INTRODUCTION TO DESIGN CONTROLLED RELEASE FORMULATION

The science of controlled release was first originated from the development of oral sustained release products in the 1940s and early 1950s. First of all, the controlled release of marine antifoulants (the 1950s) and controlled release of fertilizer (1970s) were formulated which had only a single application in the soul science. The development of the pharmacology and pharmacokinetics demonstrated the importance of drug release rate in determining therapeutic effectiveness of therapy. This becomes the reason behind the development of controlled release. The modified release dosage forms are entirely new. The first time Rhozes formulates mucilage coated pills about A.D 900. This technique widely adopted in the10th century by European countries, in the form of gold, silver and pearl coated tablets; this coating modifies the drug release rates. Advancement in the coating technology including sugar & enteric coating on the pills & tablets in the late 1800s. The further coating developed to the enteric coating of tablets followed by incorporation of the second drug to sugar coating layer, this happened near about 1938. However, the first patent for oral sustained release preparation went in the favour of Lipowski; his preparation contained small coated beads that were releasing the drug slowly & constantly. This idea later developed by Blythe and launched the first marketed sustained release product in 1952. Over the past 30 years as the complication involves in the marketing of new drug increased and various advantages recognized of Controlled release drug delivery system (CRDDS), the greater attention is being paid in this field. Today the oral controlled drug delivery system becomes major drug delivery systems mainly drugs having high water solubility and short biological half-life. Other than oral, the various routes like transdermal, ocular, vaginal & parenteral route use for controlled release of various drugs.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized.

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

Targeted-release drug products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended-release characteristics.

The term controlled-release drug product was previously used to describe various types of oral extended-release dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery.

Conventional Drug Delivery System

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption.

As can be seen in the graph (Figure 1), administration of the conventional dosage form by extravascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

The conventional dosage forms like solution, suspension, capsule, tablets and suppository etc. have some limitations such as:

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond the therapeutic range.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug

with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

CONTROLLED RELEASE

An ideal dosage regimen of drug therapy is one which rapidly attained the required plasma concentration and maintained for the entire period of treatment. The frequencies of drug administration primarily depend on the biological half-life of the drug and mean residential time (MRT). Conventional drug delivery system often produces over or under medication result in various adverse drug reactions (ADRs) due to unpredictable drug release pattern. The CRDDS alters the drug distribution along with are duction in drug toxicity. The term-controlled release (CR) implies the predictability and reproducibility in the drug release kinetics which means the drug release from the delivery system proceed at the rate profile not only expected kinetically but also reproducible from one division to another. CRDDS intended to exercise control drug release in the body; this may be temporal or spatial nature or both. The term sustained release also mentioned during the description of controlled release. Sustained release (SR) used to describe a pharmaceutical dosage form formulated to retard the release of API such a way that its appearance in the systemic circulation is delayed or prolonged and plasma concentration sustained in duration. The onset of drug action delayed and duration of therapeutic effect is maintained.

Advantages of Controlled Drug Therapy

- Reduction in dosing frequency easily acceptance of patient.
- Loss of drug can be reduced by targeting.
- Decreasing GI side effects and toxicological effects.
- Fluctuation in plasma drug level minimized.
- Better patient compliance.
- Convenient to administration compared to other routes of administration.
- Stability of drug can be increased.
- Uniform drug effect achieved.

 Delivery of drug in the vicinity of site of action.

 Maintenance of optimal and effective dosage levels for long action.

 Improve bioavailability of same drugs.

 Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.

Disadvantages of Controlled Drug

 They are costly.

 Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.

 Poor systemic availability in general.

 Effective drug release period is influenced and limited by GI residence time.

Need of Controlled Drug Delivery Systems

Controlled release of active ingredients from oral dosage forms may be required for the following reasons

 Avoidance of undesirable local side effects.

 Local treatment of diseases of GI tract.

 Protection of active ingredients against the influence of digestive fluids.

 Influencing the pharmacokinetics of active ingredients.

Rationale of Controlled Drug Delivery Systems

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties. As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary and, for each drug, there exists a therapeutic window of plasma concentration, below which therapeutic effect is insufficient, and

above which toxic side effects are elicited. This is often defined as the ratio of median lethal dose (LD 50) to median effective dose (ED50).

Selection of drug candidates:

Biological or elimination half-life Should be between 2 to 6 hrs

Elimination rate constant (KE) Required for design

Total clearance (CLT) dose independent

Intrinsic absorption rate should be greater than the release rate

Apparent volume of distribution (Vd) Vd effect the required amount of the drug

Absolute bioavailability Should be 75% or more

Steady state concentration (Css) lower Css and smaller Vd

Toxic concentration The therapeutic window should be broader

CLASSIFICATION OF ORAL CONTROLLED RELEASE SYSTEMS

The majority of oral controlled release drug delivery systems depends on, diffusion, dissolution or a combination of diffusion and dissolution mechanisms to produce slow release of drug. Depending upon the manner of drug release these systems are classified as

1. Diffusion controlled release systems
2. Dissolution controlled release systems
3. Dissolution and diffusion-controlled release systems
4. Ion exchange resins
5. pH independent formulations
6. Osmotic controlled release systems
7. Altered density release systems
8. Prodrugs
9. Delayed release systems

DIFFUSION-CONTROLLED DELIVERY SYSTEMS

Diffusion process has been utilized in design of controlled release drug delivery systems for several decades. This process is a consequence of constant thermal motion of molecules, which results in net movement of molecules from a high concentration region to a low concentration region. The rate of diffusion is dependent on temperature, size, mass, and viscosity of the

environment. Molecular motion increases as temperature is raised as a result of the higher average kinetic energy in the system.

This equation shows that an increase in temperature is exponentially correlated to velocity (v2). Size and mass are also significant factors in the diffusion process. At a given temperature, the mass of molecule is inversely proportional to velocity Larger molecules interact more with the surrounding environment, causing them to have slower velocity. Accordingly, large molecules diffuse much slower than light and small particles. The viscosity of the environment is another important parameter in diffusion, since the rate of molecular movement is associated with the viscosity of the environment. Diffusion is fastest in the gas phase, slower in the liquid phase, and slowest in the solid phase.

Mathematically, the rate of drug delivery in diffusion-controlled delivery systems can be described by Fick's laws. Fick's first law of diffusion is expressed as:

Where

J = flux of diffusion

D = diffusivity of drug molecule

= concentration gradient of the drug molecule across diffusion barrier with thickness dx

According to the diffusion principle, controlled-release drug delivery systems can be designed as a reservoir system or a matrix system. Drugs released from both reservoir and matrix type devices follow the principle of diffusion, but they show two different release patterns

CR is drug concentration in the reservoir or matrix compartment, CP is solubility of drug in the polymer phase, CD is the concentration in the diffusion layer, hm is the thickness of the membrane, hd is thickness of the diffusion layer, and hp + dhp indicates the changing thickness of the depletion zone of matrix. In a reservoir system, if the active agent is in a saturated state, the driving force is kept constant until it is no longer saturated. For matrix systems, because of the changing thickness of the depletion zone, release kinetics is a function of the square root of time. A typical reservoir system for transdermal delivery consists of a backing layer, a rate-limiting membrane, a protective liner, and a reservoir compartment. The drug is enclosed within the reservoir compartment and released through a rate-controlling polymer membrane

Membranes used to enclose the device can be made from various types of polymers. The rate of

release can be varied by selecting the polymer and varying the thickness of the rate-controlling membrane. The drug in the reservoir can be in solid, suspension, or liquid form. Analysis of diffusion-controlled reservoir or matrix drug delivery systems requires a few assumptions:

1. The diffusion coefficient of a drug molecule in a medium must be constant.
2. The controlled drug release must have a pseudo-steady state.
3. Dissolution of solid drug must occur prior to the drug release process.
4. The interfacial partitioning of the drug is related to its solubility in polymer and in solution as defined by

With the above assumptions, the cumulative amount Q of drug released from a diffusion-controlled reservoir-type drug delivery device with a unit surface area

the release rate is directly proportional to the solubility of the drug in polymer

and inversely proportional to thickness of the polymer membrane. Delivery systems designed on this principle can be administered by different routes: intrauterine such as Progestasert, implants such as Norplant, transdermal such as Transderm-Nitro, and ocular such as Ocusert. A matrix system, often described as monolithic device, is designed to uniformly distribute the drug within a polymer as a solid block. Matrix devices are favored over other design for their simplicity, low manufacturing costs, and lack of accidental dose dumping, which may occur with reservoir systems when the rate controlling membrane ruptures. The release properties of the device depend highly upon the structure of the matrix: whether it is porous or nonporous. The rate of drug release is controlled by the solubility of the drug in the polymer and the diffusivity of the drug through the polymer for nonporous system. For a porous matrix, the solubility of the drug in the network and the tortuosity of the network add another dimension to affect the rate of release. In addition, drug loading influences the release, since high loading can complicate the release mechanism because of formation of cavities as the drug is leaving the device. These cavities will fill with fluids and increase the rate of release. The cumulative amount released from a matrix-controlled device is described by.

is a constant for relative magnitude of the concentration in the diffusion layer and

depletion zone, Dp is the diffusivity of drug in the polymer devices, and other parameters are the same as described for At a very early stage of the release process, when there is a

very thin depletion zone, the following will be true:

DISSOLUTION/COATING-CONTROLLED DELIVERY SYSTEMS

Controlled release of drug can be achieved by utilizing the rate-limiting step in the dissolution process of a solid drug with relatively low aqueous solubility. The dissolution rate can be quantitatively described by the Noyes-Whitney equation

The surface area A of the drug particle is directly proportional to the rate of dissolution. For a given amount of drug, reducing the particle size results in a higher surface area and faster dissolution rate. However, small particles tend to agglomerate and form aggregates. Using a specialized milling technique with stabilizer and other excipients, aggregation can be prevented to make microparticles smaller than 400 nm in diameter to improve the dissolution of the drug in the body. The saturation solubility C0 can also be manipulated to change the rate of dissolution. Both the physical and chemical properties of a drug can be modified to alter the saturation solubility. For example, salt forms of a drug are much more soluble in an aqueous environment than the parent drug. The solubility of a drug can also be modified when the drug forms a complex with excipients, resulting in a complex with solubility different from the drug itself. Controlled or sustained release of drug from delivery systems can also be designed by enclosing the drug in a polymer shell or coating. After the dissolution or erosion of the coating, drug molecules become available for absorption. Release of drug at a predetermined time is accomplished by controlling the thickness of coating. In Spansule® systems, drug molecules are enclosed in beads of varying thickness to control the time and amount of drug release. The encapsulated particles with thin coatings will dissolve and release the drug first, while a thicker coating will take longer to dissolve and will release the drug at later time. Coating-controlled delivery systems can also be designed to prevent the degradation of the drug in the acidic environment of the stomach, which can reach as low as pH 1.0. Such systems are generally referred as enteric-coated systems. In addition, enteric coating also protects the stomach from ulceration caused by drug agents. Release of the drug from coating-controlled delivery systems may depend upon the polymer used. A combination of diffusion and dissolution mechanisms may be required to define the drug release from such systems.

DISSOLUTION AND DIFFUSION CONTROLLED SYSTEMS

The main characteristic is that the drug reservoir is surrounded with a partially soluble layer. The part of dissolution membrane allows to diffusion of the drug through pores in the polymer

membrane. The drug release from these systems explained by following equation:

Release rate = AD(C1-C2)/L

Where A = Surface area,

D = Diffusion coefficient

L = Diffusion path length

C1= Concentration of drug in the system

C2= Concentration of drug in the dissolution medium.

BIODEGRADABLE/ERODIBLE DELIVERY SYSTEMS

Biologically degradable systems contain polymers that degrade into smaller fragments inside the body to release the drug in a controlled manner. Zero-order release can be achieved in these systems as long as the surface area or activity of the labile linkage between the drug and the polymeric backbone is kept constant during drug release. Another advantage of biodegradable systems is that, when formulated for depot injection, surgical removal can be avoided. These new delivery systems can protect and stabilize bioactive agents, enable long-term administration, and have potential for delivery of macromolecules.

OSMOTIC CONTROLLED RELEASE SYSTEM

This type of delivery device has a semipermeable membrane that allows a controlled amount of water to diffuse into the core of the device filled with a hydrophilic component. A water-sensitive component in the core can either dissolve or expand to create osmotic pressure and push the drug out of the device through a small delivery orifice, which is drilled to a diameter that correlates to a specific rate. In an elementary osmotic pump, the drug molecule is mixed with an osmotic agent in the core of the device (Fig. 4a). For drugs that are highly or poorly water soluble, a two-compartment push-pull bilayer system has been developed, in which the drug core is separated from the push compartment (Fig. 4b). The main advantage of the osmotic pump system is that constant release rate can be achieved, since it relies simply on the passage of water into the system, and the human body is made up of 70 percent water. The release rate of the device can be modified by changing the amount of osmotic agent, surface area and thickness of semipermeable membrane, and/or the size of the hole.

This principle has been used for a long time in analytical and protein chemistry. It is an attractive

one of controlled drug delivery because drug release characteristics related to the ionic charges of the resin containing drug and should therefore be less susceptible to environmental conditions like enzyme content and pH at the site of absorption. Drug release can be modified by application of coating on the drug-resin complex.

The ion exchange resin system can be designed by binding drug to the resin. After the formation of a drug/resin complex, a drug can be released by an ion exchange reaction with the presence of counterions. In this type of delivery system, the nature of the ionizable groups attached determines the chemical behaviour of an ion exchange resin (Figure 5).

Factors that affect the selectivity coefficient include type of functional groups, valence and nature of exchanging ions, and nature of nonexchanging ions. Although it is known that ionic strength of GI fluid is maintained at a relatively constant level, first-generation ion-exchange drug delivery systems had difficulty controlling the drug release rate because of a lack of control of exchange ion concentration (Figure. 5a). The second-generation ion-exchange drug delivery system (Penn kinetic system) made an improvement by treating the drug-resin complex further with an impregnating agent such as polyethylene glycol 4000 to retard the swelling in water (Figure. 5b). These particles are then coated with a water-permeable polymer such as ethyl cellulose to act as a rate-controlling barrier to regulate the drug release.

Resin- Drug+ Resin- Drug+

Resin+ Drug_

Resin+ Drug_

INDEPENDENT FORMULATIONS

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates

through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drug release.

The GI tract presents different features that are not fond in other routes of drug administration. The variable nature of the chemical environment through the GIT is a constraint on dosage form design. Indeed, drugs administered orally would encounter a spectrum of pH ranging from 1 to 1.6. The pH dependency of drug release from controlled release formulations has been demonstrated by study of papaverine hydrochloride

ALTERED DENSITY CONTROLLED RELEASE SYSTEMS

The GI transit time varies depends on person. In most human subjects, it is the range of 8 to 62 hrs has been found. The specific density of these subunits is found to be a more significant factor than their diameter in influencing their GI transit time, specifically; increasing density from 1to 1.6 increases the average transit time from 7 to 25 hrs. This approach helped in design of floating drug delivery systems and swelling systems.

High Density Approach

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

Low Density Approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug forsustained release purpose.

PRODRUGS

A prodrug is chemically modified one which will liberate the active pharmaceutical ingredient in the body either enzymatic or hydrolytic cleavage. The main objective of a prodrug for oral administration is to increase absorption rate or to reduce local side effects.(i.e. GI irritation by aspirin).

DELAYED RELEASE SYSTEMS

The development of these systems involves release of drug only at a specific site in the GIT. The drugs formulated in such a systems include

1. Known to cause gastric distress,
2. To sensitive of gastric juice or intestinal enzymes,

3. Absorption occurs at a specific intestinal site or

4. To localization at a specific GIT site.

The most common ones are intestinal release systems and colonic release systems.

MATRIX TYPE ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Matrix type drug delivery systems releases drug by both dissolution as well as diffusion controlled mechanisms. Drug release from the system depends on different solubility properties of drug dispersed in polymers. One of the simplest method involves the fabrication of sustained release dosage forms involve the direct compression of blended drug, polymer and additives. To develop tablet formulation in which the drug is dispersed in a matrix of the polymer. In another way drug and polymer may be granulated prior to compression.

Advantages of matrix tablets

1. Minimize the local and systemic side effects
2. Improvement efficacy in treatment
3. Minimization of drug accumulation
4. Improvement the bioavailability of the some drugs
5. It is a versatile and low cost
6. Reducing toxic effects by slowing absorption
7. Increase stability of drug by protection from hydrolysis
8. The ability to provide special effects

Disadvantages of matrix tablets

1. The release rate can be effected by various factors like food, GI transit time, etc
2. The matrix must be removed from the body after releasing the drug
3. The drug release rate vary with square root of time

Classification of matrix tablets

Matrix drug delivery systems broadly divided into two classes are

Reservoir type matrix systems – in this system drug release controlled with membrane.

Monolithic matrix systems – in this systems drug dispersed in a matrix or encapsulated.

Depending on the type of polymer

Matrix tablets classified into following types

Lipophilic matrices (Plastic matrices)

This concept was first discovered in 1959. In method of oral sustained release systems, drug is

blended with polymer and compressed into a tablet. In fact sustained release produced by the dissolved drug has diffused through a net work of channels of matrix. The rate controlled step involves liquid penetration into the matrix.

E.g.: Polyvinyl chloride (PVC), Polyethylene (PE), Ethyl cellulose (EC), Acrylate polymers and their copolymers.

Wax matrices

These are prepared by using lipid waxes and their derivatives. In this systems release of drug occurred through pore diffusion and erosion. Release characteristics are more sensitive to digestive fluids than to insoluble polymers matrix. E.g.: Carnauba wax with stearyl alcohol or stearic acid is commonly used.

Hydrophilic matrices

These are widely employed in oral controlled drug delivery system due to their flexibility. The drug is formulated into gelatinous capsules or in tablets, polymers with high gelling capacities. In fact a matrix means mixing of one or more drugs with a polymer that leads to swelling when exposed to liquid environment. Commonly used polymers are as follows

Natural or semi synthetic polymers include agar-agar, alginates, molasses, carob gum, and polysaccharides such as mannose, galactose and chitosan, modified starches.

Cellulose derivatives are Hydroxylpropylmethyl cellulose (HPMC), Methyl cellulose 400&4000cps, Hydroxyethyl cellulose (HEC), and Sodium carboxymethyl cellulose (NaCMC).

Polymers of acrylic acid, carbopol-934 commonly used.

Mineral matrices

The polymers extracted from seaweed species for system development. E.g.: Alginic acid obtained from brown sea weeds by using alkali.

Biodegradable matrices

These consist of polymers those comprised of monomers through cross linking between functional groups in the back bone. These are biodegraded into oligomers by metabolically with the help of enzymes. E.g.: Proteins, Polysaccharides, Polylactic acid, Polyglycolic acid etc.

Depending on porosity of matrix

Matrix systems also classified according to its intrinsic character i.e. porous nature. They are

1. Micro porous system: Size range of pores is 50 to 200Ao slightly larger than diffusant

molecule size.

2. Macro porous system: Size range of pores is 0.1 to 1micrometers, which is larger than diffusant molecule size.

3. Non-porous system: There is no pores and drug diffuse through the network of matrix.

The present work is planned to prepare and evaluate novel drug delivery systems of highly soluble drugs alfuzosin hydrochloride and citicoline using hydrophilic and hydrophobic polymers. Alfuzosin is indicated for treatment of BPH. Citicoline is used in the treatment of neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and head injuries with improve patient mental ability.

FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

A. Biological factors

1. Biological Half-life

Drug molecules with short half-life are excellent candidate for sustained-release formulation, since this can reduce dosing frequency. However, this is limited, in that drugs with very short half-lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large.

Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs. So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms.

Some examples of drug with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

2. Absorption

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate the absorption rate constant will probably be poor candidates for sustaining systems. If a drug is absorbed by active transport, or transport is limited to a specific region of intestine, sustained-release preparations

may be disadvantageous to absorption.

3. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism is known and the rate constants for the processes are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however, that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propranolol and lidocaine.

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems. The drugs should not have intestinal first pass effect and should not induce (or) inhibit metabolism are good candidates for sustained release dosage forms.

4. Therapeutic window: The drugs with narrow therapeutic index are not suitable for CRDDS. If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity.

5. Absorption window: The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS. Drugs which absorbed throughout the GIT are good candidates for controlled release

6. Patient physiology: The Physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly.

B. Physiological properties

1. Dose size

In general, single dose of 500-1000 mg is considered maximal for a conventional dosage form.

This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

2. Ionization, PKa & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the PKa of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble.

For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For sustained release formulations much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

Compounds with very low solubility are inherently controlled, since their release over the time course of a dosage form in the GIT will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/mL. Thus for slightly soluble drugs, diffusion systems will be poor choice, since the concentration in solution will be low.

For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are digoxin, warfarrin, griseofulvin and salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms.

3. Molecular size and diffusivity

The ability of drug to diffuse through membrane is called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm2 sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm2/sec. Thus, high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

4. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes.

5. Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation. In general the drugs, which are unstable in GIT environment, are poor candidates for oral sustained release forms.

6. Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are mostly recirculated and not eliminated drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.