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Review Article

A REVIEW ON SUSTAINED RELEASE TABLETS

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For some time now modified drug release has been studied and used extensively during the development of pharmaceutical drug products because of its advantages over immediate release formulations. Now days as the expense and complications involved in marketing new drug entities are increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems (DDS). Hence we will change the area of focusing it is suitable to designing sustained drug delivery is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The design of oral sustained release DDS depends on various factors such as, physicochemical properties of drug, type of delivery system, disease being treated, and patient condition, and treatment duration, presence of food, gastrointestinal motility, and co-administration of other drugs.

Key Words: Immediate release (IR), Sustained release (SR), drug delivery systems (DDS), controlled release (CR), Gastro-rentative drug delivery system (GRDDS).

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.[1,2] 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 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.[3,4]

Terminology: [5,6]

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 reduces 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.[5,6]

Potential advantages and disadvantages of sustained release dosage forms

Advantages: [7,8,9]

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: [10,11,12]

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:[13]

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[14]

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 Amoxycillin 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[15]

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[16,17]

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. [18,19]

a) Desirable half-life.

b) High therapeutic index c) Small dose

d) Desirable absorption and solubility characteristics.

e) Desirable absorption window.

f) First past 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 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.

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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: [20,21,22]

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.

Factors considering for selection of drugs for the development of Modified release dosage forms: [23,24]

i. Molecular size and diffusivity: Diffusion may be defined as a mass transfer of individual molecules of a drug substance and mainly by random molecular motion associated with concentration gradient**.** During time course of the drug it must diffuse through various biological membranes in the body. The drugs in the form of modified release dosage form must diffuse through a matrix or polymeric membrane. The ability of drug diffuse through polymers is called as diffusivity and is a function of its molecular weight or molecular size. The drugs or polymers which are having high molecular weight show very slow release kinetics in sustained release device by diffusion through polymeric membrane

ii. PKa- Ionization constant: Ionization constant is one of the important properties used to measure the strength of an acid or base and determine the charge on the drug molecule at any given pH. The ionized forms of drugs are poor candidates for sustained or controlled dosage form at the absorption site. The drug molecules are active only at unionized state and cross rapidly through lipoidal membranes than ionized molecules.

iii. Partition coefficient: The partition coefficient is used to measure of how hydrophilic or hydrophobic a drug substance is or it's a measure of Hydrophilicity-Lipophilicity balance. Partition coefficient influences both permeation of drug across the biological membrane and diffusion across the rate controlling membrane or matrix. The drugs with high partition coefficient are very oil soluble and will partition rapidly into various membranes in the body and show greater activity.

iv. Drug Stability: The drug stability is most important parameter in the dosage form design. When the drug administered orally, it losses through hydrolysis or degradation in the GIT. So it is necessary to improve the relative bioavailability of drug that is unstable in gastric region and such drugs should suitable for delayed release dosage form in order to release the drug in the intestine. The drugs which are having stability problems in the gastric region are less suitable for modified release dosage form and design the drug to deliver uniformly throughout the gastric region.

v. Aqueous solubility: Solubility may define as the maximum amount of drug substance that goes into the solution form in a specific amount of solvent. The solubility of drug substance mainly depends on concentration, pressure and

solvent used. High solubility may define as highest dose strength is soluble in 250mL or less of aqueous media over the pH range of 1-7.5.The drugs with aqueous solubility influences drug dissolution rate and it establishes the concentration in solution. The dissolution rate is related to aqueous solubility and explained by Noyes-Whitney equation. The drug with high solubility and a rapid dissolution rate is difficult to control or decrease the dissolution rate and slow its absorption. The drug with low solubility difficult to sequester a highly soluble dosage form and retard the drug release in case of high drug dose. The drug with very low solubility and slow dissolution rate will exhibit very limited absorption and not provide a considerably much benefits than immediate release dosage forms.[25]

Selection of Polymers: Development of modified release dosage forms for highly soluble drugs is becomes challenge to the formulation scientist. These drugs will release the drug readily at a faster rate and produces untoward effects on oral administration. So, considerable attention was needed for the selection of polymers to retard the drug release for highly soluble drugs. Based on flexibility, desirable drug release and cost effective, hydrophilic polymers are most suitable to retard the drug release and various water swellable or water soluble with high molecular weight polymers were used in hydrophilic matrices such as Hydroxy propyl methyl cellulose and Polyethylene oxide. HPMC is most commonly used polymer in matrix formulations because of their features like pH independent performance, excellent stability, suitable for direct compression and granulation techniques. Polyethylene oxide also commonly used polymer in matrix formulations because of their versatile application for direct compression, granulation technique, fast hydration and gel formation.[26]

Methods to achieve oral sustained drug delivery[27,28]

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 nonreactive 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[29,30]

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 invivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

1. In – Vitro Methods

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[31]

The requirement of establishing good in-vitro invivo 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.

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[32]

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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