Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A MODERN FORMULATION APPROACH

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ABSTRACT

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. In the recent years, focus on the development of controlled release drug delivery systems has increased. The basic rationale of controlled release drug delivery system optimizes the biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure or control of the condition is achieved, in the shortest possible time by using smallest quantity of drug administered by the most suitable route. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy, shorter treatment period and less frequency of dosing can be achieved. This review briefly emphasizes about the Sustained release drug delivery system characteristics, formulation design and drug release mechanisms.

KEYWORDS

SRDS, controlled release, formulation approach, improved therapy**.**

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INTRODUCTION

Sustained release drug therapy

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, controlled release, extended action, timed

release, depot and repository dosage forms are terms designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities.[1]

Controlled release systems also denotes systems which can provide some control whether this be of a temporal or spatial nature or both, of drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time.[2]

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue it is considered as controlled release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Advantages: [3]

1. The frequency of drug administration is reduced
2. Patient compliance can be improved
3. Drug administration can be made more convenient used to identify drug therapy systems that are
4. The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced, because a more even blood level can be maintained
5. Better control of drug absorption can be attained, since the high blood level peak that may be observed after administration in an extended action form
6. The characteristic blood level variations due to multiple dosing of conventional dosage form can be reduced
7. The total amount of drug administration can be reduced, thus
   - Maximizing availability with minimum dose
   - Minimize or eliminate local side effects
   - Minimize or eliminate systemic side effects
   - Minimize drug accumulation with chronic dosing
8. Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients
9. Improve efficacy in treatment
   - Cure or control condition more promptly
   - Improve/ control i.e. reduces fluctuation in drug level.
   - Improve bioavailability of some drugs
   - Make use of special effect e.g. sustained release aspirin for morning relief of arthritis by dosing before bed time.
   - Economy

Disadvantages [4]

1. Administration of sustained release medication does not permit prompt termination of therapy
2. Flexibility in adjustment in dosage regimen is limited
3. Controlled release forms are designed for normal population i.e., on the basis of average drug biological half-lives.
4. Economy factors may also be assessed, since most costly process and equipment are involved in manufacturing so many controlled release dosage forms.

Limitations[5]

- If the active compound has a long half-life (over six hours), it is sustained on its own.
- If the pharmacological activity of the active compound is not related to its blood levels, slow releasing then has no purpose.
- If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
- 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.
- Not effectively absorbed in lower small intestine
- Large doses are required (mare than 1 gm)
- Drug with low therapeutic index
- Precise dose to individuals is required

CHARACTERISTICS THAT MAKES DRUGS SUITABLE FOR SUSTAINED RELEASE DDS

PHYSICOCHEMICAL CHARACTERISTICS[6-10]

Dose Size

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

Aqueous Solubility

Compounds with very low solubility (less than 0.01mg/ml) are inherently sustained, since there release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained-release system has been reported to be 0.1mg/ml, so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system. Diffusional systems will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

Partition Coefficient

When a drug is administered to the GI tract it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic, therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility.

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 the solid state; therefore, this is the preferred composition of delivery for problem cases. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transits in the GI tract are beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. Compound that is unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation.

Protein Binding[11]

It is well known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are four the most part recirculated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, especially if high degree of drug binding occurs. There are, however, other drug - protein interaction that have bearing on drug performance.

Drug pKa and P^H

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0% .delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation.

Molecular size and diffusivity

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10^{-6}-10^{-9} cm^2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10^{-12} cm^2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides in Table No.1.

BIOLOGICAL CHARACTERISTICS

Biological Half-Life[12-15]

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other processes that permanently remove drug from the bloodstream. Therapeutic compound with short half-lives are excellent candidates for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hours, are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained-release product. Since the purpose of forming a sustained-release product is to place control on the delivery system, it is necessary that the rate of release much slower than the rate of absorption. If we assume that the transits time of most drugs and devices in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23 $hours^{-1}$ to give 80-95% over this time period. The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining system.

Distribution

The distribution of drugs into tissue can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid. One aspect of this distribution is binding of drug to tissue and proteins in blood. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. For design of sustained/controlled release products one would like to have as much information on drug disposition as possible but, in reality, decisions are usually based on only a few pharmacokinetic parameter, one of which is the apparent volume of distribution. Drugs that are

significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during specific period, allowing more complete conversion of the drug to its metabolites. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

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, which leads to toxicity.

Size of dose:

If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty.

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'**.** These candidates are also not suitable for SRDDS.

Plasma concentration response relationship:

Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system.

CLASSIFICATION OF SR FORMULATIONSYSTEMS [15-20]

The most common methods used to achieve sustained release of orally administered drugs are as follows:

Diffusion systems

Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized reservoir devices and matrix devices Figure No.1.

Reservoir Devices

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. It is also possible to use polymer coatings to achieve sustained release. For this purpose the polymer itself should not dissolve, but rather should allow the drug to diffusion through the polymer membrane to the outside, in the case of oral drug delivery, to gastrointestinal tract Figure No.2.

Matrix Devices

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process interface between the bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion ate of dissolved drug leaving the matrix in Figure No.3.

Types of diffusion matrix system

The matrix system can be divided into two categories depending on the types of retarding agents or polymeric materials.

1. Hydrophobic matrix system
2. Hydrophilic matrix system
3. Fat-wax matrix system

1. Hydrophobic matrix system

This is the only system where the use of polymer is not essential to provide Sustained drug release, although insoluble polymers can been used. As the term suggests, the primary rate controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes glycerides fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the

physical dimension of hydrophobic matrix during drug release. Diffusion of active ingredient from the system is the release mechanism and the corresponding release characteristic can be described by Higuchi equation also known as square root of time release kinetics.

2. Hydrophilic matrix system[21]

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path. It has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The presence of water decreases the glass transition temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motilityof the polymeric chain favors the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. The main polymers used in hydrophilic matrices are hydroxy propyl methyl cellulose (HPMC) and Hydroxy propyl cellulose (HPC), Xanthan gum, Carbopol and Alginates in Figure No.4-7.

Fat-Wax matrix tablet

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

Dissolution sustained systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

i) Soluble reservoir system

In this system drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract by alternating layers of drug with the rate controlling coats. A pulsed delivery can be achieved, if the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. This is not a true sustained release system; the biological effects can be similar. An alternative method is to administer the drug as group of beads

that have coating of different thickness. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance dose of drug can be achieved by applying thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

ii) Soluble matrix system

It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

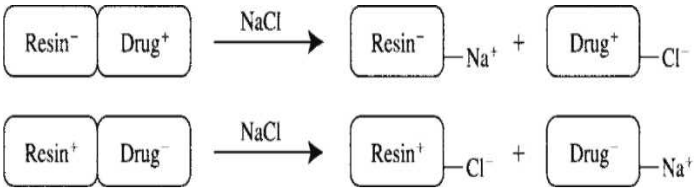
iii) Dissolution- sustained pulsed delivery system

Ease of drug modulation through level, choice of polymeric systems & function coating.

A hydrophilic matrix tablet consists of mixture of drug, polymer & excipients (filler/diluents as well as other excipients) prepared by hydrophilic polymer in the matrix. Formulators often choose from a range of hydrophilic polymer as stand alone or in combination with different polymers for release rate control.

Ion exchange resins sustained release systems

Ion exchange resins are cross-linked water-insoluble polymers carrying ionisable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversibleex with ionisable drugs upon prolonged exposure of the drug to the resin. A resin bound drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway and the amount of cross-linked polymer in the resin moiety governs the rate of drug release. Sriwongjanya et al. has found the effect of ion exchange resin with drug containing opposite charge in matrix system. After this investigation they concluded that the release of drug containing opposite charge retarded by the addition of ion exchange resin to HPMC-matrices due to formation of complex between drug and resin.



Ion exchange reaction can be expressed as

[A*] + [R~][B+] ~ *[fi$^+$]* + [R~][A+]

Where [A^+] = concentration of free counter ion

[B+] = concentration of drug freed from resin

[A^] = concentration of counter ion bound to the resin

Methods using osmotic pressure

In this method, the release controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. This technology provides zero order release used for hydrophilic drugs. Drug may be osmotically active or combine with osmotically active salt eg: NaCl. Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semi permeable membrane due to difference in concentration of solutes. Osmosis is the diffusion of fluid through a semi permeable membrane from a solution with a low solute concentration to a solution with a higher solute concentration until there is an equal concentration of fluid on both sides of the membrane. A semi permeable 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. The osmotic systems are classified in major two types, i.e. type-A & type-B. In type-A system, the core contains both, the drug and electrolytes. The electrolytes provide osmotic pressure and maintain the rate of drug release. In type-B system, the drug solution is present in a semi permeable membrane surrounded by the electrolytes. Both the systems are shown in **figures.** The ODDS can be conveniently classified in to following types:

Single chamber osmotic pump

- Elementary osmotic pump (EOP)

Multi chamber osmotic pump

- Push pull osmotic pump.

Specific types

- Controlled porosity osmotic pump.
- Monolithic osmotic systems.
- Osmotic bursting osmotic pump.
- OROS-CT
- Multi particulate delayed release systems (MPDRS)
- Liquid Oral Osmotic System (L-OROS)

pH Independent formulations

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, pthalic 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 formulation is prepared by mixing a basic or acidic drug with one or morebuffering 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.

Altered density formulations

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract. The delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released. In high density approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4g/cm^3. In low density approach, the 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. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product. This system is generally used when, the single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension is required.

- Osmotic pump with non-expanding second chamber.

Swelling and expansion systems

Conventional hydrogels swell slowly upon contact with water due to their small pore size, which usually ranges in the nanometers and low-micrometer scale. However if the hydrogel has a pore size of more than 100 um, swelling is much faster and may lead to a large increase in size. Swelling ratios of over 100 can be achieved. These swollen systems become too large to pass through the pylorus and thus may be retained in the stomach even after housekeeper wave, provided they have a sufficiently high mechanical strength to withstand the peristaltic movement in the stomach.

Floating systems

If the dosage form has a lower density than the gastric fluids, it will float on a top of the stomach content, allowing for an increased time span to release the drug before the system is emptied out into small intestine. The gastric fluid has a density of approximately lgm/cm. If the density of the dosage form is lower than that, it will float on the gastric fluids. These systems require the presence of sufficient fluid in the stomach and the presence of food as discussed above. Several types of low density ingle-unit dosage forms (tablets) and multiple-unit dosage forms (pellets) have been developed. If a dosage form has density of larger than approximately2.5gm/cm, it will sink to the bottom of the stomach and pellets may be trapped in the folds of the gastric wall.

Bio adhesive or Mucoadhesive systems

It has also been suggested to use bio adhesive or mucoadhesive polymers such as polyacrylic acid and chitosan to achieve gastric retention. The basic idea here is that the mucoadhesive or bio adhesive polymers leads to the dosage forms sticking on to the mucus of the gastric wall. Whilst the bio adhesive or mucoadhesive approach is a sensible one for buccal or sublingual formulations, due to rapid turnover of the mucus in the stomach, for gastro retentive systems this approach is not as straightforward. Finally magnetic materials may be

added to the dosage forms. These systems can then be held in place by an external magnate, but this approach requires a precise positioning of the external magnate and is not likely to have a high patient compliance.

Biodegradable Matrices[22-24]

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

Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix: Matrix tablets can be divided into 3 types.

Macro porous systems

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

Micro porous system

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

Non-porous system

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

MASRX and COSRX Sustained-Release Technology[24-26]

MASRx Technology

The objective is to assess factors affecting drug release from guar-gum-based once-daily matrix sustained-release formulations (MASRx). The tablets were designed to hydrate completely into the tablet core. In the process, the tablet core expanded and released the drug in a sustained-release manner.

COSRx Technology

Formulations base on constant sustained-release matrix (COSRx) technology can also be developed using guar gum as a major rate-controlling polymeric material. Depending on the solubility of the drug, low- or high-viscosity guar gum can be used. The formulation involves a guar-gum-base tablet and a combination of water-soluble and water-insoluble polymeric tablet coat. When the tablet is placed in a dissolution medium, there is slow diffusion of water through the polymeric wall leading to swelling and gelations of the guar gum/drug core. As the hydration a progress, the tablet continues to swell until the wall breaks, forming a sandwich-like structure. The release of drug proceeds primarily out of the sides of the tablet as it passes through the intestinal tract. The tablets provide a nearly zero-order drug release following a programmed period of delayed drug release.

DRUG RELEASE MECHANISM FROM SUSTAINED RELEASE DDS[3, 4]

Zero Order Kinetics

A zero order release would be predicted by the following equation,

$$Qt - Q0 = K_0t$$

Where,

Q_t = Amount of drug release dissolved in time't'.

Q_o = Initial amount of drug concentration in solution.

K_0t = Zero order rate constant.

When the data was plotted as cumulative % drug release verses time, if the plot is linear then data obeys zero order kinetics with slope equal to K_o. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First Order Kinetics

A first order release would be predicted by the following equation

$$\text{Log } Qt = \text{Log } Qo - K_1t/2.303$$

Where,

Q_t = Amount of drug released in time't'.

Q_o = Initial amount of drug concentration in solution.

K_1t = First order rate constant.

When data was plotted as log cumulative % drug remaining verses time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.

Higuchi's Model

Drug release from the matrix device by diffusion has been described by Higuchi's Diffusion equation

ft= Q = VD5/T (2C- 5Cs)Cst

Where,

Q = Amount of drug released in time't'.

D = Diffusion coefficient of the drug in the matrix.

Cs = Solubility of the drug in the matrix.

8= Porosity of matrix.

t= Tortuosity.

t = Time (h).

The equation may be simplified then equation becomes;

$$ft= Q = KhX\ t^{1/2}$$

Where, K_H = Higuchi dissolution constant.

When data was plotted according to this equation, i.e., cumulative drug released verses square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

Peppas Korsmeyer Equation

In 1983 Korsmeyer *et al.* (Korsmeyer *et al.,* 1983) developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$$At/Aoo= kt^n$$

Where,

k = Constant.

n = Release.

t = Time.

A_t and Aoo= Absolute cumulative amount of drug released at time't'.

This is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

5. Hixon-Crowell Equation:

Drug released from the matrix device by diffusion has been described by Hixon-Crowell diffusion equation;

$$W0^{1/3}- Wt^{1/3}=? t$$

Where,

W0 = Initial amount of drug.

W_t = Remaining amount of drug.

t = Time.

? = Constant (Kappa).

This expression applies to pharmaceutical dosage form such as tablets where the dissolution occurs in planes that are parallel to drug surface if tablet dimensions diminish proportionally in such manner that the initial geometrical form keeps constant all the time.

Pharmacokinetics and Pharmacodynamics Consideration in SRDDS

To achieve controlled drug delivery, it is desirable to have a zero-order drug input.

Under steady state, rate in = rate out then,

$$R_0 = CssCL$$

This equation shows that the input rate of a controlled release is determined solely by steady state concentration and plasma clearance, $t_{1/2}$.A common pharmacokinetic parameter is not directly needed to determine the input rate. However, it does play a role in determining the benefits of formulating a drug into controlled-release dosage form. Usually drugs of $t_{1/2}$more than 8 hours are not suitable candidates for controlled or sustained release dosage forms because they do not provide benefits over conventional dosage forms. In addition, $t_{1/2}$ may be useful in determining the dosing interval of controlled release dosage forms. Similarly, volume of distribution is not major consideration in designing controlled-release delivery systems, although often a larger volume of distribution requires a higher drug load to achieve therapeutic blood level. As a result, a PK/PD model required to obtain a rational design of a controlled-release dosage form. Typically a graded response can be represented by

$$E= PC + E_0$$

Where, P is the proportionality constant, C is the plasma concentration, and E_0 is the base line effect. In some cases, a more satisfactory relationship is obtained by using,

$$E = P \log C + E_0$$

In fact, in most cases, the relationship is much more complex than simple linear one, and sometimes it can be represented only by an expression closely related to enzyme kinetics,

$$E = E0 + (EmaxC^n) / (E^n50) + C$$

Table No.1: Examples of Various Delivery Approaches

Type of device	Product name	Active ingredient	Route	Developer/ manufacturer
Diffusion (reservoir)	Estraderm	Estradiol	Transdermal	Alza/Novartis
	Norplant	Levonorgestrel	Sub-dermal implant	Wyeth-Ayerst Laboratory
	Ocusert	Pilocarpine	Ocular	Alza
	Progestasert	Progesterone	Intrauterine	Alza
	Transderm	Scopolamine	Transdermal	Alza/Novartis
Diffusion (matrix)	Nitro-Dur	Nitroglycerine	Transdermal	Key Pharmaceutical
	Nitrodisc	Nitroglycerine	Transdermal	Searle
Mixed (matrix-reservoir)	Catapress-TTS	Clonidine	Transdermal	Alza/BoehingerIngelheim
	Deponit	Nitroglycerine	Transdermal	Pharma-Schwarz
Hydro dynamically	Medopar CR	Levodopa and benserazide	Oral tablet	Roche
balanced system	Valrelease	Diazepam	Oral tablet	Roche
Ion exchange	Colestid	Colestipol	Oral tablet or granules	Upjohn
	Questran	Cholestyramine	Oral tablet or powder	Bristol Labs
	Tussionex	Chlorpheniramine and hydrocodone	Oral suspension	Fisons
	Pennkinetic			
Coating	Compazin	Prochlorperazine	Oral capsules	Smith Kline Beecham
	Spansule			
	Dexedrine CR	Dextroamphetamine	Oral capsules	Smith Kline Beecham
	Fefol-Vit	Ferrous sulfate and vitamins	Oral capsules	Smith Kline Beecham
	Ecotrin	Aspirin	Oral tablet	Smith Kline Beecham
	Voltaren	Diclofenac	Oral tablet	Geigy
Nanocrystal Technology	Rapamune	Sirolimus	Oral tablet	Elan/Wyefh-Ayerst Laboratory
Osmotic pumps	Calan SR	Verapamil	Oral tablet	Alza/G. D. Searle

	Cardura XL	Doxazosin	Oral tablet	Alza/Pfizer
	Covera HS	Verapamil	Oral tablet	Alza/G. D. Searle
	DUROS	Potential carrier for macromolecules	Implant	Alza
	Ditropan	Oxybutynin	Oral tablet	Alza/UCB Pharma
	Minipress XL	Prazosin	Oral tablet	Alza/Pfizer
	Teczem	Enalapril and diltiazem	Oral tablet	Merck/Aventis
	Volmax	Albuterol	Oral tablet	AIza/Muro Pharmaceuticals
Liposome	AmBisom	Amphotericin B	Parenteral	NeXstar Pharmaceuticals
	Amphotec	Amphotericin B	Parenteral	Sequus Pharmaceuticals
	Doxil	Doxorubicin	Parenteral	Sequus Pharmaceuticals
	DaunoXo	Daunorubicin	Parenteral	NeXstar Pharmaceuticals

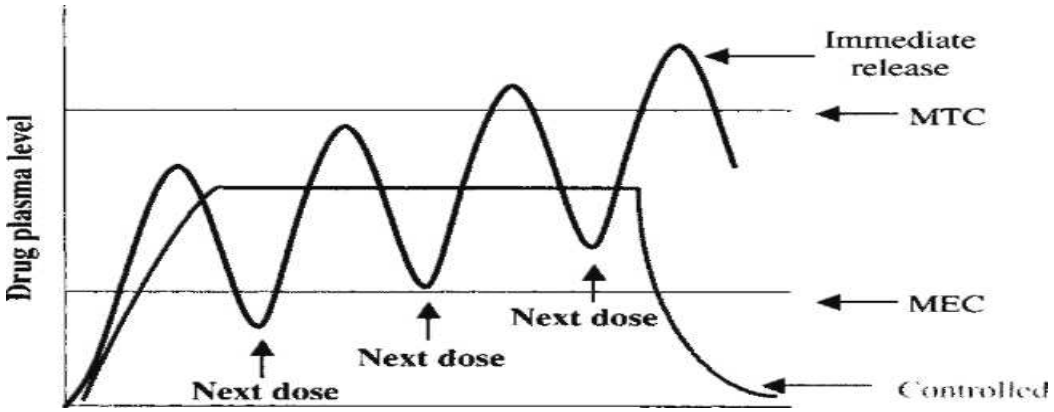


Figure No.1: Therapeutic or toxic levels of immediate- versus controlled-release dosage form

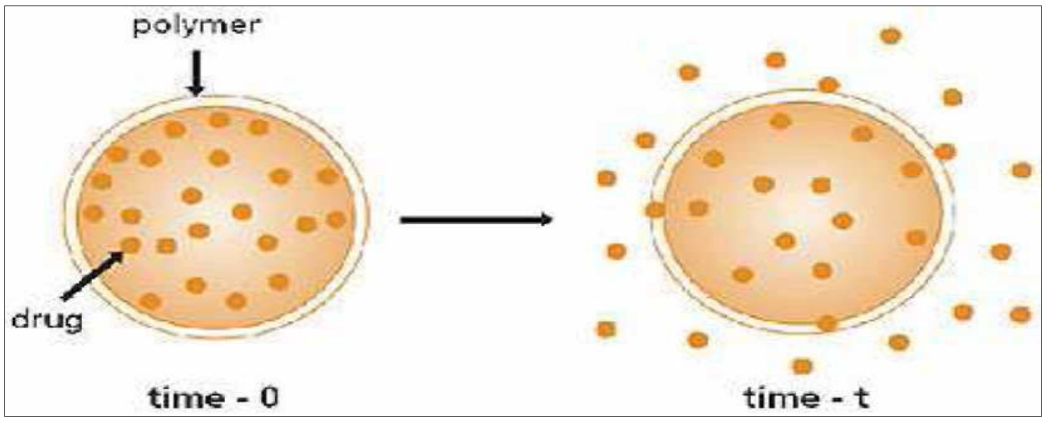


Figure 2: Schematic Representation of Diffusion Type reservoir System

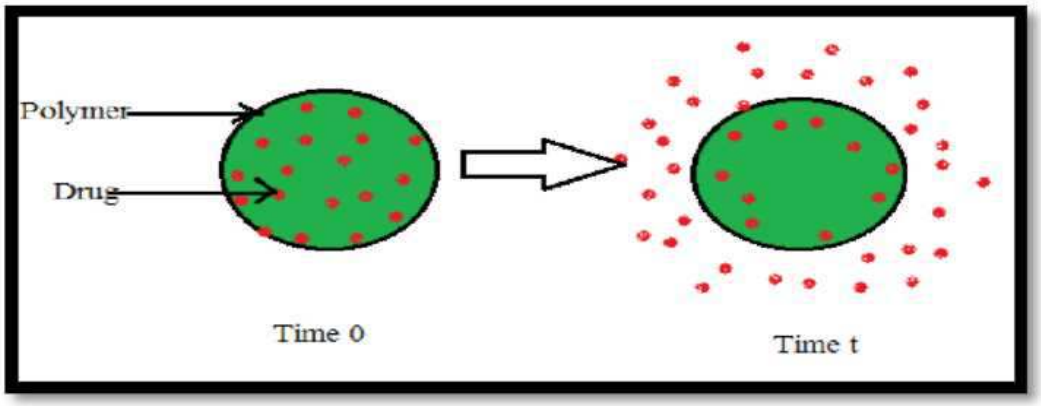


Figure No.3: Schematic Representation of Diffusion Type matrix System

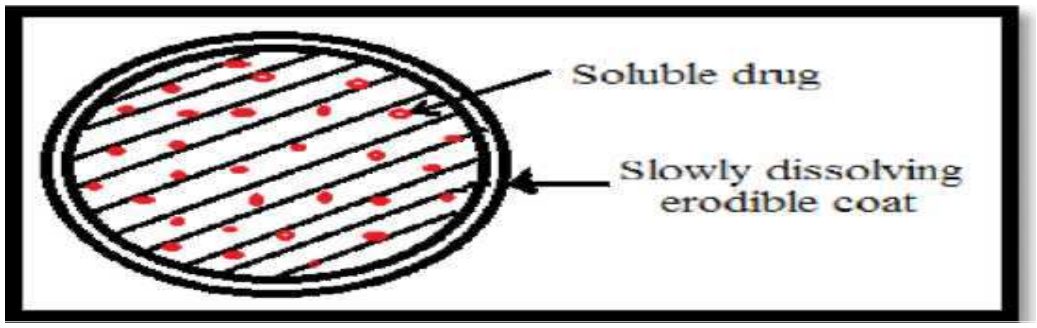


Figure No.4: Schematic Representation of Dissolution Type reservoir System

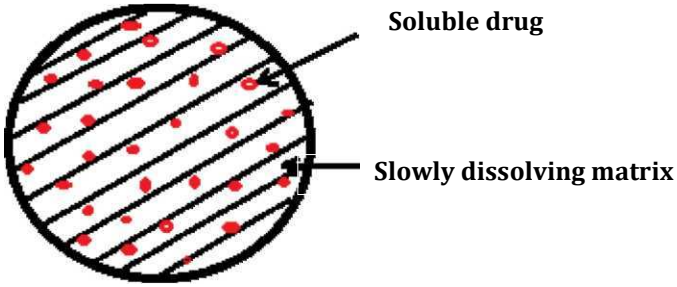


Figure No.5: Schematic Representation of Dissolution of matrix System

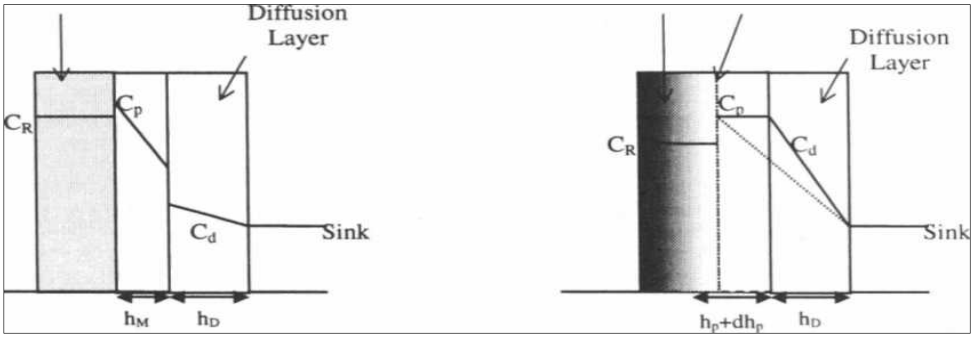


Figure No.6: Illustration of reservoir versus matrix systems

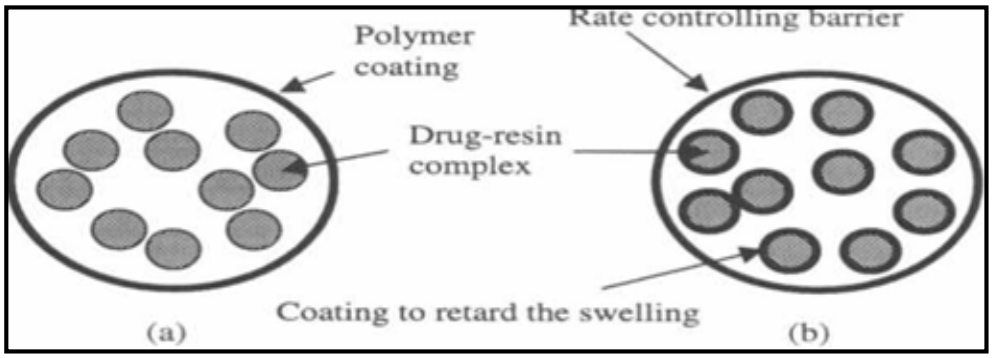


Figure No.7: Schematic illustrations of first generation (a) and second generation (b) ion exchange drug delivery system.

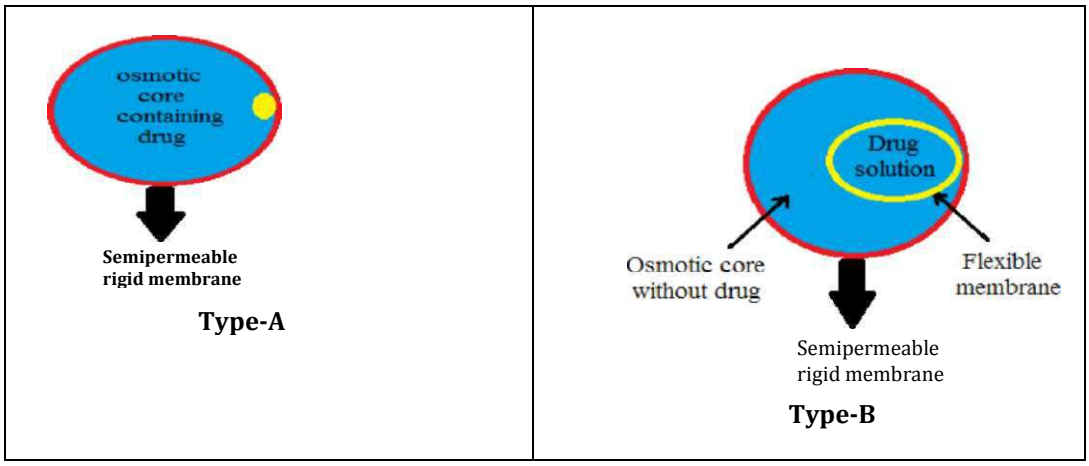


Figure No.8: Type A and B Osmotic Systems

CONCLUSION

Controlled-release delivery devices have been developed for more than 30 years. Most of the devices utilize the fundamental principles of diffusion, dissolution, ion exchange, and osmosis. Optimal design of a drug delivery system will require a detailed understanding of release mechanisms, properties of drugs and carrier materials, barrier characteristics, pharmacological effect of drugs, and pharmacokinetics. With development in the field of biotechnology, there is an increase in the number of protein and other macromolecular drugs. These drugs introduce new challenges and opportunities for design of sustained drug delivery systems. Moreover, the reasonable cost of oral Sustained release drug delivery system has lead to ease of market penetration as replacement of oral conventional drug delivery system.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Narasaraopet Institute of Pharmaceutical Sciences, Department of Pharmaceutics, Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, East Godavari, Andhra Pradesh, India for providing the facilities to complete this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Anuj Patnaik N. *et al.*, Sustained release drug delivery system: a modern Formulation approach, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(5), 2013, 586-601.