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Sustained release drug delivery system

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ABSTRACT
Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. This article contains the basic information regarding sustained-release formulation and also the different types of the same.

Introduction

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[1].

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the reparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form[2-5]. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems6. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug, that is dissolved or dispersed. In fact, matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers[7]. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs[8]. Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® technology) and osmotic pumps with laser drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients[9].

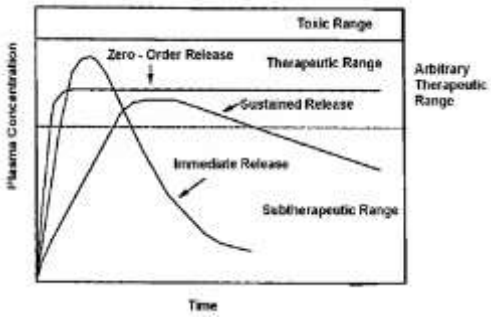

Figure: Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation.

Drawbacks of Conventional Dosage Forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short Half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentrationtime profile is obtained which makes attainment of steady state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur[10].

Terminology

Controlled and Sustained Release, both have been used in inconsistent and confusing manner. Both represent separate delivery process. SR constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. SR system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat

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action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. The ideal way of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems.

This approximation is achieved bycreating a constant concentration in the body or an organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount of drug removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, enterohepatic recycling, sweat, fecal and so on. Since, for most of the drugs these elimination processes are firstorder, it can be said that a certain blood level, the drug will have a specific rate of elimination. The idea is to deliver drug at this exact rate for an extended period. This is represented mathematically as following,

Rate in = Rate out = $k_{elim} \times Cd \times Vd$

Where *Cd* is the desired drug level, *Vd* is the volume of distribution, and *kelim* is the rate constant of drug elimination from the body. Often such exacting delivery rates prove to be difficult to achieve by administration routes other than intravenous infusion. Non-invasive routes, for example. oral are obviously preferred.

Designing sustained-release drug delivery system

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the epithelial membrane to the blood. There are a variety of both physicochemical and biologicalfactors that come into play in the design of such system[11].

Oral Controlled Release Systems

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1) Continuous release systems

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

The various systems under this category are as follow,

A. Dissolution controlled release systems
B. Diffusion controlled release systems
C. Dissolution and diffusion controlled release systems
D. Ion exchange resin- drug complexes
E. pH dependent formulation
F. Osmotic pressure controlled systems

Dissolution Controlled Release Systems

These types of systems are easiest to design. The drug present in such system may be the one:

· With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.

· That produces slow dissolving forms, when it comes in contact with GI fluids.

Having high aqueous solubility and dissolution rate. Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate.

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by

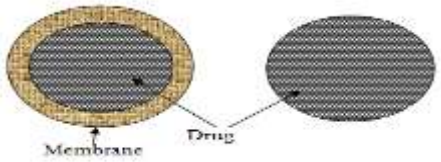
dm/dt=ADS/h

Where,

S = Aqueous solubility of the drug.
A = Surface area of the dissolving particle or tablet.
D = Diffusivity of the drug and
h = Thickness of the boundary layer.

Matrix (Or Monolith) Dissolution Controlled Systems

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employ waxes such as beeswax, carnauba wax which control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices.



b) Reservoir Dissolution Controlled Systems

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

Diffusion controlled release systems

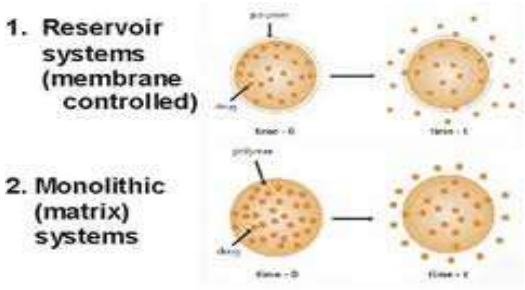
In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation 2

$$\frac{dm}{dt} = ADK \frac{\Delta C}{\ell} \quad \ldots\ldots 2$$

Where,

A = Area,
D = Diffusion coefficient,

K = Partition coefficient of the drug between the drug core and the membrane,
ℓ = Diffusion pathlength and
C= Concentration difference across the membrane.



Diffusion Controlled Drug Release

In order to achieve a constant release rate, all of the terms on the right side of equation 2 must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution.

$$Q = \left[\frac{}{\downarrow} \quad (2C^{D} \varepsilon S)\, S \right] \quad \ldots\ldots\ldots\ldots 3$$

Equation 3 describes the amount of drug released from the systems as derived by Higuchi,
Where, Q = Amount of drug released per unit surface area,
D = Diffusion coefficient of the drug in the release media,
ε = Porosity,
τ = Tortuosity of the matrix,
S = Solubility of the drug in the release media and
C = Concentration of the drug in the tablet.
The two types of diffusion controlled systems are,

Matrix Diffusion Controlled Systems

In this type, the drug is dispersed in an insoluble matrix of rigid, non-swellable hydrophobic material or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as Poly-vinyl chloride and Stearic acid. With the plastic materials, the drug is generally kneaded with the solution of Poly-vinyl chloride in an organic solvent and then granulated. The granules are then compressed into tablets, swellable matrix systems are popular for sustaining the releaseof highly water soluble drugs. The materials for such matrices are,
Hydrophilic gums: Guar gum, Tragacanth
Synthetic: Polyacrylamides
Semi-synthetic: Hydroxypropylmethyl cellulose, Carboxyl methyl cellulose

The drug release in this type of controlled release systems follows Fickian first order diffusion under equilibrium condition[12, 13].

Matrix Tablet

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown in Table 1, which includes both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and crosslinked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface[14.15].

Sr No.	Matrix characteristic	Material
1.	Insoluble ,inert	Polyethylene, Polyvinyl chloride,Ethyl cellulose
2.	Insoluble, erodible	Carnauba wax, Stearic acid, Polyethylene glycol

Matrix Tablets can be classified as,

Hydrophilic Matrix Tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behavior from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,

Cellulose Derivatives

Hydroxyethylcellulose, Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps, Sodium carboxymethylcellulose and Methylcellulose 400 and 4000 cps.

Non-Cellulose Natural or Semisynthetic Polymers

Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of mannose and Galactose, Chitosan and Modified starches.

Polymers of Acrylic Acid

Polymers which are used in acrylic acid category is Carbopol 934. Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums.

Fat-Wax Matrix Tablet

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as

dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

Plastic Matrix Tablet (Hydrophobic Matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
3. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses.

For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

Biodegradable Matrices

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymetic process into olegomers and monomers that can be metabolised or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (*Phaephyceae*) by the use of dilute alkali. Matrix system can also be classified according to their porosity and consequently, macroporous, microporous and non-porous systems can be identified as,

1. Macroporous Systems

In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Microporous System

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50-200 A°, which is slightly larger than diffusant molecules size.

3. Non-Porous System

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present16. Different drugs and polymers used in sustained-release based on matrix table is given in the following table.[17-23]

Table-2: Different Drugs and Polymers Used in Sustained-Release Based on Matrix Tablet

Drug	Polymer
Metoclopramide Hydrochloride	Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose(CMC), Ethyl Cellulose (EC)
Ibuprofen	Ethyl cellulose,Cellulose acetate phthalate
Metoprolol Succinate	HPMC K100M,Xanthan gum
Ambroxol Hydrochloride	HPMC
Tramadol Hydrochloride	Xanthan gum,Guar gum
Tramadol Hydrochloride	HPMC K15,Karaya gum
Aceclofenac	Carbopol 971P

Drug Release From Matrix Systems

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

d) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation,

$$\frac{dM}{dh} = \frac{Co.dh - Cs}{2}$$

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory,

$$dM = \frac{(Dm.Cs)}{h}.dt$$

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory,

$$dM = \frac{(Dm.Cs)}{h} \cdot dt \quad \ldots\ldots\ldots\ldots 5$$

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation 4 and 5 and integrating

$M = [Cs \cdot Dm \cdot (2\,Co - Cs \cdot t)]1/2$ …… 6

When the amount of drug is in excess of the saturation concentration, then

$M = [Cs \cdot Dm \cdot Co \cdot t]1/2$. …… 7

Equation 6 and 7 indicates the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the

simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix,

$M = [2 D. Ca . p / T. (2 CO – p. Ca) t]1/2$ ….. 8

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium

T = Diffusional pathlength

For pseudo steady state, the equation can be written as,

$M = [2 D . Ca . CO (p / T) t]1/2$…..…… 9

The total porosity of the matrix can be calculated with the following equation,

$p = pa + Ca / \rho + Cex / \rho ex$ ..…… …. 10

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

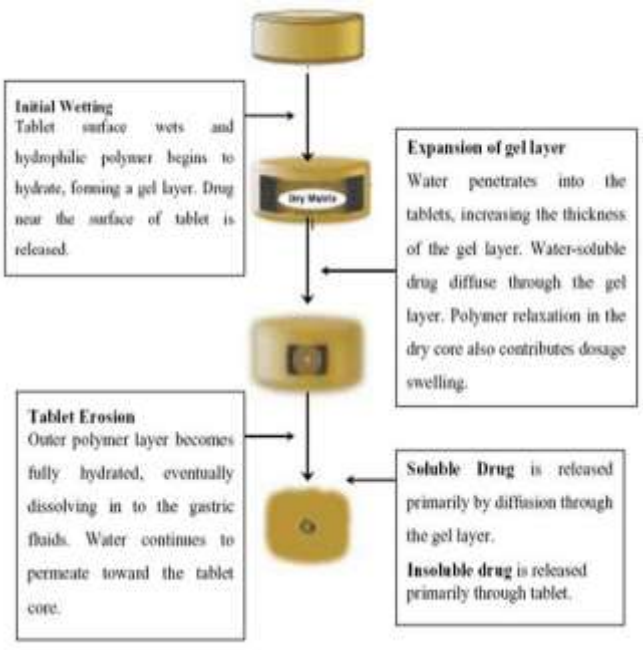
Cex = Concentration of water soluble excipients

For the purpose of data treatment, Equation 10 can be reduced to,

$M = k . t1/2$ ..…….. 11

Where k is a constant, so that the amount of drug released versus the square root of time will be linear. If the release of drug from matrix is diffusion-controlled. In this case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters,

• Initial concentration of drug in the matrix
• Porosity
• Tortuosity
• Polymer system forming the matrix
• Solubility of the drug[24].



Reservoir devices

These systems are hollow containing an inner core of the drug surrounded in the water insoluble polymer membrane. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate. The disadvantage of reservoir devices over matrix diffusion controlled system is a chance of sudden drug dumping.

Dissolution and Diffusion Controlled Release Systems

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

Delayed transit and continuous release systems

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are mucoadhesive systems and size based systems.

Delayed Release Systems

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

✓ Destroyed in the stomach or by intestinal enzymes
✓ Known to cause gastric distress
✓ Absorbed from a specific intestinal site
✓ Meant to extent local effect at a specific GI site

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release systems[25, 26]

Biological factors influencing oral sustained-release dosage form design

- Biological half life.
- Absorption.
- Metabolism.

Biological Half Life

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with halflives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

Absorption

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tarct is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum

apparent absorption rate constant of 0.17-0.23 h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds try to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bioadhesive materials.

Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

Drug should have law half-life(<5 hrs)
Drug should be freely soluble in water.
Drug should have larger therapeutic window.
Drug should be absorbed throughout the GIT.

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

Physicochemical factors influencing oral sustained-release dosage form design

Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5- 1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

Ionization, *pka* and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined. Compunds with very low solubility (<0.01 Smg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

Partition Coefficient

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug[27].

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