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A REVIEW ON: SUSTAINED RELEASED TECHNOLOGY

Dusane Abhijit Ratilal*, Gaikwad Priti D, Bankar Vidyadhar H, Pawar Sunil P
P.S.G.V.P.M's College of Pharmacy, Shahada, Dist. Nandurbar, 425 409, Maharashtra, India

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*Corresponding author
Email: anytimeabhijit@gmail.com

ABSTRACT
Of all drug delivery systems, oral drug delivery remains the most preferred option for administration for various drugs. Through this route tablet, capsule, suspensions, solutions, syrups are administered. 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. 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. Wide variety of polymers is available for retarding the release rate of drug hence sustains the action of drug. 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. Oral sustained release (SR) or controlled release (CR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamic properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. This review describes the various types of sustained release or controlled release dosage forms, along with these factors influencing the design and performance of sustained/controlled release products are also discussed.

KEYWORDS: Absorption window, Controlled release, Half-life, Sustained release.

INTRODUCTION

Sustained release, sustained action, prolonged action controlled release, extended released, depot release are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug. Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance (various: some acrylics, even chitin; these substances are often patented) such that the dissolving drug must find its way out through the holes in the matrix.

Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser-drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be later excreted through normal digestion.

In some SR formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface. There are certain considerations for the formation of sustained-release formulation,

i. If the active compound has a long half-life (over 6 hours), it is sustained on its own.
ii. If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
iii. If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
iv. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.[1]

The goal in designing delayed release sustained or controlled delivery system is to,

i. Reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.
ii. It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection or for the life time of the patient, as in hypertension or diabetes.
iii. It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.
iv. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
v. The safety margin of high potency drug can be increase and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient.[2, 3]

Drawbacks Of Conventional Dosage Forms

i. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
ii. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
iii. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
iv. 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.[4,5]

Advantages Of Sustained Release Formulations Include

i. Uniform release of drug substance over time.
ii. Reduction in frequency of intakes.
iii. Reduced adverse side effects.
iv. Better patient compliance.
v. A sustained release dosage form can be created using lipid excipients to form either a water insoluble matrix or a hydrophobic film around an active drug.[6]

Benefits Of Modified Drug Delivery System

i. Decreased in dosing frequency.
ii. Reduced peak to through ratio of drug in systemic circulation.
iii. Reduced rate of rise of drug concentration in blood.
iv. Sustained and Consistent blood level with in the therapeutic window.
v. Enhanced bioavailability.
vi. Customized delivery profiles.
vii. Reduced side effects.
viii. Improved patient compliance.[7]

Modified release drug products have been successfully marketed for many years. These products include dosage forms for oral and transdermal administration, as well as injectable and implantable system. Some marketed modified release product are given Table 1.

Physiology Of Gastrointestinal Tract

It is well recognized that the stomach may be used as a 'depot' for sustained-release (SR) dosage forms both in human and veterinary applications. The stomach is anatomically divided into three parts fundus, body and pylorus. The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter digestive series of electrical events which cycle both through the stomach and small intestine every 2–3 hrs. The activity is called the inter digestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases as described by Wilson and Washington.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[8-10]

Classification Of Drug Delivery Systems (DDS)

1. Diffusion-Controlled Drug Delivery System

i. Oral
ii. Matrix-type systems
iii. Hydrophobic matrix systems
iv. Hydrophilic matrix systems
v. Reservoir-type systems
vi. Transdermal
vii. Drug in adhesive systems
viii. Monolithic adhesive systems
ix. Multilaminate adhesive systems
x. Inert matrix systems
xi. Semisolid matrix systems
xii. Reservoir matrix systems
xiii. Other diffusion controlled systems
xiv. Intrauterine devices and intravaginal rings
xv. Intraocular inserts
xvi. Subcutaneous implants

2. Dissolution-Controlled Drug Delivery System

i. Based on dissolution-controlled release of solid particles
ii. Based on dissolution-controlled release coated technologies
iii. Based on dissolution-controlled release matrix technologies

3. Osmotic Controlled Drug Delivery System

a. Osmotic delivery systems for solids
Type I: Single compartment
Type II: Multiple compartments
b. Osmotic delivery systems for liquids

4. Biodegradable Polymeric Drug Delivery System

i. Microparticles
ii. Nanoparticles
iii. Implants

5. Ligand-Based Targeting Drug Delivery System

6. Programmable Drug Delivery System

i. Pulsatile systems
ii. Feedback-controlled systems

7. Stimulus Responsive

i. Physically modulated: Temperature
ii. Chemically modulated: pH dependent[11]

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,

$$dm/dt = ADK\,\Delta C/l$$

Where,
A = Area,
D = Diffusion coefficient,
K = Partition coefficient of the drug between the drug core and the membrane,
l = Diffusion path length and
C= Concentration difference across the Membrane.

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 for example 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 equation,

$$dm/dt = ADS/h$$

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

a) Matrix (or Monolithic) 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 employs waxes such as Bees wax, 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.[12,13]

Biodegradable Polymeric Drug Delivery System

Nanoparticles made from solid lipids are attracting increasing attention as colloidal drug carriers for i.v. application. The nanoparticles are in the submicron size range (50–1000 nm) and they are composed of physiological lipids. At room temperature the particles are in the solid state. Therefore, the mobility of incorporated drugs is reduced, which is a prerequisite for controlled drug release. They are stabilized with non-toxic surfactants like Poloxamer and Lecithin. Due to the production by high pressure homogenization they can be produced on large industrial scale. In addition, this production method avoids the use of organic solvents. Compared to traditional carriers the SLN have combine advantages of polymeric nanoparticles and o/w fat emulsions for parenteral administration. To-date, several studies concerning optimization of production parameters, long term stability, recrystallization behaviour, morphological characterization and *in-vivo* toxicity have been undertaken. In addition, investigations about drug incorporation and release are an important tool in the design and evaluation of a potential drug carrier system. A basic problem in early work with lipid particles in the nanometer range was the generally observed burst release of drugs; a prolonged release could not be achieved. The lack of a prolonged release would severely limit the applicability of the system for drug delivery. The aim of this investigation was therefore, to assess if a prolonged release is basically possible. Tetracaine (base), Etomidate (base) and Prednisolone were used as lipophilic model drugs. The crystalline state of the particles was analyzed and a mechanism suggested leading to the observed differences in release behavior of the drug-loaded particles.[14]

4. OSMOTIC DRUG DELIVERY SYSTEM

Osmotic drug delivery systems are new approach for a controlled release dosage form. Various patents available for osmotic drug delivery system like Rose-Nelson pump, Higuchi-leeper pump, Higuchi-Theeuwes pump, Elementary Osmotic Pump etc. An ODD is useful for poorly soluble drug, for pulsatile drug release, zero order release. Various techniques available for preparation of ODDS include Push-Pull Osmotic Pump, Osmotic Brusting Osmotic pump, Liquid Oral Osmotic System, Sandwiched Osmotic Tablets (SOTS), Delayed Delivery Osmotic Device, Monolithic Osmotic System and Controlled Porosity Osmotic Pump. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract. These systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice and nature of the rate-controlling membrane. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate. [15]

5. PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children and hypercholesterolemia. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, recent update and PDDS product currently available in the market.[16]

6. FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.[17]

FACTORS GOVERNING THE DESIGN OF SUSTAINED RELEASED DOSAGE FORMS

Physico-Chemical Properties

1. Molecular Size and Diffusivity

A drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended-release systems must diffuse through a rate-controlling polymeric membrane or matrix. The ability of a drug to diffuse in polymers, its so-called diffusivity (diffusion coefficient D), is a function of its molecular size (or molecular weight). For most polymers, it is possible to relate log D empirically to some function of molecular size as[18],

$$\log D = -S_v \log u + k_v = -S_M \log M + k_m$$

Where,

V = Molecular volume,

M = Molecular weight,

S_v, S_M, k_v, k_m = Constants.

The value of D, thus is related to the size and shape of the cavities as well as size and shape of drugs. Generally, values of the diffusion coefficient for drugs of intermediate molecular-weight (i.e 150 to 400 Da) through flexible polymers range from 10-6 to 10-9 cm^2/sec, with values in the order of 10-8 being most common.[19] A value of approximately 10-6 is typical for these drugs through water as the medium. For drugs with a molecular weight greater than 500 Da, their diffusion coefficients in many polymers are frequently so small that they are difficult to quantify (i.e less than 10-12 cm^2/sec). Thus, high-molecular-weight drugs should be expected to display very slow release kinetics in extended release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.[20]

2. Aqueous Solubility

Solubility is defined as the amount of material that remains in solution in a given volume of solvent containing undissolved material. It is the thermodynamic property of a compound. The fraction of drug absorbed into the portal blood is a function of the amount of drug in the solution in the G.I tract, i.e., the intrinsic permeability of the drug. For a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and the partition into the absorbing membrane.[21] The aqueous solubility of a

drug influences its dissolution rate, which in turn establishes its concentration in solution and hence, the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility, as shown by the Noyes-Whitney equation that, under sink conditions is,

$$dC/dt = k_D\, A.C_s \quad \ldots(1)$$

Where,
dc/dt = Dissolution rate,
k_D = Dissolution rate constant,
A = Total surface area of the drug particles,
C_s = Aqueous saturation solubility of the drug.
The dissolution rate is constant only if a remains constant, but the important point to note is that the initial rate is directly proportional to Cs. Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer from oral bioavailability problems. The aqueous solubility of weak acids or bases is governed by the pKa of the compound and the pH of the medium.
For a weak acid,

$$S_t = S_0\,(1+Ka/\,[H^+]) = S_0(1+10^{pH\text{-}pKa}) \quad \ldots(2)$$

Where,
S_t = Total solubility (both the ionized and unionized forms) of the weak acid,
S_0 = Solubility of the unionized form,
K_a = Acid dissociation constant,
$[H^+]$ = Hydrogen ion concentration in the medium.[22]
Similarly,
For a weak base

$$S_t = S_0\,(1+[H+]/Ka) = S_0(1+10^{pKa\text{-}pH}) \quad \ldots(3)$$

Where,
St = Solubility (both the conjugate acid and freebase forms) of the weak base,
S_0 = Solubility of the free-base form,
K_a = Acid dissociation constant of the conjugate acid.
Equations 2 and 3 predict that the total solubility of a weak acid or base with a given pKa can be affected by the pH of the medium. Considering the pH partition hypothesis, the importance of equations 2 and 3 relative to drug absorption is evident. The pH – partition hypothesis simply states that the unionized form in the stomach (pH =1 to 2), their absorption will be excellent in such an acidic environment. On the other hand, weakly basic drugs exist primarily in the ionized form (conjugate acid) at the same site and their absorption will be poor. In the upper portion of the small intestine, the pH is more basic (pH = 5 to 7), and the reverse will be expected for weak acids and bases. The ratio of Equation 2 or 3 written for both the pH of the gastric or intestinal fluid and the pH of blood is indicative of the driving force for absorption based on pH gradient. Ideally, the release of an ionizable drug from an extended release system should be programmed in accordance with the variation in pH of the different segments of the gastrointestinal tract so that the amount of preferentially absorbed forms and thus the plasma level of the drug, will be approximately constant throughout the time course of drug action.[21] The Bio-pharmaceutical Classification System (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral drug absorption. Classification of drugs according to BCS,

Class I : High solubility-High permeability
Class II : Low solubility-High permeability
Class III : High solubility-Low permeability
Class IV : Low solubility-Low permeability

3. High solubility

Largest dose dissolves in 250 ml of water over a pH range 1-8.

4. High permeability

Extent of absorption is > 90% Class III and Class IV drugs are poor candidates for sustained release dosage forms. Compound with solubility below 0.1 mg/ml face significant solubilization obstacles and often compounds with solubility below 10 mg/ml present difficulties related to solubilization during formulation.[22] In general, extremes in aqueous solubility of a drug are undesirable for formulation into an extended-release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into an extended release system may not provide considerable benefits over conventional dosage forms. Even, if a poorly soluble drug were considered a candidate for formulation into an extended-release system a constraint would be placed on the type of delivery system that could be used. For example, any system relying on diffusion of the drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is drug concentration in the polymer or solution and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it is often quite difficult to decrease its dissolution rate and slow its absorption.[23] A drug of high water solubility can dissolve in water or gastrointestinal milieu readily and tends to release from its dosage form in a burst and thus is absorbed quickly, leading to a sharp increase in the drug blood concentration. Compared to less soluble drugs, it is often difficult to sequester a highly water soluble drug in the dosage form (such as tablet) and retard the drug release, especially when the drug dose is high. Preparing a slightly soluble form of a drug with normally high solubility is one possible method for producing extended release dosage forms.[24] The pH dependent solubility, particularly in the physiological pH range would be another problem for SR/CR formulation because of the variation in the pH throughout the gastro intestinal tract and hence variation in dissolution rate.

Examples of Drugs Which are Poor Candidates for Sustained Release Systems

- **i.** Drugs, limited in the absorption by their dissolution rates are: Digoxin, Warfarin, Griseofulvin and Salicylamide.
- **ii.** Drugs poorly soluble in the intestine (acid soluble basic drugs) are: Diazepam, Diltiazem, Cinnarizine, Chlordiazepoxide and Chlorpheniramine.

5. pKa - Ionization Constant

The pKa is a measure of the strength of an acid or a base. The pKa allows determining the charge on drug molecule at any given pH. Drug molecules are active in only the undissociated state and also unionized molecules cross these lipoidal membranes much more rapidly than the ionized species. The amount of drug that exists in unionized form is a function of dissociation constant of a drug and pH of fluid at absorption site. For a drug to be absorbed, it must be in unionized form at the absorption site. Drugs which exist in ionized form at the absorption site are poor candidates for sustained/controlled dosage forms.[25]

6. Partition Coefficient

Partition coefficient influences not only the permeation of drug across the biological membranes but also diffusion across the rate controlling membrane or matrix between the time when a drug is administered and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (i.e, its membrane permeability) in its apparent oil/water partition coefficient defined as,

$$K = C_O/C_W \quad \ldots(5)$$

Where,
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, drugs with extremely large values of K are very oil-soluble and will partition into membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug generally is defined by the Hansch correlation, which describes a parabolic relationship between the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient.[26] The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. As a first approximation, the more effectively a drug crosses membranes, the greater its activity. There is also an optimum partition coefficient below this optimum result in decreased lipid solubility and the drug will remain localized in the first aqueous phase it contacts. Values larger than the optimum result in poorer aqueous solubility but enhanced lipid solubility and the drug will not partition out of the lipid membrane once it gets in. The value of K at which optimum activity is observed is approximately 1000/1 in n-octanol /water. Drugs with a partition coefficient that is higher or lower than the optimum are, in general, poorer candidates for formulation into extended release dosage forms.[27]

7. Stability

One important factor for the loss of drug is through acid and/or metabolism in the GIT when administered orally. It is possible to significantly improve the relative bioavailability of a drug that is unstable in G.I. by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach the most appropriate controlling unit would be one that release its contents only in the intestine. The release in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling such as in this case would be one that releases its contents, only in the stomach. So, drugs with significant stability problems in any particular area of the G.I. tract are less suitable for formulation into controlled release systems that deliver the contents uniformly over the length of GIT.[28, 29]

Acid Unstable Drugs (Stomach)

For example: Rabeprazole, Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rifamipicin, Mesalazine, Erythromycin, Riboflavin

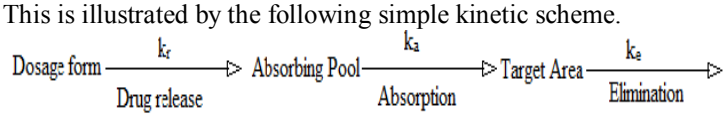
Alkaline Unstable Drugs (Drugs that are Unstable in Intestine and Colon)

For example: Captopril, Ranitidine.

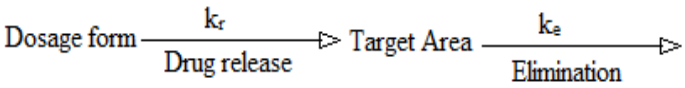
PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

1. Release Rate and Dose

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments and suppositories. For purposes of this discussion, these dosage forms can be considered to release these active ingredients into an absorption pool immediately. This is illustrated by the following simple kinetic scheme.



The absorption pool represents a solution of the drug at the site of absorption, and the terms k_r , k_a and k_e are first order rate constants for drug release, absorption, and overall elimination, respectively. Immediate release from a conventional dosage form implies that $k_r >>> k_a$ or alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate limiting step in delivery of the drug to its target area. For non immediate-release dosage forms, $k_r <<< k_w$ that is release of drug from the dosage form is the rate-limiting step. This causes the above kinetic scheme to reduce to,



Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared with the drug release phase. Thus, the effort to develop a non-immediate-release delivery system must be directed primarily to altering the release rate by affecting the value of kr. Although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases, this is the ideal starting goal of an extended-release delivery system. In fact, in some cases optimum therapy is achieved by providing oscillating, rather than constant drug levels. An example of this is antibiotic therapy, where the activity of the drug is required only during the growth phase of the microorganism.[30]

The ideal goal in designing an extended-release system is to deliver drug to the desired site at a rate according to the needs of the body (i.e., a self-regulated system based on feedback control). However, this is a difficult assignment. Although some attempts have been made to achieve this goal, such as with the self-regulating insulin pump, there is no commercial product representing this type of system as yet. In the absence of feedback control, we are left with a simple extending effect. The pivotal question is at what rate should a drug be delivered to maintain a constant blood drug level. This constant rate should be the same as that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow zero-order kinetics, as shown by,

$$k^0_r = \text{Rate In} = \text{Rate Out} = k_e . C_d . V_d$$

Where,
k^0_r = Zero-order rate constant for drug release (amount/time),
k_e = First-order rate constant for overall drug elimination (time-1),
C_d = Desired drug level in the body (amount/volume),
V_d = Volume of the space in which the drug is distributed.
The values of k_e, C_d, and V_d needed to calculate k^0_r are obtained from appropriately designed single-dose pharmacokinetic studies. The above equation provides the method to calculate the zero-order release rate constant necessary to maintain a constant drug blood or tissue level for the simplest case, where drug is eliminated by first order kinetics. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level.[31] It is important to recognize that while zero-order release may be desirable theoretically, non-zero-order release may be equivalent clinically to constant release in many cases. Aside from the extent of intra and inter subject variation is the observation that for many drugs, modest changes in drug tissue levels do not result in an improvement in clinical performance. Thus, a non-constant drug level may be indistinguishable clinically from a constant drug level. To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage form generally consists of two parts: an initial priming dose, D_i, that releases drug immediately and maintenance or sustaining dose, Dm. The total dose, W, thus required for the system is,

$$W = D_i + D_m$$

For a system in which the maintenance dose release drug by a zero-order process for a specified period of time, the total dose is,

$$W = D_i + k_r^0 T_d - k_r^0 T_p$$

Where,
Td = Total time required for extended release from one dose.
If the maintenance dose begins release of drug at the time of dosing (t = 0), it will add to that which is provided by the initial dose, thus

increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose,

$$W = D_i + k_r^0 Td - K_r^0 T_p$$

The correction factor $k_r^0 Tp$ is the amount of drug provided during the period from t = 0 to the time of the peak drug level T_p. No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose does not begin to release drug until time T_p. It already has been mentioned that a perfectly invariant drug blood or tissue level versus time profile is the ideal starting goal of an extended release system. The way to achieve this, in the simplest case, is use of a maintenance dose that releases its drug by zero-order kinetics. However, satisfactory approximations of a constant drug level can be obtained by suitable combinations of the initial dose and a maintenance dose that releases its drug by a first – order process. The total dose for such a system is,

$$W = D_i + (k_e C_d / k_r V_d)$$

Where,

k_r = First-order rate constant for drug release (time-1),

k_e, C_d, V_d = As defined previously.

If the maintenance dose begins releasing drug at t = 0, a correction factor is required just as in the zero-order case. The correct expression in this case is,

$$W = D_i + (k_e C_d / k_r) V_d - D_m k_e T_p$$

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most extended-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal extended-release system that releases drug by zero-order kinetics, the multiple dosing regimens is analogous to that used for a constant intravenous infusion.[32] Since an extended-release system is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in a conventional dosage form will give some indication of the total amount of drug needed in an extended release preparation. For the drugs requiring large conventional doses, the volume of the sustained dose may be too large to be practical or acceptable, depending on the route of administration. The same may be true of drugs that require large release rate from the extended-release system (For example, drugs with short half-lives). If the dose of a drug is high (For example, those that requiring a daily dose exceeding 500 mg), it becomes more challenging to develop sustained release oral dosage forms. For short half-life drugs, to provide a once a day tablet, it requires not only that a large amount of drug to be incorporated in a dosage unit to provide the daily dose, but also the dosage units be small in size to allow for ease of swallowing by the human. The requirement for small sizes would leave little space in the dosage unit for other ingredients needed to control the drug release. The size of the dosage unit becomes even more critical with highly water-soluble drugs since even a larger amount of inactive in gradients (For example, more than 50% of the total weight) is usually needed to provide the sustained release property, according to the conventional SR methods.[33]

BIOLOGICAL FACTORS

1. Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into an extended release system. The most critical in case of oral administration is $K_r <<< K_a$. Assuming that the transit time of drug through the absorptive area of gastrointestinal tract is between 9-12 hours, the maximum absorption half-life should be 3-4 hours. This corresponds to a minimum absorption rate constant Ka value of 0.17-0.23/hr necessary for about 80-95% absorption over a 9-12 hr transit time.[34] For a drug with a very slow rate of absorption ($K_a << 0.17$/hr), the first order release rate constant K_r less than 0.17/hr results in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drug will be difficult to be formulated into extended release systems where the criterion $K_r <<< K_a$ must be met.[35] If the drug were erratically absorbed because of variable absorptive surface of gastrointestinal tract, design of the sustained release product would be more difficult or prohibitive. Example, The oral anticoagulant Dicoumarol, Iron.

Drugs Absorbed by Active Transport System are Unsuitable for Sustained/Controlled Drug Delivery System

Methotrexate, Enalapril, Riboflavin, Pyridoxine, 5-Fluorouracil, 5-Bromouracil, Nicotinamide, Fexofenadine, Methyl-dopa.

Drugs Absorbed Through Amino Acid Transporters in The Intestine

Cephalosporines, Gabapentine, Baclofen, Methyl-dopa, Levo-dopa.

Drugs Transported Through Oligo – Peptide Transporters

Captopril, Lisinopril, Cephalexine, Cefadroxil, Cefixime.

Drugs Required to Exert a Local Therapeutic Action in the Stomach are Unsuitable for Sustained Controlled Drug Delivery

Misoprostol, 5-Fluorouracil, Antacids, Anti helicobacter pylori agents.

2. Absorption Window

Some drugs display region specific absorption which is related to differential drug solubility and stability in different regions of G.I.T, as a result of changes in environmental pH, degradation by enzymes, etc. These drugs show absorption window, which signifies the region of G.I tract where absorption primarily occurs. Drugs released from sustained/controlled release systems, after absorption window has been crossed goes waste with little/no negligible absorption. Hence absorption window can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of sustained/controlled release drugs.[36, 37]

Examples of Drugs Exhibiting the Site Specific Absorption in Stomach or Upper Parts of Small Intestine (Absorption Window) are

Acyclovir, Captopril, Metformin, Gabapentin, Atenolol, Furosemide, Ranitidine, Levo-dopa, Sotalol, Salbutamol, Riboflavin, Sulfonamides, Loratadine, Cephalosporines, Tetracyclin, Verapamil, Thiamine, Sulpiride, Baclofen, Nimesulide, Cyclosporine, Quinolines.

3. Distribution

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in the overall elimination kinetics. Apparent volume of distribution and ratio of drug in tissue to plasma (T/P) concentration are used to describe the distribution characteristics of a drug. For drugs which have apparent volume of distribution higher than real volume of distribution i.e., drugs which are extensively bound to extra vascular tissues. For example, Chloroquine, the elimination half life is decreased i.e., the drug leaves the body gradually provided drug elimination rate is limited by the release of drug from tissue binding sites and that drug is released from the tissues to achieve concentrations exceeding the threshold level or within the therapeutic range, one can assume that such drugs are inherently sustained. The larger the volume of distribution, the more the drug is concentrated in the tissues compared with the blood. It is the drug in the blood that is exposed to hepatic or renal clearance, so that when the distribution volume is large these mechanisms have fewer drugs to work on. By contrast, if the volume of distribution is small, most of the drug in the body is in the blood and is accessible to the elimination process. To avoid the ambiguity inherent in apparent volume of distribution as estimation of amount of drug in body, the T/P ratio is used. If the amount of drug in central compartment 'P' is known, the amount of drug in peripheral compartment 'T' and hence the total amount of drug in the body can be calculated by,

$$T/P = k_{12} (k_{21} - \beta)$$

Where,
β = Slow disposition rate constant.

4. Metabolism

The metabolism of a drug can either inactivate an active drug or convert an inactive drug to active metabolite. Complex metabolic patterns would make the sustained release design much more difficult particularly when biological activity is wholly or partly due to a metabolite as in case of Isosorbide 2, 5-dinitrate. There are two areas of concern related to metabolism that significantly restrict SR product design. First, if a drug upon chronic administration is capable of either inducing or inhibiting enzyme synthesis, it will be a poor candidate for a SR/CR product because of the difficulty of maintaining uniform blood levels of a drug. Second, if there is a variable blood level of a drug through either intestinal (or tissue) metabolism or through first pass effect, this also will make formulation of sustained dosage form difficult, since most of the process are saturable, the fraction of the drug loss would be dose dependent and that would result in significant reduction in bioavailability if the drug is slowly released over a extended period of time.[38]

Fluctuating Drug Blood Levels Due to Intestinal Metabolism upon Oral Dosing

For example, Salicylamide, Isoproterenol, Chlorpromazine, Clonazepam, Hydralazine and Levodopa.

Fluctuating Drug Blood Levels Due to First Pass Hepatic Metabolism upon Oral Dosing

For example; Nortriptyline, Phenacetin, Morphine, Propranolol.

Fluctuating Blood Levels due to Enzyme Induction are Poor Candidates for Sustained Release Dosage Forms

Griseofulvin, Phenytoin, Primidone, Barbiturates, Rifampicin, Meprobamate, Cyclophosphamide.

Fluctuating Blood Levels due to Enzyme Inhibition are Poor Candidates for Sustained Release Dosage Forms

Isoniazid, Cimetidine, Amiodarone, Erythromycin, Fluconazole, Ketoconazole, MAO–inhibitors, P-Aminosalicyclic acid, Allopurinol, Coumarins.

5. Dose Dependent Bioavailability

In case of Propoxyphene bioavailability is dose dependent. Only 18% of 65 mg dose, 28% of 130 mg dose, 33% of 195 mg dose reaches the systemic circulation due to first pass effect. It makes the SR/CR dosage form less desirable.

6. Elimination Half Life

Half life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half and is determined by both clearance (Cl) and volume of distribution (VD),

$$t_{1/2} = 0.693.V_d/Cl$$

Half life is increased by increasing in volume of distribution or a decrease in clearance and vice-versa. The larger the volume of distribution the more the drug is concentrated in the tissues compared with the blood. If the volume of distribution is small, most of the drug in the body is in the blood and is accelerated to the elimination process. For drugs that follow linear kinetics, the elimination half life is constant and does not change with dose or drug concentration. For drugs that follow non-linear kinetics, the elimination half-life and drug clearance both change with dose or drug concentration. Drugs with short half lives (<2hrs) and high dose impose a constraint on formulation into sustained/controlled release systems because of the necessary dose size and drugs with long half-lives (>8hr) are inherently sustained.[39] Sustained release products for drugs with intrinsically long biologic half-lives are available. As expected, little or no therapeutic advantages have been demonstrated in these products over conventional dosage forms. For examples, Meprobamate (11.3 hr), Amytriptyline (21 hr). Sustained release corticosteroids are unnecessary from the stand point of therapy, undesirable from the point of view side effects and un-physiological from that of the diurnal variations in Cortisol secretions. Infact, sustained formulations of Prednisolone sodium phosphate and Methyl prednisolone have been shown to be equally effective as conventional oral tablets offering no advantages over the latter.

7. Drug -Protein Binding

The drug can bind to components like blood cells and plasma proteins and also to tissue proteins and macromolecules. Drug protein binding is a reversible process. As the free drug concentration in the blood decreases, the drug-protein complex dissociates to liberate the free drug and maintain equilibrium. Due to this reversible binding of a drug, the free drug levels of the drug are maintained for long time in the blood leading to a long biological half-life. A protein bound drug due to its high molecular size is unable to enter into hepatocytes, resulting in reduced metabolism. The bound drug is not available as a substrate for liver enzymes there by further reducing the rate of metabolism. The glomerular capillaries do not permit the passage of plasma-protein and drug protein complexes. Hence only unbound drug is eliminated. The elimination half-life of drugs generally increases when the percent of bound drug to plasma increases. Such drugs need not be formulated into sustained/controlled release formulations. Since blood proteins are mostly re-circulated, not eliminated, high drug protein binding can serve as a depot for drug producing a prolonged drug action. The role of protein binding as a factor in formulation of SR/CR dosage forms can be explained by considering angiotensin-II antagonist class of drugs. The drugs of this class are highly protein bound (99%). Tasosartan is a long acting AT-II receptor blocker with a protein binding of 99.8%, while it's long acting active metabolite Enoltasosartan has a protein binding 99.9%. In a study AT-II receptor blockade effect of single dose of Tasosartan (100 mg oral, 25 mg iv) and Enoltasosrtan (25 mg iv) were compared. It was found that Tasosartan induced rapid and sustained blockade of AT-II receptors. Tasosartan blocked 80% of AT-II receptors 1-2 hrs of drug administration and still had 40% effect at 32 hrs. In contrast the blockade induced by the Enoltasosartan was markedly delayed and hardly reached 60-70% despite i.v administration and high plasma levels. This delayed *in-vivo* blockade effect for Enoltasosartan appears to be due to high and tight protein binding, leading to decrease in affinity for receptors and slower receptor association rate.[40]

8. Duration of Action

Duration of action is the time period for which the blood levels remain above the MEC and below the MSC levels (or) more specifically within the therapeutic window. Drugs acting for long duration are unsuitable candidates for formulation into SR/CR forms. Receptor occupation, Tissue binding, Half life, Metabolism, Partition coefficient, Irreversible binding to cells are some parameters which are responsible for long duration of action of drugs.[41]

9. Therapeutic Index

It is most widely used to measure the margin of safety of a drug.

$$TI = TD_{50} / ED_{50}$$

The longer the value of T.I the safer is the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its T.I value is greater than 10.

CONCLUSION

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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Table 1: Example of marketed modified release product

Name	Marketer	Dosage form	Indication
Carbotrol	Shri Us	Oral capsule	Epilepsy
Glucotrol Xl	Pfizer	Oral Tablet	Hyperglycaemia
Adderall XR	Shri Us	Oral capsule	ADHD
Procardia Xl	Pfizer	Oral Tablet	Angenia
Ortho Evra	Ortho – Mcneil	Trans Dermal Patch	Hypertension
Dura gesic	Janssen	Trans Dermal Patch	Contraceptiv
Climaa	Berlex	Trans Dermal Patch	Chronic pain
Cata Press TTS	Boehringer	Trans Dermal Patch	Oestrogen replacement
Doxil	TAP	Intravenous infusion	Ovearian cancer Kaposi's sarcoma
Viadour	Ortho biotech Bayer	Subcupaneous Implant	Advance prostate cancer