< 2.5) such as Cromolyn sodium
Pharmacokinetics 1. Short $t_{½}$ (2 – 5hr) such as Theophylline (4 hr), Sodium diclofenac (2 hr), Nifedipine (2.5 hr), Diltiazem (3.5 hr), Glipizide (3.4hr) 2. Well absorbed from all regions of GI tract	1. Drugs that exhibit slow absorption 2. Carrier mediated transport such as several vitamins 3. Site specific absorption such as vit B_{12} 4. Degradation in the GI tract such as Nitroglycerin, Penicillin G, Erythromycin 5. First pass hepatic metabolism such as Nitroglycerin, Propranolol 6. Induces or inhibits metabolism such as Rifampicin, Barbitu-rates, PAS
Pharmacodynamic 1. Therapeutic range of blood conc. wide enough 2. Response ∞ blood concentration	1. Having large dose 2. Drugs whose metabolites are also active

6) Side effect

The side effects of some drugs are mostly observed with the fluctuations in the plasma concentrations. The occurrences of side effects can be reduced by controlling the plasma concentration of drug within therapeutic range at any given time. The SR dosage form is the most widely used when the drug has the local side effects (at the GI tract) rather than a systemic side effect. The properties of a drug which induce local or systemic side effect can be modified by formulating them in a suitable oral SR dosage form that uses a specific controlled release mechanism[37]. It has been demonstrated that the toxic effects of valproic acid can be altered by administering the drug as a constant infusion than as a bolus. It is reported that brocadepatemtab, a controlled release product of levodopa, lowered the frequency of drug induced dyskinesis and the patients in the study could tolerate the larger daily dose of the drug. On the other hand, a sustained release prednisolone tablet produced adrenocortical suppression to similar extent produced by same dose in conventional tablets.

An attempt was made to reduce the frequency of drowsiness after taking chlorpheniramine maleate in form of porous matrix tablets. This was found unsuccessful. The success or failure of these products the side effect is related to the type and success of preparing a controlled release product.

The technique of making controlled release products has been widely used to reduce the frequency of gastro-intestinal side effects than that of systemic side effects. Drugs prone to cause gastric irritation are aspirin, ferrous sulphate, potassium chloride, nitrofurantoin, etc. It is assumed that by slowing the rate of release of such drugs, the chance of GI irritation could be reduced; because at any time, smaller amounts of the drug are being exposed to the gastro-intestinal mucosa. Similar observations were found in case of sustained release products of ferrous sulphate and aminophylline. However, after ingestion of time-release tablets of aspirin (Bayer's product) gastric bleeding was reported. Thus, preparation of controlled release products cannot be considered as a fool proof technique for reducing GI side effects.

Gastric irritation is one of the common side effects of potassium therapy. To avoid this problem, enteric coated tablets are usually used; but this creates another problem, called intestinal erosion and stenosis due to increase of potassium ions locally. Wax-matrix controlled release formulation of potassium chloride can resolve this problem satisfactorily. Such formulation releases potassium over 4 – 6 hr.

Similarly, by using sustained release sodium chloride tablet the occurrence of side effects such as nausea and vomiting has been reduced.

Thus, the properties of drugs can cause local and systemic side effects which can sometimes be avoided by using a suitable controlled release system. The specific controlled release mechanism used depends on the drug property causing the side effects.

7) Disease state

Disease state and circadian rhythm are not the properties of a drug. They become important when drug considered for formulating SR dosage form. For example, aspirin is a drug of choice for rheumatoid arthritis but, it is not suitable for SR dosage form. Even then, aspirin SR dosage form can be advantageous to maintain its therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness. Similarly, asthma attacks usually occur before bedtime, due to a low cortisol level. The highest cortisol level occurs between 12 midnight and 4 a.m. These variations involve the design an oral SR delivery in accordance to circadian rhythm.

During the treatment, pathological changes play an important role in designing a suitable drug delivery system. For example, while designing an ocular controlled-release product, for an external inflammation, the time course of changes in protein content in ocular fluids and in the integrity of the

ocular barriers should be considered. Sometimes, the manifestations of the disease state may be used as an advantage. For example, higher tyrosinase level in melanoma cells can be targeted for preferential bioconversion of 2,4-dihydroxyphenylalanine in these cells[38].

Alkaloids of Belladonna and synthetic anticholinergics are among the drugs used in the treatment of peptic ulcer. Since the use of this type of drugs in this disease state is controversial, these drugs are prescribed as adjuncts to therapy because they can decrease gastric secretion of acid and pepsin induced by vagal stimulation. Belladonna alkaloids are relatively short-acting; its sustained release dosage form can help to control the secretion of gastric acid and pepsin. A study assessed the duration of action of belladonna alkaloids released from its spansules and reported that the therapeutic concentration of the alkaloids could be extended up to 8 to 12 hr. Unfortunately, gastric acid and pepsin secretion was not measured. Although similar extension of therapeutic concentration was not found in all sustained release preparations, the reason for such difference might be the design of the products concerned.

Another disease state is angina pectoris which would be benefited by sustained release medications. Although the efficacy of orally administrable, traditional dosage form of nitroglycerin is controversial, its sustained release dosage forms are available. In fact, therapeutic benefit of sustained release nitroglycerin administered by oral route is also controversial. In another study, the benefits of using sustained release formulation of pentaerythritol tetranitrate in angina pectoris was found to be controversial. No satisfactory justification could be made by anyone. In 1959, A. Wilson stated that prophylaxis carries with it the danger of concealing the warning symptoms of pain, eventually resulting to over-exertion with potentially harmful results.

8) Route of administration

The therapeutic efficacy of a drug greatly depends on the route of administration of the drug. In designing a controlled/sustained release dosage form, the oral and parenteral routes have been acknowledged the most attention. However, recently the transdermal route is gaining attention. Based on technological achievement of a suitable sustained or controlled release dosage form, the area of the body where the drug would be administered can hinder. Sometimes, the drug delivery, through certain routes of administration, can exert a negative influence on drug efficacy, particularly in case of chronic administration. Hence, other routes of administration should also be considered. The effects of sustained or controlled release systems may also be influenced by physiological conditions depending on the route of administration, such as first-pass, GI motility, blood supply, and appropriation of small foreign particles by the liver and spleen.

Advancement in biotechnology has increased the number of peptides and proteins, and has made specific demands on the route of delivery and on the

design of the delivery systems. Thus, for certain drugs, the routes of administration are very important. Moreover, route of administration is selected because of treatment requirement. Various route of administration through which drugs can be administered are buccal, sublingual, oral, ocular, nasal, pulmonary, intrauterine, skin, vaginal, rectal, etc.

9) Target sites

To reduce the unwanted side effects, it is necessary to maximize the fraction of applied dose reaching the target organ or tissue. By local administration or by using suitable carrier systems, this can be partially achieved. However, absorptive surfaces of most of the routes are impermeable to macromolecules or other targeted delivery systems. Thus, it requires either intravascular or intra-arterial administration of drug. There are two approaches to achieve drug targeting – (1) the first approach is the chemical modification of the parent compound to a derivative which is activated only when it reaches the target site. (2) This approach uses the carriers such as liposomes, microspheres, nanoparticles, antibodies, cellular carriers (erythrocytes and lymphocytes), and macromolecules to direct the drug to its site of action.

There are various methods to modify the chemical structure of drug molecules. The most common method is the making the prodrug and the most sophisticated is the chemical delivery system approach.

A prodrug is an inactive chemical derivative of a particular drug substance and becomes converted in vivo into the active drug molecule when exposed to a required environment. But it cannot provide site specific delivery, of course with few exceptions. On the other hand, in a chemical delivery system transformation of the active drug takes place by synthetic means into an inactive derivative. When this derivative is placed in the body, will undergo several predictable enzymatic transformations primarily at the site of action. For local delivery of drug in eye, brain and testes, this approach has proven successful.

Most of the macromolecules are impermeable to the GI tract and most of the drug-carrier complexes are not stable in the hostile environment of the GI tract. Thus, administration of large drug-carrier complex is restricted to intramuscular, intravenous, or intraarterial injection, or to direct injection into the target tissues such as a tumor. If macromolecular and particulate carrier is administered intravascularly sequestration by mononuclear phagocytes of the reticuloendothelial system takes place rapidly. Presently this is the major problem in drug targeting. Since, these drug-carrier complexes are rapidly eliminated from the body, very small fraction of the injected carrier ultimately reaches the target.

A second method is to impart specificity to the drug carrier by joining specific ligands to its external surface. These include erythrocyte membrane

glycoproteins, heat aggregated immunoglobulins, monoclonal antibodies, and native immunoglobulins. None of these techniques has been found to be successful because of the difficulties in preserving the *in vivo* recognition ability and avoiding activation of any immunological response.

Vascular system itself is another problem in targeting drug carriers. To recognize the target, a drug-carrier must first extravasate. The vascular endothelium of most tissues and organs is essentially impermeable to molecular assemblages such as liposomes (0.025 – 5.0 μm) and nanoparticles (< 1μm). The tissues and organs are continuous with an effective pore diameter of 2 nm. Under certain conditions, impermeability of the capillary endothelial lining may be a useful property: (1) confinement of drug within a physiological compartment, (2) use of particles whose direction or release characteristics are under external control, and (3) delivery of drug to the lung, liver, and spleen.

Two forms of external control have been discovered. Liposomes can be made from lipids with release characteristics. These are a function of a temperature gradient due to either local inflammation or localized heating through collimated radiation. Drug is released from circulating liposomes as they pass through the target region.

Microspheres have also been used for passive targeting to organs such as the liver, spleen, lung and kidney. Intravenous injection of particles between 7 to 12 μm leads to mechanical filtration by the lungs, whereas particles between 2 to 12 μm leads to blockage in the first capillary bed encountered. Such blockage can lead to first order targeting of, for example, the liver and kidney, and second-order targeting to tumor-bearing organs.

10) Acute or chronic therapy

The duration of drug therapy depends on whether complete cure or control of disease state is desired. Hence, during designing a sustained or controlled release system, the length of drug therapy becomes an important factor. For example, designing of a contraceptive implant which can work for one year and designing of an analgesic formulation which works for a day would be different. In general, long-term toxicity of rate-controlled drug delivery system is different from that of conventional dosage form.

11) Patient

The design and development of a controlled or sustained release dosage form depends on whether the patient is ambulatory or bedridden, young, or old, obese or gaunt, etc. For example, an implant or intramuscular injection can perform differently when administered to a bedridden patient and administered to an ambulatory patient. However, such variation includes individual patient variation. Variation in performance due to individual patient variation cannot be controlled by a research scientist. Rest of the variations

are controllable and should be considered during design. For example, a single unit-controlled release oral product is prone to intra- and inter-patient variation due to variation in GI motility[39].

APPROACHES FOR SR/CR FORMULATION

Methods for Preparation of Controlled Release tablets.[40]

1) *Wet Granulation Technique*

a) Milling and gravitational mixing of drug, polymer, and excipients
b) Preparation of binder solution
c) Wet massing by addition of binder solution or granulating solvent
d) Screening of wet mass
e) Drying of the wet granules
f) Screening of dry granules
g) Blending with lubricant and disintegrant to produce "running powder"
h) Compression of tablet

2) *Dry Granulation Technique*

a) Milling and gravitational mixing of drug, polymer and excipients
b) Compression into slugs or roll compaction,
c) Milling and screening of slugs and compacted powder
d) Mixing with lubricant and disintegrant
e) Compression of tablet

3) *Sintering Technique*

a) Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
b) Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.
c) The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described because of sintering.
d) The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization of drug release.

MECHANISM OF DRUG RELEASE FROM SR/CR FORMULATION

The most of the oral controlled release systems depend on dissolution, diffusion, or a combination of both mechanisms to achieve a slow release of drug in the gastrointestinal tract. To assess drug release kinetics, some of the

in vitro systems can be considered and various systems have been designed and used also[41, 42]. On the basis of mechanism followed the release of drug from a sustained or controlled release product can be classified into following types.

1. Dissolution-controlled products
2. Diffusion-controlled products
3. Diffusion and dissolution-controlled system
4. Ion exchange resins
5. pH-independent product
6. Osmotically controlled release
7. Altered density formulations

1. Dissolution-controlled products

In this type of systems, dissolution is controlled as rate limiting step and such systems are very simple to prepare. A sparingly soluble drug is having slow dissolution characteristics; hence would be inherently beneficial for preparing sustained release dosage form; for example, digoxin, griseofulvin, salicylamide, ferrous sulphate, etc. On the other hand, the drugs which are highly soluble in water can be transformed into suitable salts or derivatives for decreasing their solubility. Unfortunately, these drugs fail to meet the criterion of constant bioavailability rate because their surface area decreases with time.

The rate of dissolution of the drug is controlled by slowly soluble polymers which surrounds the drug or remains as a thin coat in a micro encapsulation. If the coating polymer is dissolved, the drug becomes available for dissolution. Hence, by varying the thicknesses of the coat and/or by changing the composition of the polymer system, the rate of drug release can be modified.

If the process of dissolution is controlled by the diffusion layer and if the rate of diffusion from the solid surface through an unstirred liquid layer to the bulk solution is rate limiting, the flux J, the rate of flow of material (dm/dt) through a unit area (A) can be expressed as:

$$J = \frac{1}{A}\frac{dm}{dt} = -D\frac{dc}{dx} \qquad (.....1.10)$$

Where,

D is the diffusion coefficient, and

$\frac{dc}{dx}$ is the concentration gradient from the solid surface to the bulk solution.

If the thickness of the diffusion layer is assumed to be h and the concentration gradient is linear; then,

$$\frac{dc}{dx} = \frac{C_b - C_s}{h} \qquad (.....1.11)$$

Where,

C_s is the concentration of the drug at the solid surface and

C_b is the concentration of the drug in the bulk solution

By combining the equation 1 and 2, the flow rate of the material can be expressed as;

$$\frac{dm}{dt} = -(DA/h)(C_b - C_s)$$

$$= kA(C_s - C_b) \qquad .....(1.12)$$

Where,

k is the intrinsic dissolution rate constant.

According to the equation 3, the rate of dissolution remains constant when, the surface area, diffusion coefficient, thickness of the diffusion layer, and concentration difference are kept constant. As dissolution process continues, all of the parameters particularly the surface area changes.

The rate of dissolution of the drug from a dosage form of various geometrical shapes can be expressed as:

$$Mt/M\infty = 1 - [1 - K_o t/c_o a]^n \qquad .....(1.13)$$

Where,

Mt is the amount of drug released in time t,

M∞ is the amount of drug released at infinite time a is the half-thickness of a slab or the radius of a sphere or of a cylinder, and n is equal to 3 for a sphere, 2 for a cylinder, and 1 for a slab.

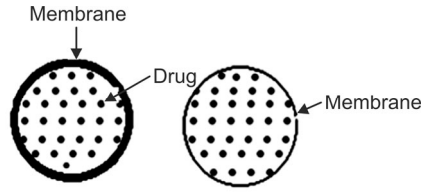


Fig.1.3 Schematic diagram of dissolution controlled drug release. (effect of membrane thickness).

Most of the dissolution control products are classified into two categories:

a) Encapsulation Dissolution controls.

b) Matrix Dissolution control.

In some of the preparations a fraction of the total dose, for immediate release, is provided to provide a pulse dose soon after administration.

a) ***Encapsulation Dissolution control***

In this method, individual particle or granule of drug is coated with a slow dissolving material. The coated particles can be compressed into tablets or filled in the capsules. The rate of dissolution of the drug (and thereby bioavailability for absorption) is controlled by micro encapsulating polymer or polymer system. Once the coating dissolves in the surrounding fluid such as gastric fluid, the drug becomes available for dissolution. By changing the thicknesses of the coat and composition of the polymer system used, the rate of drug release can be varied. These products should not be chewed because the coating may be damaged. One of the advantages of encapsulated or pelleted products is that the onset of absorption is less sensitive to or independent of the stomach emptying. The entrance of the pellets into the small intestine (where the majority of drug are absorbed) is usually more uniform than with non-disintegrating sustained-release tablet formulations. The time required for dissolution of the coat depends on its thickness and aqueous solubility. Spansule sustained release product was first introduced into the market in early 1950s and various studies have been conducted to assess its *in-vivo* performance[44-47] and clinical effectiveness[48]. This type of products can be prepared either by coating (Fig 1.3) or by microencapsulation method (Fig 1. 4).

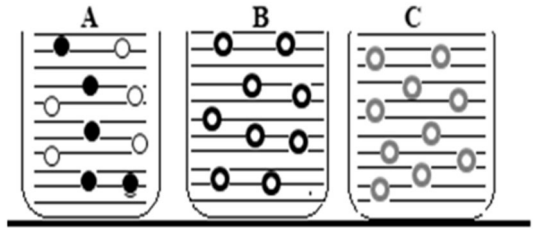


Fig. 1.4 Schematic representation of microencapsulation.
A. Establishing three-phase system,
B. Deposition of coating material
C. Solidification of coating material

- **Seeds or Granule coated products**

Various drugs have been formulated as sustained release coated granules and compressed into tablets. For example, combination of anti-spasmodic-sedative drugs, anti-cholinesterase and aspirin. In various ways drug-coated beads or granules are prepared. Commonly nonpareil seeds are coated with drug followed by a coat of slowly dissolving material such as carbohydrate sugars and cellulose, polyethylene glycol, polymeric material, and wax.

Usually one-quarter to one-third of the seeds is used to prepare non-sustained form for immediate drug release. Rest of three quarters or two-third seeds are divided into groups and polymeric coating of different thicknesses are applied. Depending on the duration of time these coats slowly dissolve and release the drug to maintain a steady level. Rosen et al [49,50]have illustrated this method with relevant example and described the release pattern of the drugs.

They have demonstrated how the release rate of the coated drug varies with change of coating material and thickness of the coat.[51, 52]

Capsules can be filled with coated granules to administer to the patients. *In vivo* photographs [53, 54] shows how the coated particles disintegrate in GIT and remain dispersed even after 10 – 12 hr. In case of compressed tablets there are some additional factors such as excipients used, effect of compression, extent of fracture of the coated particles during compression, etc. which influence the sustained action of the drug. Green[55] reported that fractured microcapsule of aspirin releases the drug immediately.

- **Microencapsulation**

Like coated particles, the rate of release the drug from microcapsules depends on the thickness of the coating and the type of polymer used. Microencapsulation process can be used to encapsulate solids, liquids, and gases. However, other forms of microencapsulation can be used for pulsed dosing or for supplying the drug through diffusion process. The microencapsulation processes are classified as shown in table 1.6.

Table 1.6 Classification of microencapsulation processes.

Process of microencapsulation	Type of material used for coating
Coacervation/phase separation	Water-soluble polymer
Interfacial polymerization	Water-insoluble and water-soluble monomers
Electrostatic method	Oppositely charged aerosols
Precipitation	Polymers soluble in water or other solvents
Hot melt	Low molecular weight lipids
Salting out	Water soluble polymers
Solvent evaporation	Polymers soluble in solvents

Out of all the microencapsulation processes, coacervation seems to be the oldest one. In *coacervation* process interaction between two oppositely charged polyelectrolytes in water is utilized to form a polymer-rich coating solution called a coacervate[56]. The solid or liquid encapsulated by the coacervate is called embryo capsule. After cooling of the system, the coating solution forms a polymer network and transform into gel. Then the gelled coacervate is crosslinked and the capsule wall is formed. By this method, both water soluble and insoluble drugs can be microencapsulated using gelatin-gum arabic coacervate system. However, for such coating the drug should be coated with carnauba wax[57] or ethyl cellulose or cellulose acetate phthalate. The Fig 1.5 shows such microencapsulation process.

In case of *interfacial polymerization method*, the drug is dissolved in an organic solvent which is immiscible with water and suitable monomers are dissolved in water. The organic phase is then dispersed in aqueous phase. The

monomers react at the liquid-liquid interface and form a capsule wall[58, 59]. For complete polymerization a suitable cross-linking agent should be present in the continuous phase. Drugs having low melting point and soluble organic liquids can be encapsulated by this process.

The *electrostatic method* is found suitable when the drug to be encapsulated and the coating material are oppositely charged[60]. Both drug and coating material are atomized and sprayed in form of aerosol. Microcapsules formed are cooled and appropriately collected.

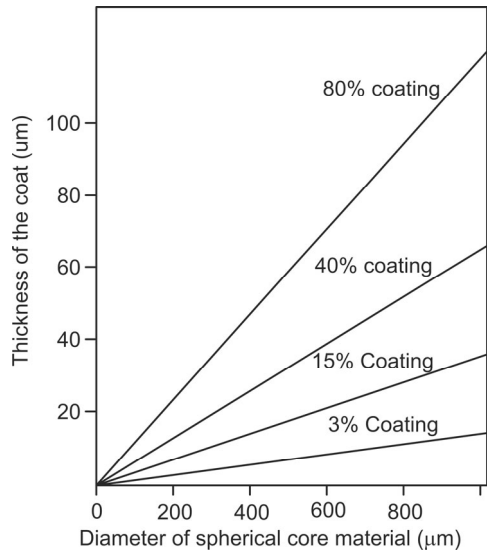


Fig. 1.5 Coating thickness vs. particle size.

There are many ways which can be brought together under *precipitation method*. In this method the polymer is either precipitated or congealed around the drug particles and forms microcapsules. For example, ethyl cellulose can be precipitated from cyclohexane by cooling, sodium alginate forms gel when meets aqueous solution of calcium chloride. Similarly, desolvation of water-soluble polymers with water-miscible solvents.

In *hot melt method*, the suitable polymer is melted first, the drug is mixed thoroughly. The hot mixture is sprayed. The molten mixture form drops which on cooling solidify. Thus, the drug to be encapsulated should be thermally stable. The coating material usually used for this purpose contains relatively low molecular weight lipids and the melt should have low viscosity even after mixing with drug.

In the *salting out* method, a suitable salt is added to the aqueous solution of polymer. By addition of salt, the polymer gets separated from the solvent (water). During this process of separation, the polymer forms a coat over the drug particles. In this method, there may be good possibility of incorporation of salt into the walls of the microcapsule formed.

In *solvent evaporation* technique, the drug and the polymer are dissolved in a water miscible organic volatile solvent. This solution is then dispersed into an aqueous solution, so that an emulsion is formed. Once the solvent is evaporated, solid microcapsules formed are left.

By changing the amount of coating material from 3 to 30% of the total weight, the thickness of the microcapsule coat can be varied from 1μm to 200μm. The thickness of the coat can be calculated theoretically from capsule

size. Among different polymers (synthetic and natural) appropriate polymer is selected based on drug to be coated, desired release characteristics, and stability of the polymer in the gastric fluid.

b) ***Matrix Dissolution control***

In this system an alternative approach is used. The drug is thoroughly mixed with a slow dissolving carrier (polymer or polymer mixture) and then compressed to make tablets. The rate of drug release of the drug from this type of formulation is controlled by the (1) rate of penetration of the dissolution fluid into the matrix, (2) porosity of the surrounding layer, (3) presence of hydrophobic additives and by the (4) the wettability of the polymer system and surface of particle.

Although zero-order release from most of the systems is desired, there are some systems that would give more advantage from release controlled by the composition of the releasing medium such as pH. The erosion of the methyl vinyl ether/maleic anhydride copolymer synthesized by Heller and Trescony[49]is very much sensitive to the pH of the aqueous medium. Thus, the rate of release of the drug is also dependent on the pH of the medium. These polymer systems are completely soluble at pH above certain value and are completely insoluble at pH below that value.

There are two general methods for preparation of wax-drug particles. In one method, the drug particles are dispersed in distilled water and the system is heated gradually up to 90°C with agitation. For a particular formulation wax is added to system with continuous stirring at the same temperature for 10 min. The wax is melted and starts engulfing the dispersed drug particles and forms spherical agglomerates. The system is stirred continuously and cooled to room temperature. The agglomerates become hard. Then the particles are filtered and dried for 24 hr at 40°C. The average size of the particles is reduced if the speed of stirring is increased. Although the aqueous dispersion method shows higher release rates of all waxes; however, no method is adequate to define the release characteristics.

Compression of spray-congealed particles releases the drug through erosion, solubilization, and leaching from the tablet. However, no model can produce the desired release characteristics. Although zero-order release is desired from most of the systems, there are systems that have more advantages from release that is controlled by the composition of the releasing medium, such as pH. Each polymer system shows a characteristic pH above which the polymer is completely soluble and below which it is completely insoluble. The pH depends on the size of the alkyl group in the copolymer ester. Thus, dissolution of the polymer and release of drug strictly depend on the pH of the medium.

2. Diffusion–Controlled products[43]

These systems are prepared with water– insoluble polymer which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through the polymer that actually makes the controlled release device. The diffusion can occur through pores in the polymer matrix or by passing between polymer chains. Theseare broadly classified into two categories:

A. Reservoir Devices

B. Matrix Devices

The basic mechanisms of drug release from these two systems are primarily different.

A. Reservoir Devices

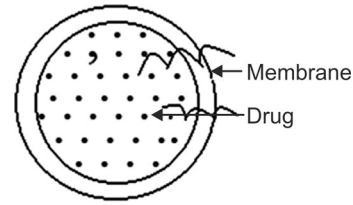


Fig.1.6 Diffusion control of drug release by a water-insoluble polymer.

In this system, a drug is enclosed by water-insoluble polymeric material; the drug is remained in the core of the particle. The drug partitions itself into the membrane and exchanges with the fluid surrounding the particles. The active agent or the drug is released into the surrounding environment by diffusion process through the rate limiting membrane. In the reservoir systems the drug delivery rate remains constant. Additional amount of drug will enter the membrane, diffuse to the periphery, and exchange with the surrounding media. A schematic diagram as shown in Fig.1.6 represents release of drug from a reservoir device.

The flux of drug, J (amount/area-time), across a membrane in the direction of decreasing concentration is expressed by Fick's law:

$$J = - D \, dC/dx \qquad \text{…..(1.14)}$$

Where, D is the diffusion coefficient in area/time and dC/dx is the change of concentration, C with distance, x. After attainment of steady state, the eqn. 5 can be integrated and written as;

$$J = - D\Delta C/l \qquad \text{…..(1.15)}$$

If the rate of release of the drug is expressed as dM/dt, then

$$dM/dt = ADK \, \Delta C/l \qquad \text{…..(1.16)}$$

Where, A = area

D = diffusion coefficient

K = partition coefficient of the drug between the membrane and core of the drug

l = diffusional pathlength, that is the ideal thickness of the coat, and

ΔC = concentration difference across the membrane.

When the partition coefficient is high, the core will be exhausted of drug within a short period and zero order release would be observed only over a short period of the time course of the drug release.

In fact, to achieve a constant rate of drug release from the reservoir, it is necessary to maintain constant area, diffusional path length, concentration, and diffusion coefficient; that is all the terms on the right-hand side of the eqn. 1.7 should remain constant. Commonly, many oral sustained release products, one or more terms changes in the product; as a result, zero-order release of drug is not observed. Methods used to develop reservoir type formulation are (1) press-coating[50, 51], and (2) air suspension methods[52-55]. These methods have been used to apply insoluble polymers to coat the drug in cores of the tablets. The microencapsulation process is commonly used to coat drug particles to incorporate into tablets or capsules[56-60]. Generally, drug is incorporated in the coating film and in the core of the microcapsule to provide the initial and sustaining doses respectively. Pan coating or polymerization technique is commonly used for coating. The coated pellets, granules or microcapsules thus produced, is then compressed into tablets. However, sufficient care should be taken during tableting so that no or minimal fracture or fusion of granules take place that can alter the release characteristics[61]. Several studies have been conducted to evaluate potential application of polymers and/or copolymers as coating materials for diffusion-controlled encapsulated dosage form[62-63]. For example, the release of phenobarbital, and salicylic acid from cast film of HPC (Hydroxypropylcellulose) by a diffusion-controlled process. Good *in vitro* release profile has been observed by laminating a blank film to the releasing side of the film. The Fig.1.7 shows the release characteristics of salicylic acid from the film of HPC.

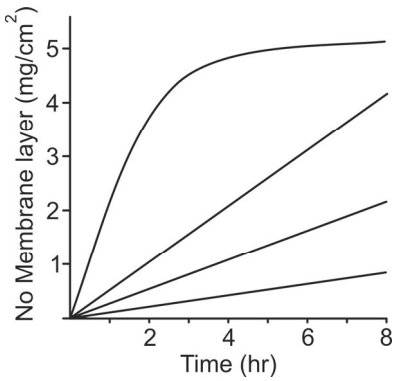


Fig.1.7 Drug release from film containing salicylic acid.

The important factors influencing the release rate of drug are:

- ***Polymer ratio in the coating***

By increasing the proportion of polyethylene glycol (PEG) in the film, the rate of release of the drug can be increased, keeping the amount drug constant. This is because PEG leaches out of the system very rapidly and the sizes of the pores are increased. As a result, the drug comes out of the system easily. Hence, by incorporating a leachable polymer in the coat, the release rate of the drug can be improved.

- ***Thickness of the film-coat***

It is expected that by decreasing the thickness of the coat, the rate of release of drug can be increased. Studies indicated the same when microcapsules of clofibrate prepared by coacervation using gelatin-sodium sulphate for coating. The Fig 1. 8 shows that the rate of drug release can be increased to more than 12 hr by increasing the thickness of the coat.

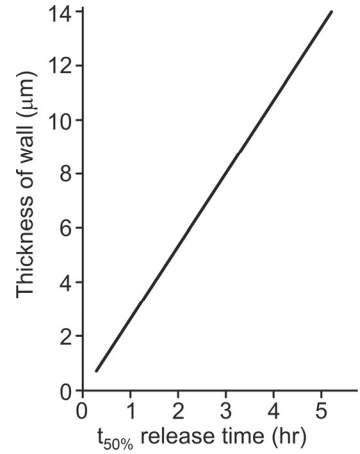


Fig.1.8 Relation between wall thickness and release rate.

- ***Hardness of the microcapsules***

*B*y increasing the hardness of the microcapsules, the rate of release of the drug can be prolonged. The effect of hardness of the tablets of sodium pentobarbital on the release of drug has been investigated and found true. The tablets were prepared using nylon. The mechanism of delayed release of sodium pentobarbital from the tablet might be leaching of the drug though network of nylon fiber constituting the microcapsules. In releasing the drug from microcapsules both dissolution and diffusion can be involved. If the coating material is properly selected, diffusion control system can be obtained.

B. Matrix Devices

In the matrix system, a solid drug or active substance is dispersed in the polymer matrix system to form a homogeneous mixture known as *matrix system*. The drug passes from the polymer matrix into the external environment through the process called diffusion. As the drug-release continues, the rate of release of the drug usually decreases with this type of system. This happens since the active agent has a progressively longer distance to travel and therefore, requires a longer diffusion time for release. Thus, the rate of drug release depends on the rate of diffusion, not on the rate of dissolution of the drug. The rate of release of the drug from such system can be expressed by an equation derived by T. Higuchi.

$$Q = [D\varepsilon/T\ (2A - \varepsilon Cs\ Cs\ t]^{1/2} \qquad \text{.....(1.17)}$$

Where,

Q is the amount of drug (g) released per unit surface area,

D is the diffusion coefficient of the drug in the release medium,

Ɛ is the porosity of the matrix,

T is the tortuosity of the matrix,

Cs is the solubility of the drug in the releasing medium, and

A is the concentration of the drug in the tablet.

The assumptions behind the equation 8 are

- A pseudo-steady state is maintained during release
- Cs << A; that is, excess of solute is present,
- C = 0 in solution at all the times (perfect sink condition)
- Drug particles are much smaller than those in the matrix,
- Diffusion coefficient remains constant, and
- No interaction between the drug and the matrix occurs.

For treatment of data obtained, the equation 8 can be reduced to

$$Q = kt^{\frac{1}{2}} \qquad \text{.....(1.18)}$$

Therefore, according to the equation 9, the amount of drug released from the matrix is plotted against the square root of the time required for the release; a straight line would be obtained, if the release is diffusion controlled. However, the rate of release of the drug from a uniform matrix system can be controlled by controlling the following parameters:

- Initial concentration of the drug in the matrix,
- Solubility of the drug,
- Porosity
- Tortuosity
- Leaching solvent composition, and
- Polymer system constituting the matrix.

When such systems are used *in vivo*, zero-order release is not commonly obtained. The reason behind this observation is most probably changing of the diffusional pathlength.

As per the expected release pattern from this type of system, a portion of the drug should be released immediately after administration (initial dose for immediate absorption) and thereafter in portions (for sustained action). This is usually done by placing the initial dose in coat of the tablet. The coated or matrix formulation can be tableted by press coating. The uncoated tablets are prepared by compressing initial dose with sustaining dose.

There are three major types of matrix diffusion control system:

- Insoluble plastics,
- Fatty, and
- Hydrophilic matrices.

Considerable basic researches have been conducted to develop insoluble matrix systems for sustained release of drug. However, some problems may be found while developing oral matrix system. For example, this has been reported that sometimes a matrix sustained release tablet is chewed after oral administration. This can bring about serious problem if the drug has narrow therapeutic window, because the drug will immediately be absorbed. Such problem can be resolved if the drug is dissolved directly in plastic matrix. As a result, the drug will not be released into the gastric fluid even after mastication. The Fig.1. 9 show such type of formulation.

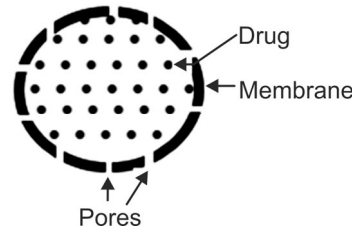


Fig.1.9 Diffusion control drug release by partially soluble polymer.

The fatty matrices are waxes which are melted, and the drug is dispersed and mixed thoroughly. The hot mixture is then cooled normally and allowed to congeal. The congealed mass is then granulated and compressed into cores. These cores are coated as per the method described previously.

In 1962, hydrophilic gums were first used to prepare sustained release products. According to this method, the drug is mixed thoroughly with nondigestible hydrophilic gum such as HPMC or sodium-CMC and then the mixture is compressed into tablets. After oral administration, the initial dose of the drug is released immediately into a medium, either water or gastric fluid. Then, hydration and gelation of the gum takes place at the interface between the tablet and medium. This produces a viscous gel which works as a barrier and retards the release of the drug into the medium. Studies indicate that release of drugs from some of the matrices follows the Higuchi's model for diffusion-controlled system[64].

3. Diffusion and dissolution-controlled system

The main feature of this system is that a partially soluble membrane encloses the drug. The Fig.1.10 shows a schematic diagram of such system. In this system a part of the membrane dissolves and allows the drug, present inside the core, to diffuse through the pores in the polymer coat. From this type of product, the release profile of the drug can be described by the equation 10.

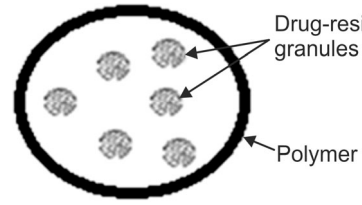


Fig. 1.10 Polymer coated drug resin system.

$$\text{Rate of release} = AD(C_1 - C_2)/l \quad \text{.....(1.19)}$$

Where, A = surface area

D = diffusion coefficient of the drug through pores,

l = diffusion pathlength,

C_1 = concentration of the drug in the core,

C_2 = concentration of the drug in the dissolution medium.

Here, the rate of release of the drug depends on the fraction of soluble polymer forming the coat. The zero-order release of KCl can be produced by such system. Such tablets of KCl decrease the gastric irritation caused by conventional tablet of KCl.

Use of lipase-lipid-drug system to provide sustained release, can demonstrate a dissolution-diffusion controlled system. In this case the erosion of matrix is due to thee lipolytic action of the lipase on the substrate. If the lipase activity accelerator such as calcium carbonate or glyceryl monostearate is added to the formulation, the rate of release of drug can be flexible. In drugs, the tablets containing lipase could produce consistently higher and more uniform blood level of the drug than those without having lipase.

4. Ion-exchange Resins

For a long time, the concept of ion exchange has been used in analytical and protein chemistry. For sustained release drug delivery system formulation, it is a preferred method because theoretically drug release characteristics depend on the ionic environment of the resin-drug complex. Hence, it is less susceptible to environmental conditions such as enzyme content and pH at the site of absorption. This method of sustained release needs the presence of ions in the solution. However, it is applicable to the skin, external ear canal, or any areas where available eluting ions are limited. This approach would be more suitable where the pool of available ions is more, such as in the subcutaneous or intramuscular route. The resin may biodegrade with an attendant alteration in the programmed release rate. In the GI tract, a constant ionic environment is present but it may vary with intake of diet, water intake, etc. Oral products using this principle can provide prolonged drug release (Fig.1.10).

Resins are water-insoluble compounds that contain anionic or cationic groups in repeating position on the resin chain. The resin can be mixed with the drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with drug solution for a longer period. The drug-resin complex thus prepared is then washed to remove contaminant ions and dried to prepare beads or particles.

If a high concentration of an appropriately charged ion is kept in contact with the ion-exchange group, the drug molecule is exchanged and diffuses out of the resin to the bulk solution as per the scheme shown below:

$$\text{Resin } [N(CH_3)]^+X^- + Z^- \rightarrow \text{Resin } [N(CH_3)]^+Z + X^-$$

Or

$$\text{Resin } (SO_3^-)\ A^+ + B^+ \rightarrow \text{Resin } (SO_3^-)\ B^+ + A^+$$

Where X^- and A^+ are the drug ions

The factors that influence the rate of diffusion of drug from resin-drug complex are

- The area of diffusion,
- Diffusion pathlength,
- Amount of solvent in the matrix of the resin, and
- Cross-linking of the resin (structural rigidity of the resin).

Hence, the porosity of the resin and particle or bead size must be controlled during formulation process. The rate of release of drug can be further controlled by coating the drug-resin complex using any one of processes described previously. Mixture of coated and uncoated drug-resin complexes in a definite ratio can be filled in capsule and can be used to obtain a desired release profile. The drug-resin complex of phenylpropanolamine when administered once in 12 hr for 2 weeks has been found to provide the same plasma concentration similar to a solution of the drug administered 5 hrly.

5. pH-independent product

There are some unusual features in the gastro-intestinal tract, which are not found in other routes of administrations. The short transit time in the GI tract reduces the length of prolongation; this is a problem for dosage form design.

The pH of various zones of GI tract varies from 7 in the mouth, to 1 – 4 in the stomach, to 5 – 7 in the small intestine. Since most of the drugs are weak acids or weak bases, their sustained release formulations depend on pH. For example, papaverine HCl being highly soluble in the upper part of GI tract is found to be released in the gastric region than in the intestine. However, to achieve pH-independent drug release, suitable buffer can be added to a formulation. Buffers used are salts of amino acids, citric acid, phthalic acid, phosphoric acid, or tartaric acid. The rate of availability of propoxyphene from a buffered controlled release formulation can show a significantly increased reproducibility[65].

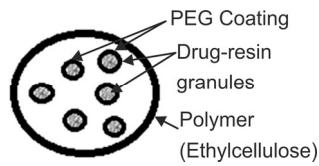


Fig.1.11 Polymer coated drug resin dispersion.

For oral controlled release of acidic or basic drugs at a rate independent of the pH in the GI tract, the granules can be prepared (Fig.1.11). The granules are prepared by mixing the drug with one or more buffering agents and required excipients and finally coated with a suitable film-forming polymer. The polymer used should permeate gastrointestinal fluid.

6. Osmotically controlled release

Osmotic pressure acts as the driving force in this type of drug delivery system and provides constant drug release. Around a core of an osmotically active drug or a core of an osmotically inactive drug combined with osmotically active salt, a semipermeable membrane is applied, and the granules are prepared. In each system, a delivery orifice is drilled by laser or by a high-speed mechanical drill. The optimum size of the orifice can be calculated by using the following equation:

$$A_S = (LV/t)(8\pi)(\eta/P)^{1/2} \quad \text{.....(1.20)}$$

Where, A_S is the cross-sectional area of the orifice,

L is the diameter of the orifice,

V/t is the volume released per unit time,

π is 3.14

η is the viscosity of the solution moving from the inside to the outside of the device, and

P is the hydrostatic pressure difference.

A_S is the total cross-sectional area of the orifices, if the osmotic device contains more than one orifice. When an osmotic system meets water or with a body-fluid, because of osmotic pressure difference, water or body fluid will flow into the core through the coating membrane as shown in Fig.1.12. The volume of liquid flown into the core per unit time, dV/dt, can be expressed as:

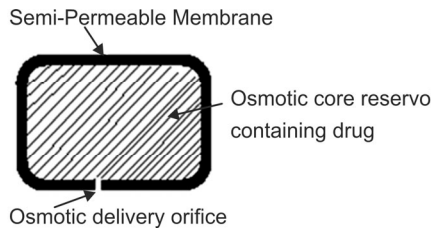


Fig.1.12 Oral osmotic pumps.

$$dV/dt = (Ak/h)(\Delta\pi - \Delta P) \quad \text{.....(1.21)}$$

Where, A is the area,

k is the permeability of the membrane,

h is the thickness of the membrane,

$\Delta\pi$ is the osmotic pressure difference, and

ΔP is the hydrostatic pressure difference.

The hydrostatic pressure difference would be small compared to the osmotic pressure difference, if the orifice, is quite large. Under this circumstance, the equation 12 can be reduced to

$$dV/dt = (Ak/h)\Delta\pi \quad \text{…..(1.22)}$$

Through the orifice of the system, drug will be pumped out at a controlled rate, dM/dt. The dM/dt would be equal to the volume of water flew into the core multiplied by the concentration of drug, C_S in unit time, dV/dt. Thus, this could be expressed as;

$$dM/dt = (dV/dt)C_S \quad \text{…..(1.23)}$$

This system is supposed to deliver the drug continuously at a zero order till the concentration of the osmotically active drug reaches below its saturation solubility. For example, preparation of indomethacin has been found to release the drug up to 70% at a zero-order rate.

Design wise the coating membrane is rigid and non-swelling. It is can maintain the structural integrity of the system during the release of drug. The coat is impermeable to the drug particles, permeable to gastrointestinal fluid. Polymers used as semi-permeable membranes have been presented in Table 1.7.

Table 1.7 Water-vapour transmission rate of some polymeric membranes.

Polymer	Rate of water vapor transmission ($g/100mm^2/day/mm$ of thickness)
Polyvinyl alcohol	100
Ethylcellulose	75
Methylcellulose	70
Polyurethane	30 – 150
Cellulose acetate	40 – 75
Cellulose acetate butyrate	50
Polyvinyl chloride, cast	10 – 20
Polycarbonate	8
Polyvinyl chloride, excluded	6 – 15
Polyvinyl fluoride	3
Polyesters	2
Ethylene vinyl acetate	1 – 3
Cellophane, polyethylene coated	1.2
Polyvinylidene fluoride	1.0
Ethylene propylene copolymer	0.8
Polypropylene	0.7
Polyvinyl chloride, rigid	0.7
Polyethylene	0.5 – 1.2

The permeability of the rate controlling membrane depends on;

- The diffusion coefficient
- Solubility of water in the polymeric membrane,
- Structure of the polymer,
- Relative pressure difference across the membrane,
- Thickness of the membrane, and
- Temperature.

The flux of water through a semipermeable membrane can be determined and be expressed as water vapor transmission rate.

A layer of bioerodable polymer should be applied to the external surface of semi permeable membrane, to control the bioavailability of gastrointestinal fluid for permeation through the semipermeable membrane. There are various methods developed to modify the osmotic pressure-controlled drug delivery system[66]; one of such development is to separate two compartments by a movable partition as shown in Fig.1.13. The osmotically active compartment downs the GI fluid and develops an osmotic pressure on the partition. The partition moves to reduce the volume of the drug reservoir compartment and releases the drug through the delivery orifice.

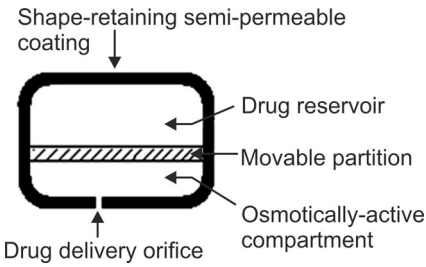


Fig.1.13 Osmotic pressure-controlled drug delivery system with movable partition.

Another modified system does not contain any delivery orifice. In such system, as the GI fluid is downed, hydraulic pressure is built up inside the system until the wall ruptures and the content of the system is released into the surrounding GI fluid. To control the drug release by varying the thickness and the area of the semi-permeable membrane, this type of bursting system can be used.

Thus, osmotically controlled release devices require only an effective osmotic pressure and do not depend on the pH and mixing in the digestive system, these can effectively sustain the release of the drug in GI tract.

7. Altered density formulations

In most of the human beings the GI transit time varies from one to another; in most cases it is less than 24 hr, but in some cases, it can vary from 8 to 62 hr also. There are various factors that influence the GI transit time, among all these the most important are:

- Physical properties of the delivery system,
- Presence of food

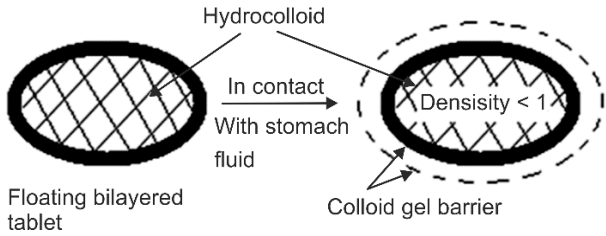


Fig.1.14 Bilayered sustained release tablet containing hydrocolloids.

This has been recently reported that the presence of food can affect the multiple-unit dosage forms to lesser extent than the single-unit dosage forms. Because the subunits of a multiple-unit dosage form are distributed throughout the GI tract. However, the GI transit time is more influenced by specific density of these subunits than the diameter of these subunits. This has been observed that by increasing the density from 1.0 to 1.6, the average GI transit time can be increased from 7 to 25 hr[67]. Although further investigation suggests that the increase in density of the delivery system from 1 to 3 has minimal effect on GI transit time in non-colostomy patients.

It is desired that a delivery system should remain at the nearest to the site of absorption until the drug is almost completely released. Various methods have been developed to prolong the gastric retention time of drug delivery systems. For example,

- Providing a bio-adhesive drug delivery system that can adhere to the mucin/epithelial surface of the GI tract.
- The density of the pellets is made heavier than that of the gastric contents, to about 1.4. In such dosage form, the drug is coated on a heavier core or mixed with heavy inert materials such as barium sulphate, titanium dioxide, iron powder, zinc oxide, etc.
- The apparent density of globular shells is less than that of gastric fluid. These low-density globular shells can be used as carrier of drug for sustained release of drugs. For example, polysterol, poprice, and even popcorn, are used as carriers. This is done by undercoating the surface of these empty shells with sugar or with a polymeric material such as methacrylic polymer and cellulose acetate phthalate. Then the undercoated shell is coated by a mixture of drug with polymers such as ethyl cellulose and hydroxypropyl cellulose. The product obtained by this process floats on the gastric fluid for a prolonged period which slowly release the drug.

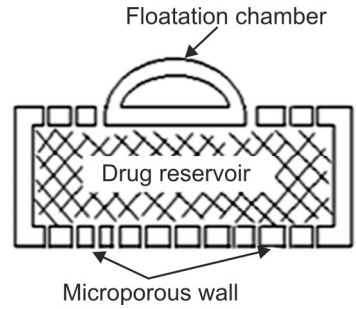


Fig.1.15 Drug delivery system with floatation chamber.

Floating tablets can be prepared by granulating a mixture of drug, excipients, and 20–75% of hydrocolloids. The hydrocolloids generally used are hydroxyethyl cellulose, hydroxy- propyl cellulose, and Hydroxy- propyl methylcellulose. The granules so prepared are compressed to tablets with required hardness. Such tablet after meeting gastric fluid remains floating and forms a water-impermeable colloid-gel barrier aroundthe surface. The bulk density of this is less than one; as a result, it floats. However, such low-density tablet requires presence of water in the stomach to remain floating. For this, frequent water intake which is inconvenient to a patient. This can be solved by making bilayered tablet which contains one layer for immediate release and the other layer for sustained release.

To use the principle of buoyancy another method is to include a gas-filled floatation chamber into the microporous compartment which contains a microporous drug reservoir, as shown in Fig.1.15. The apertures are present at its top and bottom walls. The gastric fluid enters through these pores and dissolves the drug. The side walls are sealed and prevent the entry of stomach fluid[68].

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EXCERCISE

MULTIPLE CHOICE QUESTIONS

1. The permeability of the rate controlling membrane depends upon
   a. Absorption
   b. Diffusion coefficient
   c. Drug release from dosage form
   d. None
2. The drugs having high solubility and low permeability are classified as-
   a. Class IV
   b. Class III
   c. Class II
   d. Class I
3. What are the characteristics of diffusion-controlled release systems?
   a. Release the drug along the entire length of GIT
   b. Diffusion of the dissolved drug
   c. Release only at a specific drug
   d. Employ waxes to control the rate of dissolution

4. For drug selection, the absolute bioavailability should be-
   a. 70% or less
   b. 75% or more
   c. 75% or less
   d. 70% or more
5. The physicochemical properties of drug include-
   a. Aqueous solubility
   b. Partition coefficient
   c. Drug stability
   d. All of the above
6. What is the characteristic of matrix dissolution-controlled release systems?
   a. Release the drug along the entire length of GIT
   b. Prolonged their residence in the GIT and release
   c. Release only at a specific drug
   d. Employ waxes to control the rate of dissolution
7. The drugs are well absorbed in-
   a. Ionized form
   b. Unionized form
   c. Both of the above
   d. None of the above
8. Which of the following is NOT the technique for the preparation of a Controlled Release Tablets?
   a. Direct compression technique
   b. Wet granulation technique
   c. Dry granulation technique
   d. Sintering technique
9. What are the characteristics of ion exchange resin drug complexes?
   a. Release the drug along the entire length of GIT
   b. Drug disperse in an insoluble matrix of rigid hydrophobic materials
   c. Hollow systems containing drug surrounded by a polymer membrane
   d. Formation of complexes between the drug and anion/cation exchange resins
10. The advantage of microencapsulation is-
    a. Sustained release of prolonged action medication
    b. Taste masked chewable tablet, powders and suspensions
    c. Single layer tablet for chemically incompatible ingredients
    d. All of the above

11. What is the characteristic of pH-independent formulations?
    a. Buffering agents that adjust pH to the desired value
    b. Drug disperse in the insoluble matrix of rigid hydrophobic materials
    c. Hollow systems containing drug surrounded by a polymer membrane
    d. Formation of complexes between the drug and anion/cation exchange resins
12. It is the fraction of drug in an oil phase to that of an aqueous phase
    a. pKa
    b. Permeation
    c. Dissolution
    d. Partition coefficient
13. Floating drug delivery systems include-
    a. Non- effervescent FDDS
    b. Effervescent FDDS
    c. Only a
    d. Both a & b
14. Ion-activated DDS is which type of activated system?
    a. Physical
    b. Biological
    c. Biochemical
    d. Chemical
15. Which of the following are the characteristics of diffusion- controlled release system?
    a. Release the drug along the entire length of GIT,
    b. Diffusion of the dissolved drug
    c. Release only at a specific drug
    d. Employ waxes to control the rate of dissolution,
16. Following is Biochemical type of activated modulated,
    a. Osmotic pressure activated,
    b. Enzyme activated DDS,
    c. Hydrolysis activated DDS,
    d. Vapour pressure activated.
17. Bio-erosion system is which type of delivery system.
    a. Activated modulated drug delivery system,
    b. Feedback regulated drug delivery system,
    c. Both of the above
    d. Vapour pressure activated.
18. The following characteristics are the good candidates for controlled release dosage form
    a. Polar, ionized
    b. Polar, Unionized
    c. Non- polar, ionized
    d. Non-polar, unionized

19. A good candidate for controlled drug delivery should have half life of-
    a. Less than 1 hour
    b. 8-10 hours
    c. More than 4 hours
    d. 2-4 hours
20. The key differences between controlled release and sustained release include:
    a. Sustained release is a slow release of medication over a period of time, whereas control release releases medication over time in correlation with concentration.
    b. Sustained release is a fast release of medication over a period of time, whereas control release releases medication over time in correlation with concentration.
    c. Sustained release is a slow release of medication over a period of time, whereas control release releases medication over time in correlation with viscosity.
    d. Sustained release is a fast release of medication over a period of time, whereas control release releases medication over time in correlation with viscosity.

SHORT ANSWER QUESTIONS

1. What are the objectives of oral sustained release dosage forms?
2. Briefly explain the Biopharmaceutical Classification System of drugs.
3. Write the classification of sustained release products.
4. Write a classification of modified release oral dosage forms.
5. Explain the significance of drug stability for the design of sustained and controlled release dosage forms.
6. What is the role of the partition coefficient of the drug in designing sustained and controlled release dosage form?
7. Briefly explain osmotically controlled release system.
8. Write significance of ion- exchange resins in sustained and controlled release systems.
9. Write a brief note on floating tablets.
10. Write the advantages of sustained release formulations over conventional formulations.

LONG ANSWER QUESTIONS

1. Write the mechanism of drug release from sustained release and controlled release formulations.
2. Explain the complete process of microencapsulation.

3. Write different methods for the preparation of controlled release tablets.
4. Explain the different physicochemical properties of the drug for the design of sustained release and controlled release formulations.
5. Discuss about the various approaches used in the design of oral sustained release or controlled release drug delivery system.
6. Explain the different biological properties of the drug for the design of sustained release and controlled release formulations.
7. Explain the basic concept of drug release from controlled release formulations.
8. Explain Diffusion and Dissolution Controlled system.
9. Explain diffusion-controlled products.
10. Explain the various requirements of drug candidate to be selected for formulation into controlled drug delivery system.

MCQ ANSWERS

1. (b)	2. (b)	3. (b)	4. (b)
5. (d)	6. (d)	7. (b)	8. (a)
9. (d)	10. (d)	11. (a)	12. (d)
13. (d)	14. (d)	15. (b)	16. (b)
17. (b)	18. (d)	19. (d)	20. (a)