

## THE PHARMA INNOVATION

### Sustained Release Drug Delivery System Potential

K.P. Sampath kumar\*, Debjit Bhowmik, Shweta Srivastava, Shravan Paswan and A.S. Dutta

1. Karpagam University, Coimbatore, Tamil Nadu, India
2. Department of Pharmaceutical sciences, Coimbatore medical college, Coimbatore, Tamil Nadu, India
3. R. K. Pharmacy college, Azamgarh, Uttar Pradesh, India

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Oral drug delivery system represents one of the frontier areas of controlled drug delivery system. Such a dosage forms having a major advantage of patient compliance. 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. Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. 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.

*Keyword:* Sustained Release Drug Delivery System, Controlled Drug Delivery

**INTRODUCTION:** 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. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system.

The design of oral sustain drug delivery system (DDS) 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. Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. 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 a method of continuous administration of drug is desirable to maintain fixed plasma drug

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Corresponding Author's Contact information:  
K.P. Sampath Kumar\*  
Karpagam University, Coimbatore, Tamil Nadu, India  
E-mail: [debjit\\_cr@yahoo.com](mailto:debjit_cr@yahoo.com)

levels. 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. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

### Terminology:<sup>1,2</sup>

Modified release delivery systems may be divided conveniently in to four categories.

- A) Delayed release
- B) Sustained release
  - i) Controlled release
  - ii) Extended release
- C) Site specific targeting
- D) Receptor targeting

#### A) Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

#### B) Sustained release:

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.

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

#### 1) Controlled Release:

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

#### 2) Extended Release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

#### C) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

#### D) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

### Potential advantages and disadvantages of sustained release dosage forms

#### Advantages:<sup>2,3,4,5</sup>

#### i) Patient Compliance:

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering sustained release drug delivery system.

#### ii) Reduced 'see-saw' fluctuation:

Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well-designed sustained release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a more steady drug concentration in blood circulation and target tissue cells.

#### iii) Reduced total dose:

Sustained release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

#### iv) Improved efficiency in treatment:

Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to

those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage forms leads to better management of the acute or chronic disease condition.

#### Challenges:<sup>3,4,5</sup>

##### i) Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

##### ii) limited choice of selecting desired dose in the unit:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

##### iii) Poor In Vitro – In Vivo correlation:

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called '*Absorption window*' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

##### iv) Patient variation:

The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs,

presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

#### **Other advantages are:**

##### *Sustained drug delivery:*

As mentioned earlier, drug absorption from oral controlled release (CR) dosage forms is often limited by the short GRT available for absorption. However, HBS type dosage forms can retain in the stomach for several hours and therefore, significantly prolong the GRT of numerous drugs.

These special dosage forms are light, relatively large in size, and do not easily pass through pylorus, which has an opening of approx. 0.1– 1.9 cms.

##### *Site specific drug delivery*

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

The eradication of *Helicobacter pylori* requires the administration of various medicaments several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using GRDDS. Floating alginate beads have been used for the sustained release of Amoxicillin trihydrate. Thus, it can be expected that the topical delivery of antibiotic through a FDDS may result in complete removal of the organisms in the fundal area due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer.

##### *Pharmacokinetic advantages*

As sustained release systems, floating dosage forms offer various potential advantages. Drugs

that have poor bioavailability because their absorption is limited to upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.

Floating dosage forms with SR characteristics can also be expected to reduce the variability in transit performance. In addition, it might provide a beneficial strategy for gastric and duodenal cancer treatment.

The concept of FDDS has also been utilized in the development of various anti-reflux formulations. Floating systems are particularly useful for acid soluble drugs, drugs poorly soluble or unstable in intestinal fluids, and those which may undergo abrupt changes in their pH dependent solubility due to food, age and disease states.

#### **LIMITATIONS**

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of Bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).
4. The drugs, which are absorbed throughout gastro-intestinal tract, which undergo first pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.
5. Some drugs present in the floating system causes irritation to gastric mucosa.

#### **Criteria to be met by drug proposed to be formulated in sustained release dosage forms.** 3,4.

- a) Desirable half-life.
- b) High therapeutic index

- c) Small dose
- d) Desirable absorption and solubility characteristics.
- e) Desirable absorption window.
- f) First pass clearance.

a) Desirable half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has a 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 form, 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.

b) 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 eg. Digitoxin.

c) 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.

d) 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.

e) 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.

f) 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.

**DESIGN AND FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM AND THE FACTORS AFFECTING THERE OF:** <sup>5,6,7,8</sup>

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 a 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.
  - i) Reservoir type.
  - ii) Matrix type
- B) Dissolution sustained system.
  - i) Reservoir type.
  - ii) Matrix type
- C) Methods using Ion-exchange.
- D) Methods using osmotic pressure.
- E) pH independent formulations.
- F) Altered density formulations.

**A) Diffusion sustained system:** <sup>6,7,8</sup>

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*.

$$J = -D \frac{dc}{dx}$$

D = diffusion coefficient in area/ time

$\frac{dc}{dx}$  = 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  $\frac{dm}{dt}$  is given by,

$$\frac{dm}{dt} = ADK\Delta C/L$$

Where A = area

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

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

$\Delta c$  = concentration difference across the membrane.

1] Reservoir type:

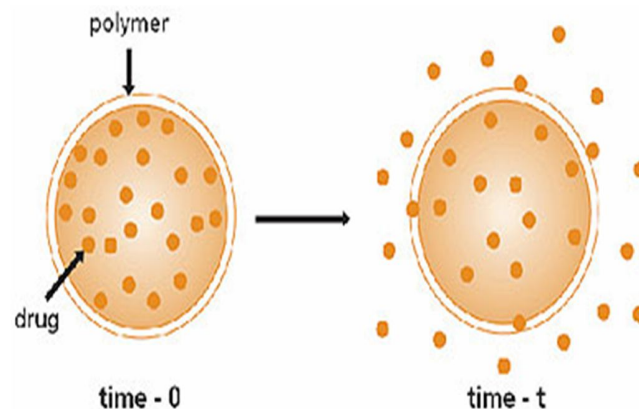


Figure No-1

*Schematic representation of diffusion sustained drug release: reservoir system.*

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.

ii] 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,

$$Q = D\varepsilon / T [2 A - \varepsilon C_s] C_s t^{1/2}$$

Where;

- Q = weight in gms of drug released per unit area of surface at time t
- D = Diffusion coefficient of drug in the release medium
- $\varepsilon$  = porosity of the matrix
- C<sub>s</sub> = 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.

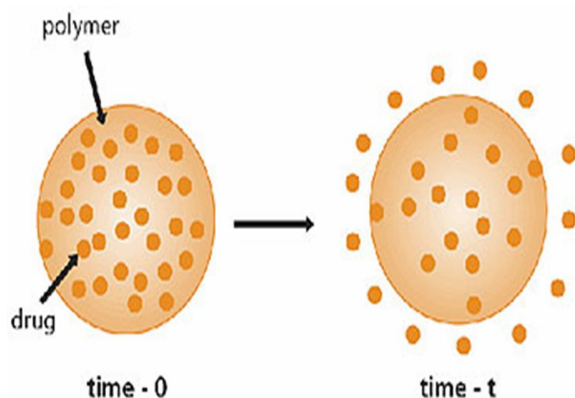


Figure No-2

*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:-

$$\text{Release rate} = AD / L = [ C_1 - C_2 ]$$

Where,

- A = Area
- D = diffusion coefficient
- C<sub>1</sub> = Drug concentration in the core
- C<sub>2</sub> = 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:**<sup>7,8</sup>

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.

#### i) 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.

#### ii) Matrix type:

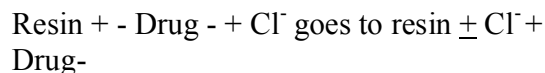
The more common type of dissolution sustained dosage form as shown in figure. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

*Two types of dissolution- sustained pulsed delivery systems:*

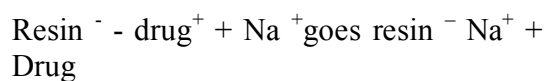
- a] Single bead- type device with alternating drug and rate-controlling layer.
- b] Beads containing drug with differing thickness of dissolving coats.

#### **C] Methods using Ion Exchange:**<sup>6,7</sup>

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  $\text{Na}^+$  and  $\text{Cl}^-$  present in gastrointestinal tract



Where  $x^-$  is  $\text{Cl}^-$  conversely



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.<sup>15</sup> The resins used include Amberlite®, Indion®, polysterol resins and others.

#### **D] Methods using osmotic pressure:**<sup>7</sup>

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:-*

- Type A contains an osmotic core with drug
- Type B contains the drug in flexible bag with osmotic core surrounding.



### **E] pH– Independent formulations:**<sup>6,9</sup>

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:**<sup>1</sup>

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, 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  $1-4\text{gm/cm}^3$ .

#### *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.

### **Factors Influencing Design of sustained Release Dosage Forms:**<sup>7,1,4</sup>

The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

#### A] **Pharmaceutics:**

This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.

#### B] **Biopharmaceutics / pharmacokinetics:**

This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

#### C] **Pharmacodynamics/ Clinical Pharmacology:**

It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.

### **Drug properties influencing the design of sustained or sustained release drug delivery system are classified as:**

1] Physicochemical properties of the drug

These include dose size, aqueous solubility, protein binding, molecular size, drug stability and partition coefficients.

## 2] Biological factors

These include absorption, distribution, metabolism, duration of action, margin of safety, side effects of drug, disease state and circadian rhythm.

## **Methods to achieve oral sustained drug delivery:**<sup>6</sup>

There are various methods employed for the fabrication of oral sustained release delivery systems. *Ritschel* has given a detailed report of these techniques. These are as follows.

- a. Hydrophilic matrix
- b. Plastic matrix
- c. Barrier resin beads
- d. Fat embedment
- e. Repeat action
- f. Ion exchange resin
- g. Soft gelatin depot capsules
- h. Drug complexes

In the following discussion, sustained release dosage form using method of matrix is discussed.

### ***Matrix devices:***

Historically, the most popular drug delivery system has been the matrix because of its low cost and ease of fabrication. Methods of altering the kinetics of drug release from the inherent first order behavior especially to achieve a constant rate of drug release from matrix devices have involved several factors.

### **Requirements of matrix materials:**

The matrix materials must comply with the following conditions,

1. They must be completely inert and non-reactive with the drug and additives in the tablet.
2. They must be able to form a stable and strong matrices when compressed either directly or more often as granules prepared by the addition of a binding agent.
3. They must be non-toxic.

### ***Hydrophilic matrix system:***

Carboxymethylcellulose sodium, hydroxymethyl cellulose, polyethylene oxide, polyvinyl-107, molidones and natural gums can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material.

Upon immersion in water the hydrophilic matrix quickly forms a gel layer around the tablet. Drug release is sustained by a gel diffusional barrier and /or tablet erosion.

## **EVALUATION OF SUSTAINED RELEASE TABLETS:**<sup>10,11</sup>

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in-vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

### **1. In – Vitro Methods**

These are:-

- a. Beaker method
- b. Rotating disc method
- c. Rotating Bottle method
- d. Rotating Basket method
- e. Stationary Basket Method

- f. Oscillating tube method
- g. Dialysis method
- h. USP dissolution method.

## 2. *In-Vivo Methods*

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:-

- a. Clinical response
- b. Blood level data
- c. Urinary excretion studies
- d. Nutritional studies.
- e. Toxicity studies
- f. Radioactive tracer techniques

## 3. *Stability Studies* :

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. The in-vitro and in-vivo release rates of sustained release product may be altered by atmospheric or accelerated conditions such as temperature & humidity.

The stability programmes of a sustained release product include storage at both nominal and accelerated conditions such as temperature & humidity to ensure that the product will withstand these conditions.

## **In vitro- In vivo Correlations:**<sup>4,10</sup>

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 aspect 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 action.

A simple in vitro-in vitro 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:

$$Q = \frac{(Q/t) \text{ in-vivo}}{(Q/t) \text{ in-vitro}}$$

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 Levy has classified in-vivo – in-vitro correlation in to:

- a) Pharmacological correlations based on clinical observations;
- b) Semi-quantitative correlations based on blood levels or urinary excretion data;
- c) Quantitative correlation arising from absorption kinetics. While most of the published correlations are of semi-quantitative nature, the most valuable are those based on absorption kinetics.

## **Bioavailability Testing:**

Bioavailability is generally defined as the rate and extent of absorption of unchanged drug from its site of application to the general circulation. Bioavailability is defined in terms of a specific

drug moiety, usually active therapeutic entity, which may be the unchanged drug or as with prodrug, for instance, a metabolite. In contrast, the term "absorption" often refers to net transport of drug related mass from its site of application into the body. Hence, a compound may be completely absorbed but only partially bioavailable as would occur, when low bioavailability is caused by incomplete absorption. Pharmaceutical optimization of the dosage form may be warranted to improve absorption characteristics of the drug and thereby also its bioavailability. Bioavailability studies are ordinarily single dose comparisons of tested drug product in normal adults in a fasting state. A crossover design, in which all subjects receive both, the product and reference material on different days is preferred. Guidelines for clinical testing have been published for multiple dose studies. Correlation of pharmacological activity or clinical evidence of therapeutic effectiveness with bioavailability may be necessary to validate the single significance of sustained release claims. While single dose studies are usually sufficient to establish the validity of sustained release dosage form design; multiple dose studies are required to establish optimum dosing regimen. They are also required when difference may exist in the rate but not the extent of absorption. When there is excessive subject-to-subject variation or when the observed blood levels after a single dose are too low to be measured accurately. A sufficient number of doses must be administered to attain steady state blood levels. According to an extensive study of sustained release Theophylline products; for example, encapsulated forms showed less peaking during multiple dosing and therefore better control of blood level within the desired limits.

#### **Regulatory Requirements:** <sup>4,12</sup>

In India, the sustained release drug products in legal sense are considered to be "*New Drugs*" as per the Drugs and Cosmetic Act 1940, and Rules there under, 1945. The guidelines and requirements are given under the schedule 'Y'.

#### **CONCLUSION**

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.

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