

*Review Article***Factors Influencing the Design and Performance of Oral Sustained/Controlled Release Dosage Forms****Ranjith Kumar Mamidala, Vamshi Ramana, Sandeep G, Meka Lingam, Ramesh Gannu and Madhusudan Rao Yamsani***

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ABSTRACT: Of all drug delivery systems, oral drug delivery remains the most preferred option for administration for various drugs. Availability of wide variety of polymers and frequent dosing intervals helps the formulation scientist to develop sustained/controlled release products. Oral Sustained release (S.R) / Controlled release (C.R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutic, 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 factors influencing the design and performance of sustained/controlled release products along with suitable illustrations.

KEYWORDS: Sustained release; Absorption window; Stability; Receptor-occupation; Lipophilicity; Clearance; Apparent volume of distribution; Half-life

Introduction

Oral drug delivery method is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. Popularity of the route may be ease of administration as well as traditional belief that by oral administration the drug is due to the well absorbed into the food stuff ingested daily (Howard and Loyd, 2005). Sustained release (S.R)/ (Since their introduction). Controlled release (C.R) pharmaceutical products have gradually gained medical acceptance and popularity. Regulatory approval for marketing and their pharmaceuticals superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized (Lachman et al., 1998). Modified release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastro intestinal disturbances.

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Terminology

Modified Release Drug Product: 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.

Types of Modified Release Drug Products

Extended Release Dosage Forms: A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form. Ex: Controlled release, Sustained release.

Sustained release: It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a pre-determined rate.

Controlled release: It includes any drug delivery system from which the drug is delivered at a predetermined rate over a long period.

Delayed Release Dosage Forms: A dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Ex: Enteric coated dosage forms.

Targeted Release Dosage Forms: A dosage forms that releases drug at /near the intended physiological site of action. Targeted release dosage forms may have extended release characteristics.

Repeat Action Dosage Forms: It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a latter time.

Prolonged Action Dosage Forms: It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period.

Advantages of Sustained/Controlled Release Dosage Forms:

- Reduction in dosing frequency.
- Reduced fluctuations in circulating drug levels.
- Avoidance of night time dosing.
- Increased patient compliance.
- More uniform effect.

Disadvantages of Sustained/Controlled Release Dosage Forms:

- unpredictable or poor *in vitro-in vivo* correlation.
- Dose dumping.
- Reduced potential for dosage adjustment.
- Poor systemic availability in general.

Factors Governing the Design of S.R /C.R Forms:

Physico-Chemical Properties

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

$$\log D = -s_v \log u + k_v = -s_M \log M + k_m$$

Where, v is molecular volume, M is molecular weight, s_v , s_M , k_v and k_m are 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} cm²/sec, with values in the order of 10^{-8} being most common (Alfonso R., 2002). 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 (ie, less than 10^{-12} cm²/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 (Joseph and Vincent, 2002).

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 then partition into the absorbing membrane. 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

$$dC/dt = k_D A C_s \quad \dots(1)$$

where dc/dt is the dissolution rate, k_D is the dissolution rate constant, A is the total surface area of the drug particles, and C_s is the 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 C_s . 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

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

Where S_t is the total solubility (both the ionized and unionized forms) of the weak acid, S_0 is the solubility of the unionized form. Ka is the acid dissociation constant, and $[H^+]$ is the hydrogen ion concentration in the medium. Similarly, for a weak base

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

Where S_t is the total solubility (both the conjugate acid and freebase forms) of the weak base, S_0 is the solubility of the free-base form, and K_a is the 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 either 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. For example, consider the ratio of the total solubility of aspirin in the blood and gastric fluid.

$$R = (1 + 10^{\text{pH}_b - \text{pK}_a}) / (1 + 10^{\text{pH}_g - \text{pK}_a}) \quad \dots(4)$$

Where pH_b is the pH of blood (pH 7.4), pH_g is the pH of the gastric fluid (pH 2), and the pK_a of aspirin is about 3.4. Substitution these values into Equation 4 gives a value for *R* of 10^{3.8}, indicating that aspirin is readily absorbed within the stomach. The same calculation for intestinal pH (about 7) yields a ratio close to 1, indicating less driving force for aspirin absorption within the small intestine. 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 (Alfonso R., 2002).

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

High solubility: Largest dose dissolves in 250 ml of water over a pH range 1-8

High permeability: Extent of absorption is > 90%

Class III and Class IV drugs are poor candidates for S.R/C.R dosage forms. Compound with solubility below 0.1mg/ml face significant solubilization obstacles, and often compounds with solubility below 10mg/ml present difficulties related to solubilization during formulation (Bechgaard et al., 1978).

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 (Madhukat et al., 2005). 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 (Guidance for Industry, 1997).

The pH dependent solubility, particularly in the physiological pH range would be another problem for S.R/C.R formulation because of the variation in the pH throughout the gastro intestinal tract and hence variation in dissolution rate. Ex: Phenytoin.

Examples of drugs which are poor candidates for S.R/C.R release systems:

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

pK_a - Ionization Constant

The pK_a is a measure of the strength of an acid or a base. The pK_a allows us to determine the charge on a 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 (James et al., 2007).

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

$$K = C_o/C_w \quad \dots(5)$$

Where C_o is the equilibrium concentration of all forms of the drug in an organic phase at equilibrium, and C_w is the 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 (Jain N.K., 1997). 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.

Example: The third generation dihydro-pyridines have an added additional property to this class of drugs: high lipophilicity. Currently one of these drugs commercially

available is Lercanidipine. As a result of the lipophilic character, this compound is relatively quickly cleared from the plasma building up within phospholipid bilayer of cell membranes. The dihydropyridine [DHP] thus accumulated can interact with its target, the DHP site of target, the L – type calcium channel which lies within the double layer of the cell membrane as well. This phenomenon explains the slow onset and long duration of action. The sustained release of drugs which exhibit this type of property will offer no special advantages over conventional dosage forms. (Gasser R et al., 1999).

Stability

One important factor for the loss of drug is through acid hydrolysis 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 a 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 (Venkataraman et al., 2000; Wagner., 1971).

Acid unstable drugs (stomach):

Examples: Rabeprazole, pantoprazole, omeprazole, lansoprazole, esomeprazole, rifampicin, mesalazine, erythromycin, riboflavin

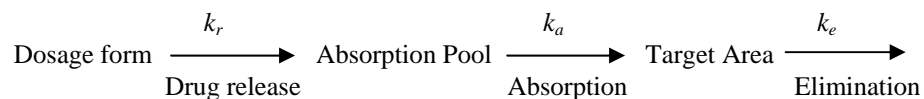
Alkaline unstable drugs (drugs that are unstable in intestine and colon):

Ex: Captopril, Ranitidine.

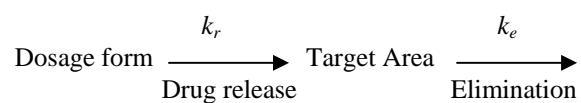
Pharmacokinetic and Pharmacodynamic Considerations

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 $k_r \gg k_a$ 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, $k_r \ll k_w$ 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 k_r .

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 (Higuchi, T., 1963).

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 feed back 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

$$K_r^0 = \text{Rate In} = \text{Rate Out} = k_e C_d V_d$$

Where k_r^0 is the zero-order rate constant for drug release (amount/time), k_e is the first-order rate constant for overall drug elimination (time^{-1}), C_d is the desired drug level in the body (amount/volume), and V_d is the volume of the space in which the drug is distributed. The values of k_e , C_d and V_d needed to calculate k_r^0 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 (Chien Y W., 1992). 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 a maintenance or sustaining dose, D_m . The total dose, W , thus required for the system is

$$W = D_i + D_m$$

For a system in which the maintenance dose releases 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 T_d is the 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

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

The correction factor $K_r^0 T_p$ 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 is the first-order rate constant for drug release (time^{-1}), and k_e , C_d , and V_d are 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 regimen is analogous to that used for a constant intravenous infusion (Alfonso R., 2002).

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 a large release rate from the extended-release system (e.g., drugs with short half-lives).

If the dose of a drug is high (e.g., 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 ingredients (e.g., more than 50% of the total weight) is usually needed to provide the sustained release property, according to the conventional SR methods (Brahma & Kim, 2007)

Biological Factors

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 incase of oral administration is $K_r \ll K_a$. 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 K_a value of 0.17-0.23/hr necessary for about 80-95% absorption over a 9-12hr transit time (Gilberts et al., 2001).

For a drug with a very slow rate of absorption ($K_a \ll 0.17/\text{hr}$), 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 $K_r \ll K_a$ must be met (Rudnic & Schwartz., 2000). If the drug were erratically absorbed because of variable absorptive surface of gastrointestinal tract, design of the sustained/controlled release product would be more difficult or prohibitive. Ex: 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-Bromo uracil, 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.**

Ex: Misoprostol, 5-fluorouracil, Antacids, anti-helicobacter pylori agents.

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 (Stanley S., 2005 and Sanjay., 2003).

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, Tetracyclines Verapamil, Thiamine, Sulpiride, Baclofen, Nimesulide, Cyclosporine, Quinolines.

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 **eg: 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 give 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. **Table 1 shows drugs with apparent volume of distribution higher than total volume of distribution.** 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.

Table 1 Drugs with apparent volume of distribution higher than total volume of distribution.

Drug	App. Vol. Distribution (lts)
Chloroquine	12950
Digoxin	500
Doxepin	1400
Flurazepam	1540
Haloperidol	1400
Azythromycin	2170
Amiodarone	4620

T/P ratio estimates the relative distribution of drug between compartments while V_{dss} estimated extent of drug distribution in the body. **Refer Table 2 for Relationship between V_{dss} and T/P ratio.**

Table 2 Relationship between V_{dss} and T/P ratio.

Drug	T/P ratio	V_{dss}
Diazepam	2.85	130
Digoxin	4.3	500
Furosemide	0.96	5
Procainamide	14.35	62
Meperidine	2	3000
Theophylline	0.9	40

Yet no conclusion can be made on the importance of volume of distribution at steady state and T/P ratio is estimating distribution characteristics of drugs. Undoubtedly, these parameters contribute to this aspect of drug disposition. **Table 3 mentions the use of T/P ratio in conjunction with total body clearance at steady state to gain further view into drug disposition** (Joseph and Vincent., 2002).

Table 3 Use of T/P ratio in conjunction with total body clearance at steady state to gain further view into drug disposition.

T/P ratio	Total body clearance	Disposition characteristics
High	High	Weak tissue binding
High	Low	Strong tissue/protein binding
Low	Low	Strong protein binding
Low	High	Weak plasma protein binding

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 S.R/C.R design much more difficult particularly when biological activity is wholly or partly due to a metabolite as in case 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 S/R/C.R 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 SR 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 (Joseph and Vincent, 2002).

Fluctuating drug blood levels due to intestinal metabolism upon oral dosing: Examples: Salicylamide, Isoproterenol, Chlorpromazine, Clonazepam, Hydralazine and Levodopa.

Fluctuating drug blood levels due to first pass hepatic metabolism upon oral dosing:

Ex: Nortriptyline, phenacetin, morphine, propranolol.

Fluctuating blood levels due to enzyme induction are poor candidates for Sustained/controlled Release dosage forms:

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

Fluctuating blood levels due to enzyme inhibition are poor candidates for Sustained/Controlled Release dosage forms:

Ex: Isoniazid, Cimetidine, Amiodarone, Erythromycin, Fluconazole, Ketoconazole, MAO –inhibitors, Para -aminosalicylic acid, Allopurinol, Coumarins.

Dose Dependent Bio-Availability

In case of Propoxyphene bio-availability is dose dependent. Only 18% of 65mg dose, 28% of 130 mg dose, 33% of 195 mg dose reaches the systemic circulation due to first pass effect. It makes the S.R/C.R dosage form less desirable.

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. **Refer table no. 4 for effect of clearance and volume of distribution in determining half life** (Joseph and Vincent, 2002).

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 (Birkett,1998). 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. Examples: Meprobamate (11.3 hr), Amytriptyline (21 hr).

Table 4 Effect of clearance and volume of distribution in determining half-life.

DRUG	CLEARANCE(L/HR)	VOLUME OF DISTRIBUTION(L)	HALF - LIFE(HR)
Ethosuximide	0.7	49	48.0
Flucytosine	8.0	4.9	4.2
Digoxin	7.0	420	40.0
Morphine	63.0	280	3.0
Haloperidol	46.0	1400	20.0
Chloroquine	45.0	12950	200.0

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, SR 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. **Refer tables 5, 6 for examples of drugs with extremely short half-lives and long half-lives** (Joseph and Vincent, 2002).

Table 5 Examples of drugs with extremely short half-lives.

Drug	Half-life (min.)
Pencillin G	45
Levodopa	45
Spiranolactone	10
Furosemide	29.5
Propylthiouracil	63
Cephalexin	54
Cloxacillin	90
Ampicillin	100

Table 6 Examples of drugs with very long half-lives.

Drug	Half-life (hr)	Drug	Half-life (hr)
Telmisartan	24	Chloroquine	200 hrs
Amlodipine	30-50	Clomiphene	5-7
Ethamsylate	72	Nabumetone	22
Etoricoxib	22	Amitryptilline	21
Carbamazepine	25-65	Digitoxin	
Piroxicam	30-86	diazepam	30
Leflunomide	2weeks	pimozide	
Meloxicam	16.2	Sertralin	26

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 S.R/C.R 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 Enoltasartan has a protein binding 99.9%.

In a study AT-II receptor blockade effect of single doses of Tasosartan (100mg oral and 25mg iv) and Enoltasortan (25mg 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 Enoltasartan was markedly delayed and hardly reached 60-70% despite i.v administration and high plasma levels. This delayed *in vivo* blockade effect for Enoltasartan appears to be due to high and tight protein binding, leading to decrease in affinity for receptors and slower receptor association rate (Marc Maillard et al., 2005). **Table no. 7 shows pharmacokinetic parameters of some highly protein bound drugs.**

Table 7 Pharmacokinetic parameters of some highly protein bound drugs.

Drug	Oral bio-availability (%)	Plasma protein binding (%)	Clearance ml/min/kg	Volume of distribution (lts/kg)	Biological half life (hrs)
Amiodarone	46	99.98	1.9	66	25
Diflunisal	90	99.9	0.1	0.1	11
Itraconazole	55	99.8	23	14	21
Nabumetone	35	>99	0.37	0.78	23

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 S.R/C.R 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. **Refer table no. 8 for receptor occupation of some antihistamines which are related to their long duration of action** (Del cavillo et al., 2006).

Table 8 Receptor occupation of some antihistamines.

Parameter	Desloratadine	Fexofenadine	Levocetirizine
Dose (mg)	5	120	5
Binding to plasma proteins (%)	85	65	91
Free drug C4h (nM)	1	174	28
Free drug C24h (nM)	0.3	1.4	4
T1/2 (h)	27	14	8
Ki (nM)	0.4	10	3
Receptor occupation after 4 h (%)	71	95	90
Receptor occupation after 24 h (%)	43	12	57
Maximum wheal inhibition after 4 h (%)	34	100	100
Wheal inhibition after 24 h (%)	32	15	60

The long duration of action of ACE inhibitors is determined by Plasma half-life and the Affinity of binding to tissue ACE (Taylor S.H., 1990). Drugs with short plasma half- life but high tissue binding such as quinapril are active for 24 hrs. Other drugs such as lisinopril have weaker tissue ACE binding but much long plasma half life is also long acting. In contrast captopril which has relatively short duration of action has weaker tissue ACE binding and short plasma half life. **Table no.9 shows comparative properties of ACE-inhibitors** (Taylor S.H., 1990).

Proton pump inhibitors forms covalent bond with parietal cells and is irreversible and inhibits acid secretion for life period of bonded parietal cell (18-24 hrs).

Since inhibition lasts for 24 hrs or more these proton pump inhibitors are dosed once daily and offer no significant advantage if formulated in sustained release dosage form.

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 TI, the safer 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. **Refer Table no 10 for T.I values of some drugs.**

Table 9 Comparative properties of ACE – Inhibitors.

	Captopril	Enalapril	Lisinopril	Perindopril	Fosinopril	Ramipril	Quinapril	Trandolapril
Prodrug	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Effect of food on Absorption	Up to 35%	Nil	Nil	Up to 35%	Little	Nil	Up to 35%	Delay
Initial plasma half –life (approx)	2 hours	11 hours	13hours	9 hours	4 hours	17 hours	3 hours	22 hours
Tissue ACE Binding (relative)	+	++	++	+++	++	++++	++++	++++
Dosage regimen For hyper tension	bid-tds	od-bd	od	od	od	od	od	od

Table 10 Therapeutic Index values of some drugs.

Drug	Therapeutic Index
Aprobarbital	5.3
Phenobarbital	2.6
Digoxin	1.5-2

Conclusion

Extremes of aqueous solubility, oil/water partition coefficient, tissue binding, extensive metabolism/ degradation of drug during transit, narrow therapeutic index and absorption window are some of the limiting factors in formulating effective sustained release products. Theoretically each of these limitations can be overcome and successful controlled drug delivery can be accomplished by using physical, chemical and biomedical engineering approaches alone or in combination.

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