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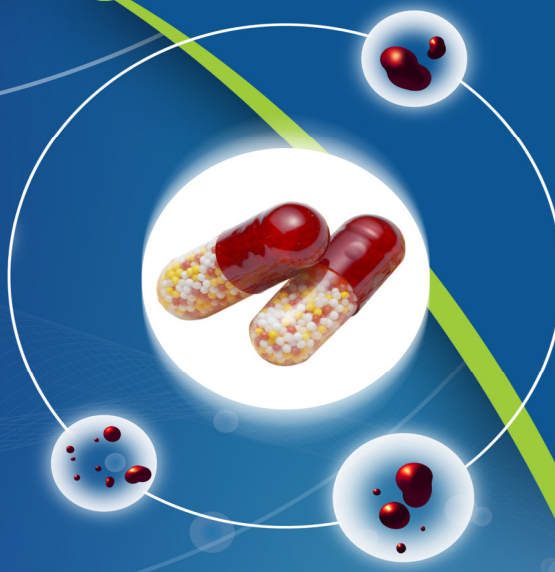

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Review Article

SUSTAINED RELEASE: EMERGING DRUG DELIVERY SYSTEM

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ABSTRACT

To achieve and maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and these results in a fluctuating drug levels in plasma. Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to 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.

Keywords: *SRDDS, Diffusion Controlled, Extended Release, Rotating Basket*

INTRODUCTION

Sustained releases are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of the drug. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form.

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For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long-term use. In such cases the goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The design of oral sustain release drug delivery system (SRDDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. During the last two decades there has been

remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. Sustained release system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order.

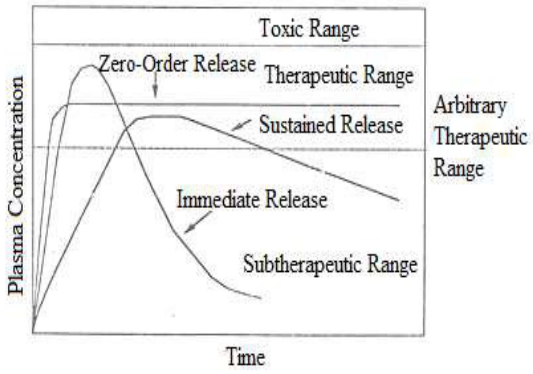

Figure 1 - Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation

SUSTAINED RELEASE DELIVERY SYSTEMS MAY BE DIVIDED CONVENIENTLY IN TO TWO CATEGORIES

Controlled Release:

- These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

Extended Release:

- Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds. [1,2]

ADVANTAGE AND DISADVANTAGES OF SRDDS

Advantages:

- Improved patient convenience and compliance due to less frequent drug administration.
- By using SRDFs efficiency of drugs can be improved by improving bioavailability.
- Reduction in fluctuation in steady-state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.
- Decreased localised side effects like reduction in G.I. irritation.
- Control the onset and duration of drug therapy by altering the dose or mode of administration.
- Avoidance of night time dosing.
- Better drug utilisation due to minimum fragmentation on chronic dosing.
- Initial cost of production of sustained release dosage form is greater than the conventional dosage form although SRDFs are economic because average cost of treatment over an extended time period is lesser than the conventional dosage form.
- Controlled drug therapy can be achieved by taking advantage of beneficial drug interaction that effect drug disposition and elimination. e.g. the action of Probenicid which inhibits the excretion of Penicillin thus prolonging its blood levels.

- A less obvious advantage, implicit in the design of SRDFs, is that the total amount of drug administered decreased thus maximum availability of drug with minimum dose is achieved.
- Safety margin of high potency drugs is increased and the incidence of both local and systemic side effects decreased in sensitive patients. Overall administration of SRDFs enables increased reliability of therapy.
- SRDFs minimise drug accumulation with chronic dosing of drug.
- Reduction in drug activity with chronic use of drug can be minimized by using SRDFs.

Disadvantages:

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first -pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH dependent solubility, etc.
- Poor in vitro-in vivo correlation.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation.
- Immediate action is not possible.
- The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.
- Need for additional patient education:
- Increase variability among dosage units.
- SRDFs normally contain a larger amount of drug which is greater than a single dose normally administered. So it is unsafe.
- Sustained release dosage forms are design for normal population i.e. on bases of average drug biological half-lives. Consequently, disease states that alter disposition, significant patient variation, and so forth are not accommodated.
- SRDFs which tend to remain intact may become ledged at some site along GIT therefore more contact time with GI mucosa. Slow release of drug from dosage form may produce high localised concentration of drug which causes irritation of GI mucosa.
- Reduced potential for accurate dosage adjustment.[3,4,5]

REQUIREMENTS OF THE DRUG WHICH CAN BE FORMULATED IN SRDFS

***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, leading to fatalities e.g. Digitoxin.

***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.

Desirable half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has short half-life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug

with elimination half-life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

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. This is chiefly because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.

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 forms.

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. [6, 7]

FACTORS INFLUENCING THE DESIGN OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

A. *Physiochemical Properties of the Drug*

The release of the drug from the dosage form is totally dependent on the drug properties. The drug properties not only decide the suitability to sustained/controlled release dosage form but also the route of administration. The properties are as below:

Solubility:

Drugs, which are having, low aqueous solubility generally suffer from low aqueous bioavailability. The gastric intestinal transit time of insoluble drug particle is limited and in some cases the solubility of drug at the major absorption site may be low. Some drugs are well absorbed in intestine while they show good solubility in stomach only. Such candidates are poor candidates for sustained/controlled oral dosage forms.

Partition Co-efficient:

The partition co-efficient is another important drug property, which influences the design of oral sustained release delivery by two ways,

- It is an important property that governs the permeation of drug particles through biological membrane.
- The diffusion of drug molecules across rate controlling membrane or through the matrix systems essentially relies on partition co-efficient.
- Drugs with low partition co-efficient value easily permeate through biological membrane; however for further functions aqueous solubility is required. So, there is always a need of balance between aqueous/oil solubility of the drugs and that balance gives the optimum flux for permeation through biological membrane.

Molecular Weight:

The diffusivity of the drug molecules through biological membrane is depending upon the molecular size. Molecular size or weight is indirectly proportional to the diffusivity. Thus smaller the molecular size or weight better the diffusion

Drug Stability:

The stability of the drugs at its site of release and exposure to biological environment is one important factor which can influence the design of oral SRDDSs. Drugs that are unstable in gastric pH can be developed as slow release dosage form and drug release can be delayed till the dosage form reaches the intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for oral SRDDSs.

Protein Binding:

Generally, the duration of drug action is a function of protein binding. Drug protein binding serves as a depot for the drug molecules and leads to highly protein binding drugs. High protein binding of drugs gives a better control over its release into plasma. The drug interaction and period of binding with protein also influence the rate and extent of absorption.

B. Physiological (Biological) Factors

The pharmacokinetic properties and the dose response parameters considerably influence the design of oral SRDFs. It is always assumed that blood or tissue concentration of the drugs is directly proportional to the biological activity.

Absorption:

The desirable quality of oral controlled delivery system is that it should release complete drug and the released drug should completely absorbed. The release of the drug from the system is the rate-limiting step, where rapid absorption relative to drug release is always expected. But it is not possible due to either of the following reasons:

- Degradation of drugs
- Protein binding
- Site-specific as well as Dose-dependent absorption
- The uniform drug absorption though incomplete may lead to successful design of an oral controlled drug delivery system.

Distribution:

The apparent volume of distribution is one of the important parameter of the drugs that describes the magnitude of distribution as well as protein binding within the body. Apparent volume of distribution is the proportionality constant of the plasma concentration of the drug to the total drug amount in the body. Thus drug candidates with higher apparent volume of distribution are more preferred in designing of controlled release dosage forms.

Metabolism:

Metabolism of a drug is either an inactivation, of an active drug or conversion of an inactive drug to an active metabolite. Complex metabolic patterns make the design more difficult, particularly when the biological activity is due to a metabolite. Drugs that are capable of inducing or inhibiting enzyme synthesis are poor candidates for sustained delivery systems due to difficulty in maintaining uniform blood levels. Drugs possessing variations in bioavailability due to first-pass metabolism or intestinal metabolism are not suitable for sustained delivery systems.

Duration of Action:

The duration of drug action significantly influences the design of oral controlled delivery systems and is dependent on the biological half-life. Various factors such as elimination, metabolism and distribution are influencing the half-life of a drug. Usually drugs with shorter half-lives require frequent

dosing to minimize fluctuations in the blood levels. These drugs are more suitable for controlled delivery systems.

Margin of Safety:

Margin of Safety of a drug can be described by considering therapeutic index, which is the ratio of median toxic dose and median effective dose Therapeutic Index = TD_{50}/ ED_{50}. In general, a drug is considered to be relatively safe with therapeutic index more than 10 i.e., larger the ratio the more safely is the drug. [8, 9]

DESIGN AND FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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. 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 zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation. Sustained (zero-order) drug release has been attempted to be achieved, by following classes of sustained drug delivery system.

A. Diffusion sustained system
   1. Reservoir type
   2. Matrix type

B. Dissolution sustained system
   1. Reservoir type
   2. Matrix type

C. Methods using Ion-exchange
D. Methods using osmotic pressure
E. pH independent formulations
F. Altered density formulations

A. 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*.

$$J = - D \, dc/dx$$

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,

$$dm/dt = ADK\Delta C/L$$

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.

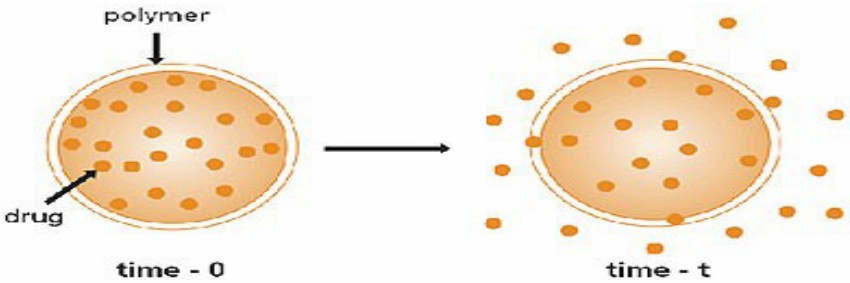

Figure 2- Schematic representation of diffusion sustained drug release: reservoir system

Reservoir type:

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. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

Characterization:-

Description: Drug core surrounded by polymer membrane which controls release rate.

Advantages:

Zero order delivery is possible, release rates variable with polymer type.

Disadvantages:

System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit potential toxicity if system fails.

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,

$$Q = D\square / T\ [2\ A - \square Cs]\ Cst\ ½$$

Where;

Q = weight in gram of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

□ = 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

Characterization:-

Description: Homogenous dispersion of solid drug in a polymer mixture.

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

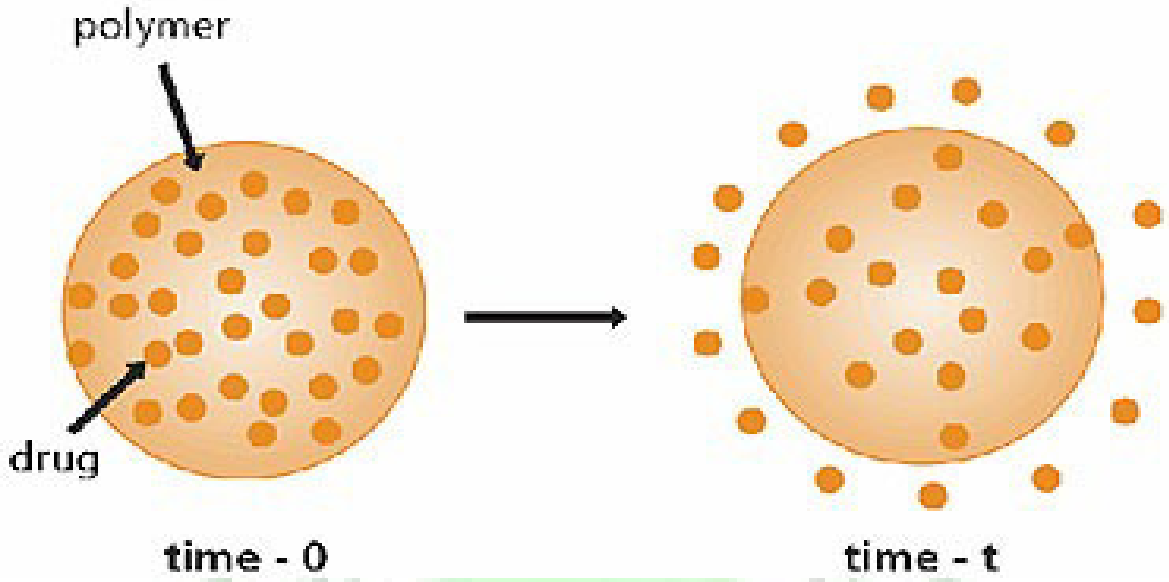

Figure 3 – Schematic representation of diffusion sustained drug release: matrix system

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:-

Release rate = AD / L = (C1- C2)

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. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.

B. 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 device 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**.**

Reservoir type:

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 as shown in figure, 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.

Although 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. This is shown in figure. 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 of drug levels at late times will be achieved from those with 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.

Matrix type:

The more common type of dissolution sustained dosage form as shown in figure. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Two types of dissolution-sustained pulsed delivery systems:-

a) Single bead– type device with alternating drug and rate-controlling layer.

b) Beads containing drug with differing thickness of dissolving coats.

C. Methods using lon Exchange

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 this complex gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract. Resin $^+$ - Drug $^-$ + Cl^-goes to resin ± Cl^- + $Drug^-$

Where, x^- is cl^- conversely

Resin $^-$ - $drug^+$ + Na $^+$goes resin $^-$ Na^+ + Drug

These systems generally utilize resin compounds of water insoluble cross – linked polymer. They contain salt – forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of the resin which is function of the amount of cross linking agent used to prepare resins .The release rate can be further sustained by coating the drug resin complex by microencapsulation process. The resins used include Amberlite®, Indion®, polysterol resins and others.

D. Methods using osmotic pressure

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. Two types of osmotically sustained systems are:-

a) Contains an osmotic core with drug.

b) Contains the drug in flexible bag with osmotic core surrounding.

E. pH– Independent formulations

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the 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 e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

F. 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 1-4gm/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. [10]

TOTAL DOSE OF DRUG REQUIRED IN SRDDS IS DIVIDED INTO TWO PORTIONS

Di (Initial/loading dose):-

It release immediately and rapidly into GI fluids and then absorbed into body compartment rapidly. It follows 1st order kinetics characterised by apparent absorbance rate. The aim of Di is initial rapid release and rapid absorbance to rapidly achieve therapeutic concentration into the body.

Di-----$^{\text{Rapid 1st order release rate}}$---->drug in sol^n---- $^{\text{Input}}$ -->drug ---$^{\text{output}}$ --->drug in GI $fluid^{Ka}$ in body in urine

Dm (Maintenance dose):-

It follows zero order kinetics i.e. rate of release of drug from maintenance dose is independent of amount of Dm remaining in given form at given time.

Rate of release of Dm is characterised by zero order rate constant Km.

The aim of Dm is release at slow and controlled rate to maintain constant plasma concentration of drug.

To ensure therapeutic concentration of drug remain constant two conditions are required

i. Zero order release rate of drug from Dm must be rate determined step (rate at which drug is absorbed subsequently in body)
ii. Rate of absorption of drug(release from Dm)=Rate of elimination from into the body(input) body(output)

Dm---$^{\text{zero order release}}$ ---->drug in sol^n---- $^{\text{Input}}$ -->drug ---$^{\text{output}}$ --->$drug^{(11)}$ in GI $fluid^{Ka}$ in body in urine

EVALUATION OF SUSTAINED RELEASE FORMULATIONS

A. In-Vitro Evaluations

Beaker Method:-

It is used for non-disintegrating pellets as well as disintegrating solid dosage forms. This method is the simplest and most widely used technique to generate in-vitro data to establish in-vivo in-vitro correlation. 250 ml of 0.1 N HCl at 37° C in 400 ml beaker is used as dissolution medium. Agitation is provided by means of a three blade polyethylene stirrer, 5 cm in a diameter and caused to rotate at 60 rpm by means of a variable speed motor. Samples are removed at known time intervals and assayed for the drug content**.**

Rotating Disc Method:-

It is used for non-disintegrating tablets or discs. In this method particles are compressed under investigation using a Carver press. The tablets were not removed after compression but one face was made flush with die surface. The other end of die was then sealed with the cork, placed in a suitable holder and immersed in dissolution medium. The solution and not the solution were then stirred with 150 rpm by means of a stirrer.

Rotating Bottle Method:-

It is used for micronized prednisolone, timed release tablets and capsules. In this method a sample of sustained release product is placed in 90 ml cylindrical screw capped bottle, one for each time interval, 60 ml of fluid is added and bottled are rotated slowly end over end on a temperature controlled water bath at 37° C. A bottle is withdrawn after half an hour for initial analysis and others are rotated for the remaining test period.

Rotating Basket Method:-

The original apparatus is based on the beaker method. The tablet is placed in a 10 mesh screen basket which is suspended below a three blade, 5 cm stirrer. This apparatus is used for phenylbutazone tablets. Good reproducibility is claimed.

Stationary Basket Method:-

This method utilizes a cylindrical stainless steel mesh basket in a lucite frame. This is mounted rigidly in a 3 liter beaker containing 2 liter of dissolution medium. A T-shaped glass stirring rod, set to rotate at 150 rpm completes the apparatus, which is placed in temperature controlled bath at 37º C ± 1º C. The test tablet is dropped into the basket and filtered samples of the dissolution fluid are taken at suitable time intervals.

Oscillating Tube method:-

This is official in U.S.P. XXI for in-vitro evaluation of solid dosage forms. It is a modified disintegration test apparatus. A 30 or 40 mesh screen, is employed in place of 10 mesh. Its use has declined in recent years because the agitation conditions are too severe. Automated dissolution systems based on the U.S.P.-NF disintegration apparatus has been described.

Dialysis Method:-

In this method choice of membrane is important. It must have short equilibrium time and adequate physical strength to retain solid particles. In this method a tablet was placed in the dissolution medium on one side of the dialysis membrane and the cell was rotated in the water bath at 15 rpm. Samples were removed from the distal chamber at appropriate time intervals.

Sintered Filter Method:-

This method involves the use of a medium porosity sintered filter funnel filled with 500 ml of simulated gastric fluid. The tablet is introduced so as to rest in centre of the sintered glass surface. The dissolution medium is allowed to pass through the filter, a process which takes approximately 2 hrs. Sample of the filtrate are collected at known intervals of time and assayed for the drug in solution.

FDA Method:-

In this method more precise control of the changes in the medium with time have been proposed for better simulation of the biological situation in the gastrointestinal tract. These suggestions recommended by the Food and Drug Administration of America, in which 100 ml of simulated gastric fluid is pumped and circulated at 37º C through and past the dosage form held in an inert matrix. 50 ml of this menstrum is removed for analysis each hour and replaced with 50 ml simulated intestinal fluid. The process is continued for the duration of the period over which the dosage form is expected to last. Although closer simulation of physiological conditions is afforded by such a system, the manpower and equipment requirement have prevented its universal application.

Tape Method:-

A weighed quantity of particles is dusted off to pressure-sensitive tape mounted on a frame and the whole assembly is inserted into a beaker. Dissolution of the drug into the stirred dissolution medium is monitored by the removal of samples at known time intervals. The obtained was reproducible.

B. In-Vivo Evaluations

In-vivo data are necessary for the development of a dosage form as well as subsequent in-vitro procedures for the evaluation of a dosage form**.** Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are:-

Clinical response

1. *Blood level data*
2. *Urinary excretion studies*

3. *Nutritional studies*
4. *Toxicity studies*
5. *Radioactive tracer techniques*

IN-VITRO IN-VIVO CORRELATIONS

The requirement of establishing good in-vitro in-vivo correlation in the development of sustained release delivery systems is self-evident. To make a meaningful in-vitro in-vivo correlation one has to consider not only the pharmaceutical aspects of sustained release drug delivery system but also the biopharmaceutics and pharmacokinetics of the therapeutic agent in the body after its release from the drug delivery system, and also the pharmacodynamics of therapeutic agent at the site of drug actions.

A simple in vitro-in vivo relationship can be established by conducting in-vitro and in-vivo evaluations of a potential drug delivery system simultaneously to study and compare the mechanism and rate profiles of sustained drug release. When the in-vivo drug release mechanism is proven to be in good agreement with that observed in the in-vitro drug release studies, then in-vitro in-vivo correlation factor is derived. For capsule type drug delivery system the factor can be represented as

Q=(Q/t) in-vivo/(Q/t) in-vitro

Where Q/t = Rate of release

'Q' values are dependent profiles of drug delivery systems. Upon the sites of administration and environmental conditions to which the animals are exposed during treatment (study). The above relationship can be used for optimization of sustained release profiles of a drug delivery system. Levy has classified in-vivo – in-vitro correlation into:

1. Pharmacological correlations based on clinical observations;
2. Semi-quantitative correlations based on blood levels or urinary excretion data;
3. Quantitative correlations arising from absorption kinetics.

While most of the published correlations are of semi-quantitative nature, the most valuable are those based on absorption kinetics

STABILITY STUDIES OF SUSTAINED RELEASE FORMULATIONS

Stability studies are essential to ensure that product will, over its designated shelf life provide medication for absorbance at the same rate as when originally formulated. These are done in both normal and exaggerated conditions of temperature, humidity, light, etc.

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they claim to have at the time of use. A sustained release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the sustained release product useless.

A published report shows how physical changes in the drug and the coating can influence the in-vitro release pattern of a liquid sustained action dosage form.

According to the method for stability prediction suggested that the 'K' values for the decomposition of a drug at various elevated temperatures are obtained by plotting same function of concentration against time. The logarithms of specific rates of decomposition are then plotted against the reciprocals of the absolute temperature and the resulting curve is extrapolated to room temperature (25º C). The K is then used to measure the stability of the drug under ordinary shelf conditions. [12]

CONCLUSION

SRDDS is the well growing field in the Pharmaceutical Industry. By using SRDDS decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The main objective of SRDDS is to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower

and less frequent dose. This article describe the advantage, disadvantage, design and evaluation parameters of SRDDS as well as give useful information regarding this well developed technology in pharmaceutical industry.

REFERENCES

1. *Lee VHL, Controlled Drug Delivery Fundamentals and Applications: Introduction, Marcel Dekker, (2nd ed) INC, New York. 1987:29.*
2. *Banker GS and Anderson NR. The Theory and Practice of Industrial Pharmacy: Tablet, Lachman, (3rd ed) Varghese Publishing House, Bombay,1990, 293-303.*
3. *Brahmankar D.M. and Jaiswal S.B., Biopharmaceutics and Pharmacokinetics, (1st ed) VallabhPrakashan, Delhi, 2007, 337.*
4. *Lachman L, Lieberman H.A., Kanig J.L., The Theory and Practice of Industrial Pharmacy:*
5. *Sustained Release Dosage Form, (3rd ed) Varghese Publication House, Bombay, 1990, 430-431.*
6. *Vyas S.P., KharR.K., Controlled Drug Delivery,(1st ed), VallabhPrakashan, Delhi, 2008, 6*
7. *John C and Morten C. The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms, (2nded) Churchill Livingstone. 2002:290-300.*
8. *Brahmankar D.M. and Jaiswal S.B., Biopharmaceutics and Pharmacokinetics: Pharmacokinetics, (2nd ed) Vallabh Prakashan, Delhi, 2009, 399-401.*
9. *Vyas S.P., Khar R.K., Controlled Drug Delivery,(1st ed), Vallabh Prakashan, Delhi, 2008, 157-160.*
10. *Robinson J.R., Lee V.H.L., V.H., Controlled drug delivery: fundamentals and applications, Informa Healthcare, Volume 20, 2011, 12-36.*
11. *Sampathkumar K.P., Bhowmik D., Shrivastava S., Paswan S., Dutta A.S., Sustained Release Drug Delivery System Potential, The Pharma Innovation, 2012, 1(2),52-56.*
12. *Brahmankar D.M. and Jaiswal S.B., Biopharmaceutics and Pharmacokinetics, (1st ed) VallabhPrakashan, Delhi, 2007, 342-347.*
13. *Popli H., Sharma S.N., 1990, "Evaluation of sustained release formulations". The Eastern*