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A CONCISE REVIEW ON SUSTAINED RELEASE DOSAGE FORM

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Abstract:

During past few years many conventional dosage forms are rapidly being replaced by novel controlled release drug delivery system in which sustained release drug delivery system has gaining more popularity because of its excellent advantages over conventional one such as, reduction in dosing frequency, reduced fluctuation in circulating drug levels, more uniform effect, maximum utilization of drug, improved bioavailability, increased patient compliance, etc. Sustained release system is considered as a wiser approach for the drug with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. Sustained release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. Sustained release drug delivery system provides better therapeutic advantages over traditional drug delivery system. The basic rationale of sustained drug delivery system optimizes of the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of the drug in such a way that utility is maximized, side-effects are reduced and cure of the disease is achieved. The present article is a brief review on various formulation approaches for Sustained release drug delivery system.

Keywords: - Sustained release drug delivery system, Dose frequency, Biological half-life, Physicochemical properties of drug.

Introduction:

Sustained release, prolonged release, sustained action, controlled release, depot release, extended release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug[1].The aim of designing sustained release dosage form is to reduce the dosing frequency or to increase overall effectiveness of the drug by targeting it at the site of action, by providing uniform drug delivery or reducing required dose. It is an ideal drug delivery system because it provides single dose administration and it delivers the active.

Terminology[2]:

Sustained Release drug delivery system: Any of the dosage form that maintains the therapeutic blood or tissue levels of drug by continuous release of medication for a prolonged period of time, after administration of a single dose. In case of injectable dosage forms it may vary from days to months.

Controlled release drug delivery system:

Controlled drug delivery is that type of system which release the medicaments from the dosage form at a predetermined specified rate for locally or systemically for a specified period of time.

Modified Release Dosage Forms:

According to USP these are those are dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or conveniences objectives not offered by conventional dosage forms.

Repeat Action Dosage Forms:

An individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

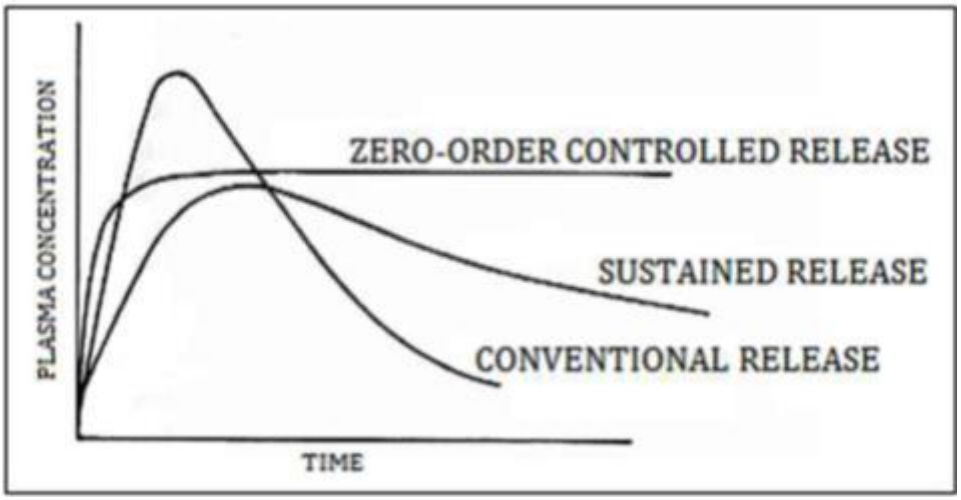


Fig. No. 1: Ideal Plasma Concentration Curves for Conventional release, Zero Order Release, Sustained Release Drug Delivery System.

Rationale: -

1. Formulation of SRDDS minimizes dosing frequency and sustained release provides availability of drug at site of action throughout the treatment to improve clinical efficiency of a drug molecule.
2. To reduce cost of treatment by reducing number of dosage requirement.
3. To minimize toxicity due to overdose which is often in conventional dosage form.
4. To enhance the activity duration of a drug possessing short half-life.
5. Uniform drug response achieved by using different combination of doses and dosage interval.
6. Frequent administration of dose produces side effect.

Limitations of conventional dosage forms[3]:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur.

Advantages[4][5]:-

i) **Patient compliance**: Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factor, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.

ii) **Reduced 'see-saw' fluctuation:** Drug concentration in the systemic circulation and tissue compartments show ‘see saw’ pattern frequently when the drug administration in conventional dosage form. The magnitudes of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain in a steady drug concentration in blood circulation and target tissue cells.

iii) **Total dose reduction**: To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv) **Improvement of deficiency in treatment:** Optimal therapy of a disease requires an effective transfer 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 form leads to better management of the acute or chronic disease condition.

v) **Economy**: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over a prolong period of time may be less.

Disadvantages of Sustained Release System [4]:

i) **Inhibition of prompt termination of therapy**

Administration of sustained release medication does not permit the prompt termination of therapy such as might be encountered if significant adverse effects are noted, cannot be accommodated.

ii) **Dosage form design**

The formulation has less scope for flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

iii) **Patient variation**

Sustained release formulations are specially designed for the normal population i.e. on the basis of average biologic half-lives of drug. If the disease condition is severe and responsible for the drug disposition or any adverse condition, then extra care should be taken.

iv) **Economic factors**

Sustained release dosage forms are specially designed system that's why it may require involvement of costlier processes and equipments in manufacturing. So economic factor should be considered prior to manufacture this type of system.

v) **Dose dumping**

Dose dumping is the condition in which quantity of drug release increases and causes dumping of drug which may leads to toxicity. This problem can be solved by using accurate choice of method for potent drugs.

vi) **Poor In-Vivo and In-Vitro correlations**

In sustained release dosage form, the rate of drug release is purposely reduced to achieve drug release possibly over a large region of gastrointestinal tract. Therefore 'Absorption window' becomes important and may give rise to poor drug absorption in-vivo in spite of outstanding in-vitro release characteristics.

vii) **Limited choice of selecting desired dose in the unit**

In conventional dosage forms, dose adjustments are much simpler e.g. tablets 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[6,7,8]

Criteria to be met to incorporate the drug in sustained release dosage form[3]

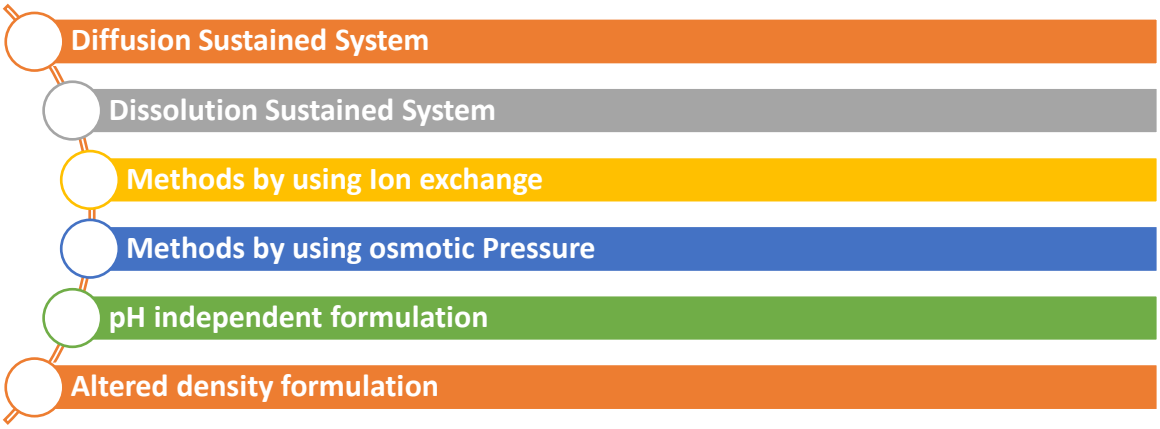
Table: Physicochemical parameter for drug selection

Sr. No.	Parameters	Description
1.	Molecular size	< 1000 Daltons
2.	Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
3.	Apparent partition coefficient	High
4.	Absorption mechanism	Diffusion
5.	General absorbability from all GI segments	Release should not be influenced by pH and enzyme

Table: Pharmacokinetic parameter for drug selection

Sr. No.	Parameters	Description
1.	Elimination half-life	Between 2 to 8 hrs
2.	Absolute bioavailability	Should be 75% or more
3.	Absorption rate constant (Ka)	Must be higher than release rate
4.	Apparent volume of distribution(Vd)	Larger Vd and MEC, larger will be the required dose
5.	Total clearance	Not dependent on dose
6	Elimination rate constant	Required for design
7.	Therapeutic concentration(Css)	The lower CSS and smaller Vd,the less amount of drug required
8.	Toxic concentration	Apart the value of MTC and MEC safer the dosage form

Formulation Strategies for oral SRDDS[2]:



Classification of Sustained Release System

The controlled release system for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

Depending upon the manner of drug release three systems are classified as follows:

1. Continuous Release systems

2. Delayed transit and controlled release systems

3. Delayed release system

Continuous release system

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

The various system under this category are as follow:

A. Diffusion controlled release system

B. Dissolution controlled release system

C. Dissolution and diffusion controlled release system

D. Ion exchange resin drug complexes

E. pH -independent formulation

F. Osmotic pressure controlled systems

A) Diffusion controlled sustained release system[9,10,11]: 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

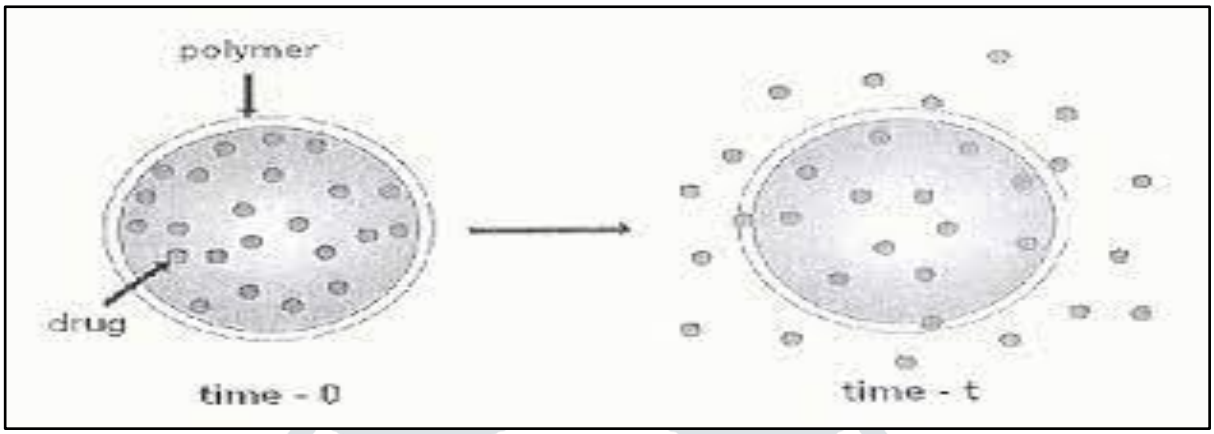
D = diffusion coefficient in area/ time dc/dx = change of concentration 'c' with distance 'x' In common form, when a water insoluble membrane surrounds a core of drug, it must diffuse through the membrane, the drug release rate dm/dt is given by,

dm/dt= ADK. C/L

Where, A = Area K = Partition coefficient of drug between the membrane and drug core. L= Diffusion path length (i.e. thickness of the coat in ideal case). C = Concentration difference across the membrane

i) Diffusion reservoir system: A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are: Zero order drug release is possible. The release rate is dependent on the type of polymer. High molecular weight compounds are difficult to deliver through the device.

Figure 1: Diagrammatic representation of Diffusion Type Reservoir System



ii] Diffusion Matrix type: It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are: Zero order release cannot be obtained. Easy to produce than reservoir devices. High molecular weight compounds are delivered through the device. ii] Diffusion Matrix type: A solid drug is distributed into an insoluble matrix and the release rate of drug which generally depend on the rate of drug diffusion and the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system.

Q = D/T [2A–Cs] Cst ½.

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. ε= porosity of the matrix. Cs = solubility of drug in release medium. T = Tortuosity of the matrix. A = concentration of drug in the tablet, gm/ ml.

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 = Diffusion path length

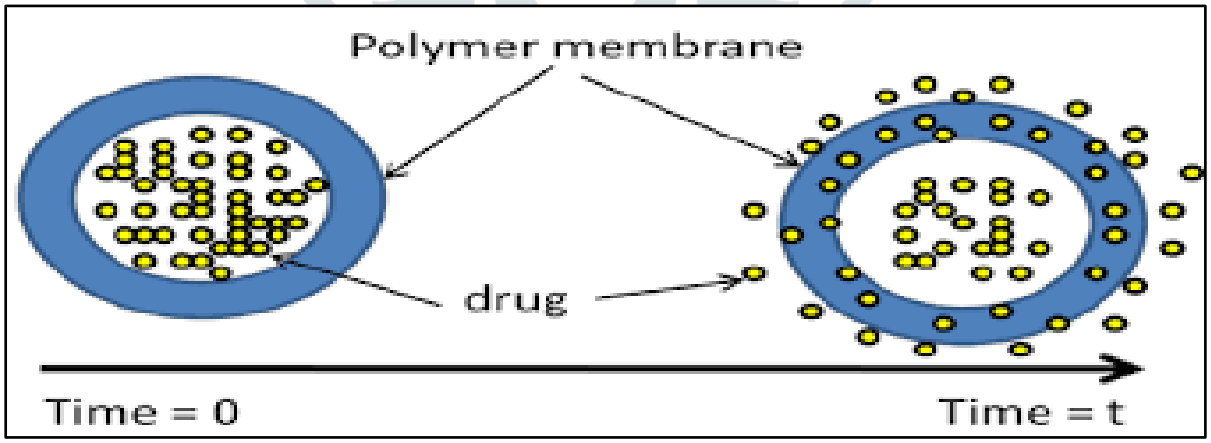


Figure 2: Diagrammatic representation of diffusion sustained drug release: matrix system.

B) Dissolution sustained systems[12]: A drug which having a slow dissolution rate this drugs are naturally sustained and for those drugs with high water solubility, decrease their dissolution rate through appropriate salt or derivative formation. These systems are generally employed in the manufacturing of enteric coated dosage forms. Protection of 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.

a) Soluble reservoir system: In this system drug is coated with erodible coat, which is slowly dissolved in the contents of GI tract by alternating layers of drug with the rate controlling coats.

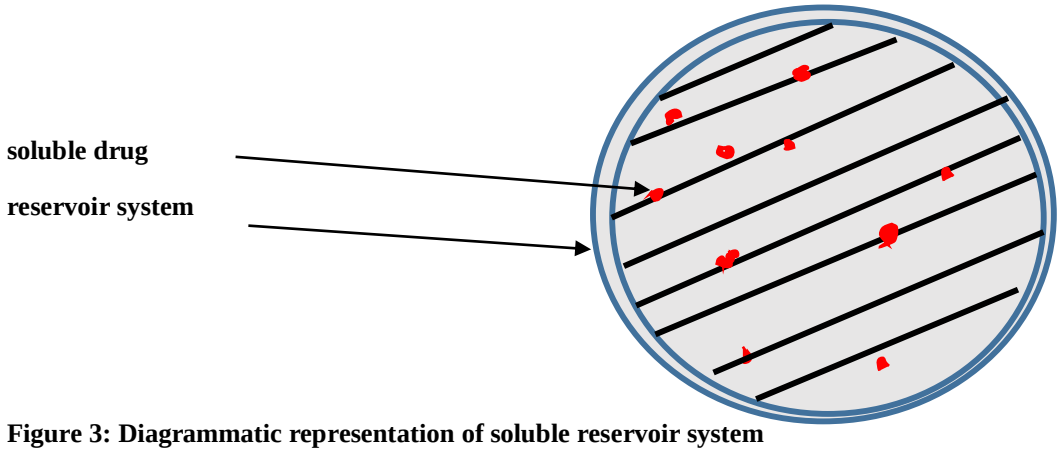


Figure 3: Diagrammatic representation of soluble reservoir system

b) Soluble matrix system: It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Figure 4: Diagrammatic representation of soluble matrix system.

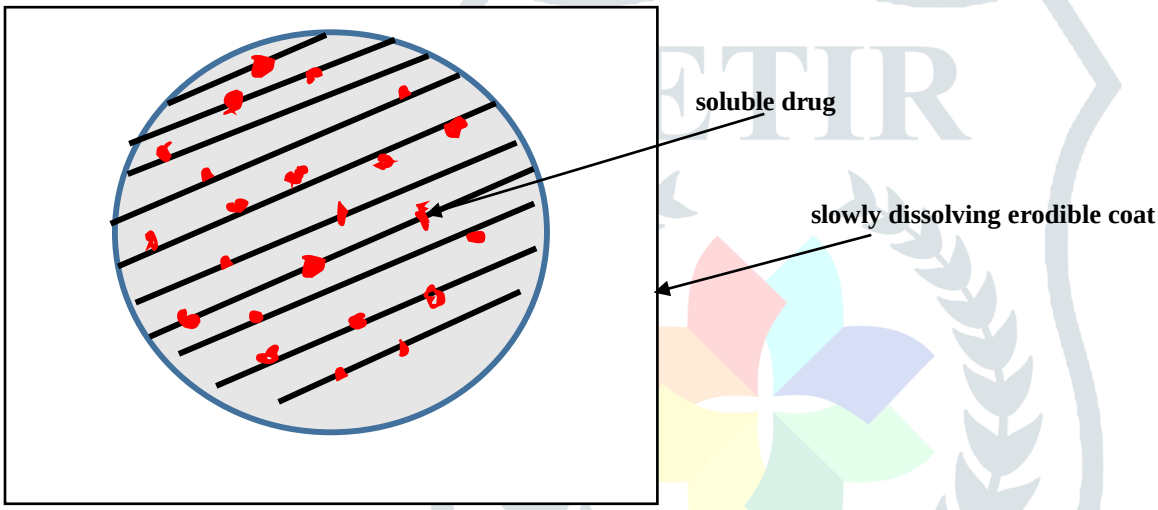


Figure 4: Diagrammatic representation of Soluble reservoir system

C. Ion exchange resin drug complexes [13]

Ion exchange resins are water insoluble, cross-linked polymers that contain acidic or basic functional groups and have the ability to exchange counter –ions within aqueous solutions surrounding them. IER have received considerable attention from pharmaceutical scientists because of their versatile properties as a drug delivery vehicle. During past few years, pharmaceutical research found that IER can be equally contributed in controlled release, transdermal, nasal, topical, and taste masking.

Drug, molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of the free drug molecules out of the resins as shown below,

Ion exchange based delivery system represent better approach for a drug that is highly susceptible to degradation by enzymatic process.

Ion exchange resin which are divided into types:

a) Cation exchange resin:

b) Anion exchange resin:

Cationic exchange resin: Contains acidic functional group generally they contain polysteryne polymer with either phenolic carboxylic phenolic group.

Anion exchange resin: Involved basic functional group capable for extracting anions from acidic solution. Ion exchange resin are used to sustain the effect of drug based on concept that negatively or positively charge drug moiety combine with appropriate resin producing insoluble poly salts resonates.

The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na+ and Cl- present in gastrointestinal tract. Resin+ – Drug– + Cl– ---------- > >> resin+ Cl– + Drug– where x- is Cl- conversely Resin– – Drug+ + Na+ ---------- > >> resin– Na+ + Drug Water insoluble cross linked polymer compounds are used for this system.[14,15]

Table: Common Ion Exchange Resins.[16]

Type	Exchange species	Polymers Backbone	Commercial Resins
Strong Cation Exchange Resins	$-SO_3H^+$	Polystyrene –DVB	INDION® 244,254, 404. TULSION® 344. AMBERLITE® IR120. Dowex 50. ZEOLITE.
Weak Cation Exchange Resin	COOH	Methacrylic Acid-DVB	AMBERLITE IRC 50.
Strong Anion Exchange Resins	N^+R_3	Polystyrene- DVB	DOWEX®-1 AMBERLITE® IR400.
Weak Anion Exchange Resins	N^+R_2	Polystyrene -DVB	DOWEX®2. Amberlite IR 4B.

These are some type of resins:

Resin type Chemical constituent Strong acidic cationic exchanger Sulfonic acid group attached to astyrene and divinyl benzene copolymer. Weak acidic cationic exchanger Carboxylic acid group linked to an acrylic acid and divinyl benzene copolymer. Strong basic anion exchanger. Quarternary ammonium groups attach to astyrene and divinyl benzene copolymer. Weak basic anion exchanger Polyalkylamine copolymer group linked to a styrene and divinyl benzene copolymer.

D) Altered density formulations [17,18]

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/cm3. 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.

E) pH– Independent formulations: [19,20]

We know that most of the drugs are either weak acids or weak bases. The release from Sustained release formulations is directly or indirectly 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 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 providing a constant rate of drug release.

FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGN

Two factors involved in oral sustained-release dosage form design.

A. Biological Factors

B. Physicochemical Factors

A. Biological Factors[3]

1. Biological half life : The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general,

drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples. [3,21,22,23]

2) Absorption: The goal of forming a SR product is to control the release rate of drug is much slower than the rate of absorption. If we presume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the extreme half-life for absorption should be in the region of 3-4 hours; otherwise, the dosage form will pass out of the probable absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. So, it accepts that the absorption of drug should occur at a relatively uniform rate over the entire length of small intestine. If a drug is absorbed by active transport or transport is restricted to a specific region of intestine, SR preparation may be disadvantageous to absorption.

3) Metabolism: Decrease bioavailability from slow releasing dosage form shown by Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slow releasing dosage form. a drug which having poor water solubility can be formulated in Sustain release dosage form. For this, various techniques which are available for enhancing the solubility of the drug after the enhancing the solubility Sustain Release formulation is possible. But during this crystallization of the drug is possible when the drug is entering into the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

4) Distribution: The rate of elimination of drug is mainly depends upon the apparent volume of distribution. So drugs with high apparent volume of distribution, influence the rate of elimination of the drug, this drugs are considered to be a poor candidate for oral SR drug delivery system. E.g. Chloroquine.

5) Protein Binding: To achieve pharmacological response unbound drug concentration is important rather than bound drug concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug which shows a main role in its therapeutic effect in spite of the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

6) Molecular size and diffusivity: In several sustained release systems Drug must diffuse through a rate controlling membranes or matrix. Ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a role of its molecular size. An important influence upon the value of the diffusivity. 'D' in polymers is the molecular size for molecular weight of the diffusing species.

7) Margin of safety: Safety of drug generally depends upon the therapeutic index, Larger the value of therapeutic index of a drug safer is the drug. Drugs having less therapeutic index are generally poor candidates for oral SR drug delivery system. [24-27]

8) Absorption window[24]: 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.

9) 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.

10) Concentration dependency on transfer of drug: Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics.

Physicochemical factor: [14]

a) Dose size: In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventional dosage form Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems Same criteria also hold for sustained release dosage form.

b) Ionization, pka and aqueous solubility: Most drugs are weak acids or bases. While the drugs which are in unchanged form permeate across lipid membranes, therefore pka of the compound and absorptive environment relationship is important Delivery systems that are dependent on diffusion or dissolution will equally be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Low soluble compounds (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug.

c) Partition Coefficient: To produce therapeutic effect in another area of body, when a drug is administered to the GI tract, it must cross a variety of biological membranes. It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds

with very low partition coefficient, it is very difficult to penetrate the membrane in case of the compound which having very low partition coefficient, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes is mainly depending on the partitioning characteristics of the drug.

d) Stability: The drugs which are orally administered subjected to both acid base hydrolysis and enzymatic degradation. For a drug in solid state degradation will continue at a reduced rate thus, this is the preferred composition of delivery for problem cases. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.[24,25,28,29].

Conclusion:

It is concluded that sustained release dosage form is one of the most productive dosage form. It helps in increasing patient compliance and also improves efficiency in treatment. Sustained release dosage form is advisable in many conditions like Drugs with shorter half life, taste masking etc. Certain criteria like molecular size, aqueous solubility must be met to incorporate the drug in sustained release dosage form. Controlled/Sustained release dosage form undergo certain mechanisms for medicament release. Some pharmacokinetic and pharmacodynamic parameter should be taken under consideration before formulating a drug into sustained release dosage from.

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