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NOVEL SUATAINED RELEASE DRUG DELIVERY SYSTEM: REVIEW

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ABSTRACT

Oral Sustained release (SR) 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. Developing oral sustained release matrix tablets for drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs like Diltiazem, Ranitidine has been formulated as sustained release matrix tablets.This article contains the basic information regarding design sustained-release formulation and also the different types of the same.

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INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patience compliance, least sterility constraints and flexible design of dosage forms. Time release technology, also known as sustained-release (SR), sustained-action (SA), extended-release (ER, XR or XL), time-release or timed-release, controlled-release (CR), modified release (MR) or continuous-release (CR or Contin), is a mechanism used in pill tablets or capsules to dissolve slowly and release a drug over a prolong period of time. The advantages of sustained-release tablets or capsules, are formulations which can be taken less frequently than instant-release formulations of the same drug and keep steadier levels of the drug in the bloodstream. One of the methods of fabricating sustained/controlled

release drug delivery system is by using hydrophilic matrices, also referred as hydrogels. Different polymers are employed due to their in situ gel forming characteristics and their ability to release entrapped drug in the specific medium by swelling and cross-linking. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery system. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers.[1-3] By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Sustained release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled. With the development of modern synthetic ion exchange resins, pharmaceutical industry adapted the ion exchange technology to achieve sustained release of drug. Recent trend towards the use of vegetable and nontoxic products demands the replacement of synthetic additives with natural one.

TERMINOLOGY

Controlled and Sustained Release, both has been used in inconsistent and confusing manner. Both represent separate delivery process. SR constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both.[4,5]

Modified Release Drug Product

The term modified release drug product is used to describe products that alter the timing or the rate of release of the drug substance.

Extended Release Dosage Forms

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

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 prolong period of time.

Delayed Release Dosage Form

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. Example: Enteric coated dosage forms.

Targeted-release drug products

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

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 of time.

Advantages of Sustained/Controlled Release Dosage Forms[6]

Decreased local and systemic side effects reduced gastrointestinal irritation.

Reduction in dosing frequency.

Improved patient compliance and reduced patient care time.

Reduced fluctuations in circulating drug levels.

Disadvantages of Sustained/Controlled Release Dosage Forms

Unpredictable or poor in-vitro and in-vivo correlation.

Dose dumping.

Reduced potential for dosage adjustment.

Poor systemic availability in general.

Criteria for a drug proposed to be formulated in sustained release dosage forms

Desirable half-life ($t_{1/2}$)

The half life of a drug is an index of its residence time in the body. In general, drugs with half lives shorter than 2 hours such as Furosemide or Levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained.[7] Digoxin and Phenytoin are the examples.

Drug	Half life ($t_{1/2}$)
Metoprolol Tartrate	3-4 Hr.
Ketoprofen	3.5-4 Hr.
Terbutaline Sulphate	3 Hr.

High therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur e.g. Digitoxin.

Small dose

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undetermined.

Desirable absorption and solubility characteristics

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into sustained release formulations is therefore unrealistic and may reduce overall absorption efficiency.

Desirable absorption window

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the *'absorption window'*. Drugs exhibiting an absorption window like Fluorouracil, Thiazide Diuretics, if formulated as sustained release dosage form are unsuitable.

First pass clearance

As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release form.

Design and Formulation of Sustained release drug delivery system

Oral Drug Delivery Systems

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form.[8]

The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion.[9] Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation as shown in Figure no.1

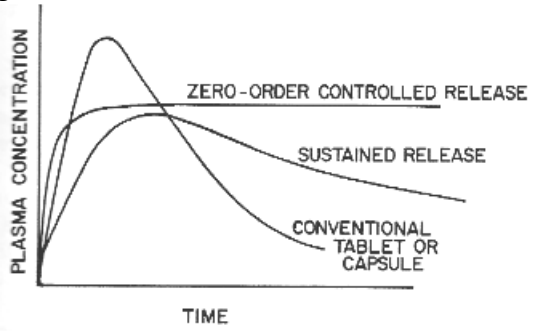


Fig. no.1 Plasma drug concentration-profiles for conventional tablet or capsule formulation, a

sustained release formulation, and a zero- order controlled release formulation.

Design

Sustained (zero-order) drug release has been attempted to be achieved, by following classes of sustained drug delivery system.[10]

1. Dissolution-sustained release
   a. Encapsulation dissolution control
   b. Matrix dissolution control
2. Diffusion-sustained release
   a. Reservoir devices
   b. Matrix devices
3. Methods using lon Exchange
4. Methods using Osmotic pressure
5. pH– Independent formulations
6. Altered density formulations
7. Gastro retentive systems

Dissolution-sustained Release

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 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 Eq. 1.

$$\frac{dm}{dt} = \frac{ADS}{h} \qquad (1)$$

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.

Drug delivery using rate of dissolution as a controlled release mechanism can be achieved by encapsulation of a drug– polymer matrix with a relatively insoluble polymeric membrane. The coated beads can be compressed into tablets or capsulated, as was carried out with the spansule products. Since the time required for the membrane coat to dissolve is a function of membrane.[11]

Diffusion -Sustained system

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area -time) across a membrane in the direction of decreasing concentration is given by *Fick's law*.

$J = - D\, dc/dx.$ (2)

Where,

D = Diffusion coefficient in area/ time

dc/dx = Change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane, the drug release rate dm/ dt is given by,

$dm/dt = A.DK\,\Delta C/L$ (3)

Where,

A = Area

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

L= Diffusion path length [i.e. thickness of coat]

ΔC= Concentration difference across the membrane.

Reservoir type

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.

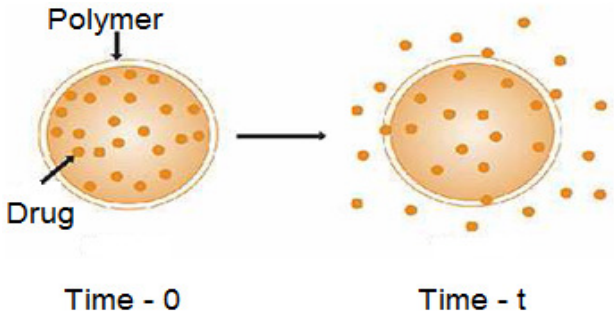


Fig. no. 2 Schematic representation of diffusion sustained drug release

In the system, a water insoluble polymeric material encases a core of drug. Drug will partition

into the membrane and exchange with the fluid surrounding the particle or tablet.

Matrix type

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. *Higuchi* has derived the appropriate equation for drug release for this system,

$$Q = D\varepsilon / T [2 A - \varepsilon Cs]. Cs.t^{1/2} \quad (4)$$

Where,

Q = Weight in gm of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

ε= Porosity of the matrix

Cs = Solubility of drug in release medium

T= Tortuosity of the matrix

A = Concentration of drug in the tablet, as gm/ ml

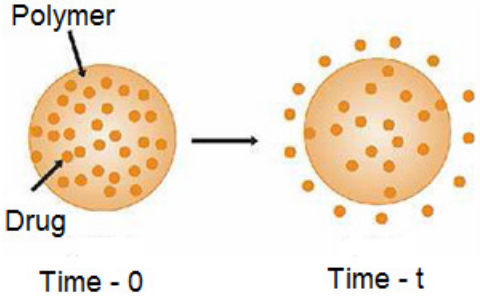


Fig. no. 3 Schematic representation of diffusion sustained drug release

A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat. The release rate can be given by following equation,

$$\text{Release rate} = AD / L = [C1 - C2] \quad (5)$$

Where,

A = Area

D = Diffusion coefficient

C1 = Drug concentration in the core

C2 = Drug concentration in the surrounding medium

L = Diffusional path length

Thus diffusion sustained products are based on two approaches the *first approach* entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The *second approach* involves enclosing the drug particle with a polymer coat.[12]

Methods using Ion Exchange

Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug–resin complex is formed by prolonged exposure of drug to the resin. It is based on the formation of drug resin complex formed when a ionic solution is kept in contact with ionic resins. The drug from these complex gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract.

$$\text{Resin} + \text{- Drug -} + Cl^- \text{ goes to resin} \pm Cl^- + \text{Drug-}$$

Where x^- is Cl^- conversely

$$\text{Resin}^- \text{- drug}^+ + Na^+ \text{goes resin}^- Na^+ + \text{Drug}$$

These systems generally utilize resin compounds of water insoluble cross – linked polymer. Nicorette® is a widely used product based on ion exchange technology as an adjunct to smoking cessation programs. It contains nicotine absorbed to a carboxylic acid ion exchange resin (nicotine polacrilex) in a flavored chewing gum.Delsym® (dextromethorphan, Pennwalt), a 12-h cough medication taken as a liquid suspension, is another example of this type of dosage form.[13,14]

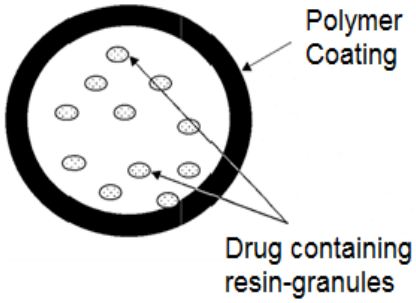


Fig. no. 4 Polymer-coated drug-resin design

In this system, drug containing resin granules is first treated with a polymer such as Polyethylene glycol 4000 to retard the rate of swelling in water and then further coated with a water- permeable polymer such as Ethylcellulose to act as rate-limiting barrier to control drug release.

D] Methods using Osmotic pressure

A semipermeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

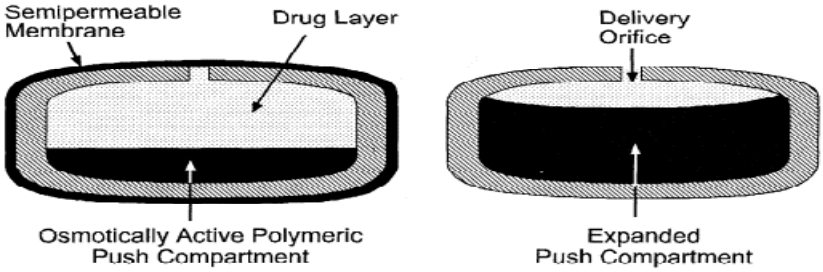


Fig. no. 5 Schematic of OROS "Push–Pull" System (a) Represents the pump before operation. (b) Represents the pump during operation.

Typically OROS systems can maintain zero-order delivery for 24 hr. OROS Push–Pull technology has been applied to several commercial products, including nifedipine (Procardia XL®), and isradipine (Dynacirc CR®). A typical release rate profile for Ditropan XL® developed by Alza Corporation demonstrates a constant zero-order drug delivery (Fig.no. 5).

Two types of osmotically sustained systems are

Type A contains an osmotic core with drug

Type B contains the drug in flexible bag with osmotic core surrounding. [15,16]

pH– Independent formulations

The gastrointestinal tract represent different chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, Citric acid, Phthalic acid, Phosphoric acid or Tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release. Examples Propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility. [17,18]

Altered density formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High density approach

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4 gm/cm^3.

Low density approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.[19]

Gastro-retentive Systems

Gastro-retentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time. A drug that is released from the dosage form in a controlled manner in the stomach will exit the stomach together with gastric fluids and have the whole surface area of the small intestine available for absorption. Some hydrogels and superporous hydrogels offer a promising approach to gastric retention. They can be made by crosslinking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. These systems have been classified according to the basic principles of gastric retention (Fig. no.7)[20]

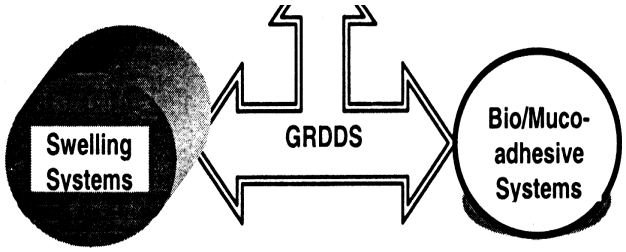
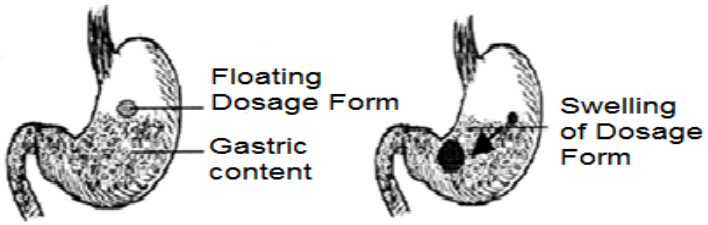


Fig. no. 7 Classification of Gastro-retentive drug delivery system

1. **Floating Drug delivery system**

Floating dosage form is also known as hydro-dynamically balanced system (HBS). It is an oral dosage form (capsule or tablet) that is designed to prolong the residence time of the dosage form within the GI tract. It is formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence ready for absorption (Fig. no.8.)[21]



a **b**

Fig. no.8. Various forms of gastro-retentive systems: (a) Floating gastro-retentive drug delivery systems (b) Swelling gastro-retentive drug delivery systems

Non-Effervescent systems

Colloidal gel barrier systems

Hydrodynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids Example-Hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC), Hydroxypropyl Methyl cellulose (HPMC), Sodium carboxy methyl cellulose (NaCMC) incorporated either in tablets or capsules.

Microporous compartment system

This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores,

dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption. Intra-gastric floating and sustained release granules of Diclofenac sodium were developed using HPMC, Ethyl cellulose and Calcium silicate as floating carriers.

Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried Calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a Sodium alginate solution into aqueous solution of Calcium chloride, causing a precipitation of Calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at (–) 40^{O}C for 24 hrs, leading to formation of porous system that maintained floating force for over 12 hrs.

Hollow Microspheres

Hollow microspheres (micro balloons), loaded with Ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The Ethanol: Dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 40^{O}C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in micro sphere of polymer with drug.

Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and Bicarbonate salts.

Volatile liquid containing systems

These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, Polyethylene, etc.

Gas generating systems

These buoyant delivery systems utilize effervescent reaction between Carbonate/ Bicarbonate salts and Citric/Tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer and the drug in outer layer for sustained release effect.

Bioadhesive DDS

Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane.

Swelling and expanding systems

These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time. These systems may be named as “plug type systems”, since they exhibit the tendency to remain lodged at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical or chemical cross-links in the hydrophilic polymer network.

High density systems

These dosage forms have a density (3 g/ml) far exceeding that of normal stomach contents (1 g/ml) and thus retained in rugae of the stomach and are capable of withstanding its peristaltic movements. The density of these systems should

atleast be 1.004 g/ml. This is accomplished by coating the drug with heavy inert materials such as Barium sulphate, Zinc oxide, Titanium dioxide, Iron powder etc.[22,23]

Parenteral Drug Delivery System

The Parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. But parenteral route offers rapid onset of action with rapid declines of systemic drug level. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It requires frequent injection, which ultimately leads to patient discomfort. For this reason, drug delivery system which can reduce total number of injection throughout the effective treatment, improve patient compliance as well as pharmacoeconomic. This rapid drug absorption is unfortunately also accompanied by a rapid decline in the drug levels in the systemic circulation. In the case of chronic conditions, daily or multiple weekly injections for years or even lifetime have resulted in poor patient compliance. For tissue regeneration therapy on the other hand, the *in-vivo* life of some cytokines are limited to hours or even minutes after injection, far from sufficient to exert biological functions *in-vivo*. To achieve constant drug level in the systemic circulation, two strategies can be employed,

1) To control the rate of absorption of a drug or
2) To control the rate of excretion of a drug. In that controlling the absorption rate of a drug (by modifying dosage forms) is easier than controlling the excretion rate (by modifying physiology of body) of a drug.

Examples of applications for prolonged release parenteral delivery include: Fertility treatment, Hormone therapy, Protein therapy, Infection treatments (antibiotics and antifungals), Orthopedic surgery and treatment of CNS disorders and Immunosupression. Modified release (MR) parenteral drug products are available in several dosage forms, including microspheres, liposomes, lipophilic solutions, solid lipid nanoparticles (SLN) and drug eluting stents. [24]

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,

$$logD = -sv.logu + kv = -sMlogM = km \quad (6)$$

Where, v is molecular volume, M is molecular weight,sv, sM, kv and km 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. [25,26]

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,

$$dc/dt = kDA.Cs \quad (7)$$

Where dc/dt is the dissolution rate, kD is the dissolution rate constant, A is the total surface area of the drug particles, and Cs 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 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,

$$S_t = S_0(1+Ka/[H^+]) = S_0(1+10^{pH-pKa}) \quad (8)$$

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

$$S_t = S_0(1+[H^+]/Ka) = S_0(1+10^{pKa-pH}) \quad (9)$$

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 *Ka* is the acid dissociation constant of the conjugate acid, Equations 8 and 9 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 8 and 9 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. 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.

$$R = (1 + 10^{pHb-pKa})/(1+10^{pHg-pKa}) \quad (10)$$

Where pHb is the pH of blood (pH 7.4), pHg is the pH of the gastric fluid (pH 2), and the pKa of aspirin is about 3.4. Substitution these values into Equation 4 gives a value for *R* of 103.8, indicating that aspirin is readily absorbed within the stomach. 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 0.1 mg/ml face significant solubilization obstacles and often compounds with solubility below 10 mg/ml present difficulties related to solubilization during formulation. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. 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.[27] Example- 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.

pKa - Ionization Constant

The pKa is a measure of the strength of an acid or a base. The pKa 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. Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined.

Partition Coefficient

Partition coefficient (the solvent:water quotient of drug distribution).When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipid therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. Partition coefficient influences not only the permeation of drug across the biological membranes but also diffusion across the rate controlling membrane or matrix. 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,

$$K = C_o/C_W \quad (11)$$

Where, C_O is the equilibrium concentration of all forms of the drug in an organic phase at equilibrium, and C_W 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. [28,29]

Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. 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 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.

Acid unstable drugs (stomach)

Examples: Rabeprazole, Rifamipicin, Mesalazine, Erythromycin, Riboflavin

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

Examples: Captopril, Ranitidine.

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 Kr<<<Ka. 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 9-12hr transit time.

Drugs absorbed by active transport system are unsuitable for sustained/controlled drug delivery system

Examples: Methotrexate, Enalapril, Nicotinamide, Fexofenadine.

Drugs absorbed through amino acid transporters in the intestine

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

Drugs transported through Oligo – peptide transporters

Examples: Captopril, Lisinopril, Cephalexine, Cefadroxil, Cefixime.

Drugs required to exert a local therapeutic action in the stomach are unsuitable for sustained drug delivery

Examples: Misoprostol, 5-fluorouracil, Antacids.

Metabolism

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

Drug should have law half-life (<5 hrs).

Drug should be freely soluble in water.

Drug should have larger therapeutic window.

Drug should be absorbed throughout the GIT.

Even a drug that is poorly water soluble can be formulated in SR dosage form. 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.[30]

Marketed Products

Table 1 Composition and Examples of Some Marketed Products

Quinglute Dura tablets (Berlex)	Contains 320 mg quinidine gluconate in a prolonged-action matrix tablet lasting 8–12 hr and provides PVC protection.
Brontil Slow-Release capsules (Carnrick)	Phendimetrazine tartrate 105 mg sustained pellet in capsule.
Sinemed CR tablets (Dupont pharma)	Contains a combination of carbidopa and levodopa for sustained release delivery. This is a special erosion polymeric tablet for Parkinson's disease treatment.
Isoptin SR (Knoll)	Verapamil HCI sustained-release tablet.
Devexx-MR	A controlled-release 24-hr Diclofenac Sodium product.
TRD-(Contin)	CR Tablet of Tramadol

CONCLUSION

Development of sustained release oral dosage forms is beneficial for optimal therapy regarding efficacy, safety and patient compliance. In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is released. The advantages of sustained-release tablets or capsules are often be taken less frequently than instant formulations of the same drug, and that they keep steadier levels

of the drug in the bloodstream. Sustained-release tablets are formulated so that the active ingredient is embedded in a matrix of insoluble substance (various: some acrylics, even chitin, these are often patented) so that the dissolving drug has to find its way out through the holes in the matrix.

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