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A Review on Sustain Release Drug Delivery System

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ABSTRACT

For each disease condition or the disordered state of the patient, appropriate treatment is very important to maintain the good health of the patient. The oral drug delivery system is the preferred way for the administration of drugs. Many technical advancements have been done resulting in the development of new techniques for drug delivery sustaining the duration of therapeutic activity and/or targeting the delivery of a drug to tissue. Sustained-release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of a drug. Considering many advantages of the sustained release dosage form, it has been found as a preferred dosage formulation for oral administration of drugs. There are different mechanism and methods of formulating sustain release formulation which may differ as per dissolution, half-life, absorption rate, partition coefficient, dose size, etc. sustained release matrix tablets are popular due to their ease in preparation, scale-up, and versatility.

INTRODUCTION

For each disease condition or the disordered state of the patient, appropriate treatment is very important to maintain the good health of the patient. For the same, the drug is administered conventionally by one or more of several well defined and popular routes of drug administration which include but not limited to oral, parenteral, rectal, alveolar, ocular and topical etc.[01,20]

Nowadays, oral drug delivery system is the preferred way for the administration of drugs because of easy administration, better patient compliance, and flexible design of the dosage forms. In the oral drug release process, first of all, the drug releases from the drug product and subjected to drug absorption, distribution, metabolism, excretion and also shows the pharmacological action. Moreover, as per the current scenario, conventional dosage forms of drugs are being replaced by the novel drug delivery systems. Drugs with matrix system structure are the dosage system which is used to prolong the drug effect and also controls the drug release which is being dissolved or dispersed.[02]

Before 1950, most of the drugs were formulated in pills or capsules formulation and that released the loaded drug immediately upon contact with water without any ability to control the drug release kinetics. In 1952, Smith Klein Beecham introduced the first sustained release formulation that was able to control the drug release kinetics and achieve 12-hour efficacy.[03]

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on the development of sustained or controlled-release drug delivery systems.[04,07]

Oral route of drug delivery system is considered to be convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.[04,05,06,09,10]

In recent aura, many technical advancements have been done resulting in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of the drug to a tissue i.e. targeted drug delivery system. These advancements have led to the development of several "Novel Drug Delivery System".[08] There are several terms used interchangeably viz. controlled release, programmed release, sustained release, prolonged

release, timed release, extended-release, etc. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance.[11-19]

The goal in designing sustained or controlled drug delivery systems 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, providing uniform drug delivery. There are many types of modified drug delivery systems. The sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems sustain the release of drug and maintain the plasma drug concentration in the therapeutic window except any fluctuation and increase the therapeutic efficacy of drug.[09]

Sustained-release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug.[10]

In conventional dosage forms, there is a need to take 3-4 times dosage in a day whereas sustained-release tablets are generally taken once or twice a day during a course of treatment to achieve the same therapeutic action.[10] The key role behind administering a single dose of a drug in sustained release dosage forms is that it can be released over an extended period to maintain the uniform concentration of a drug in the blood which may lead to better patient compliance and provide the enhanced clinical output of the drug.

The rationale for the development of SRDDS (Sustained Release Oral Drug Delivery System):

1. Formulations of SRDDS minimize dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve the clinical efficiency of a drug molecule.

2. To reduce the cost of treatment by reducing the number of dosage requirements.

3. To minimize toxicity due to overdose which is often conventional dosage form.

4. To enhance the activity duration of a drug possessing short half-life.

Terminologies Related to SRDDS:

1. Delayed-release

Delayed-release systems use repetitive, intermittent dosing of a drug. These systems are composed of one or more immediate releasing units in a single dosage form. The delayed-release may be based on time or due to the influence of environmental conditions, like gastrointestinal pH.[21]

Extended-release

a. Sustained release

Sustained release is defined as any drug or dosage form modification that prolongs the therapeutic activity of the drug.[13]

b. Controlled release

The drug delivery system has been designed to deliver the medication at a predetermined rate over an extended period. This system follows zero-order release (independent upon initial concentration of drug) whereas SRDDS follows first-order release.[21]

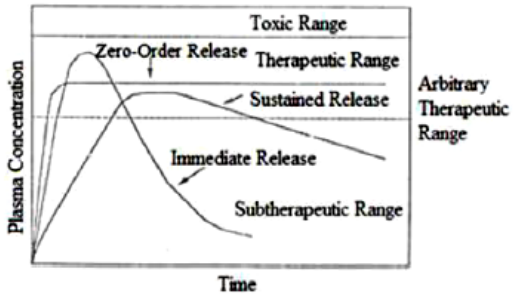

Figure No. 1: Arbitrary therapeutic range of different dosage form in blood[13]

Principle of Sustained Release Drug Delivery

The conventional dosage forms release their active ingredients immediately into an absorption pool or at the site of absorption. This is illustrated in the following simple kinetic scheme in the figure:

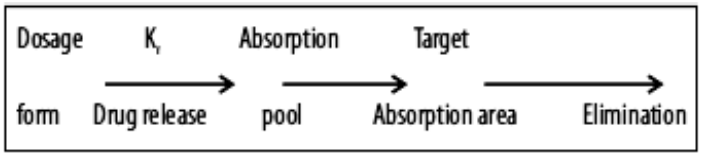

Figure No. 2: Schematic representation of the kinetics of the sustained release drug delivery system

The absorption pool represents a solution of the drug at the site of absorption. Kr, Ka, and Keare the first-order rate constant for the drug release, drug absorption, and overall drug elimination respectively. Immediate drug release from a conventional dosage form implies that K>>>>K. However, for non-immediate release dosage forms, K r<< K i.e. the release of drug from the dosage form is the rate-limiting step. The drug release from the dosage form should follow zero-order kinetics, as shown by the following equation:

K = Rate In = Rate Out = Ke Cd Vd Where, Kr°: Zero-order rate constant for drug release-Amount/time,

Ke: First-order rate constant for overall drug elimination-time,

Cd: Desired drug level in the d body – Amount/volume, and

Vd: Volume space in which the drug is distributed in the litre

Advantages of Sustain-Release Matrix Drug Delivery System

1. Reduction of frequency of drug administration.

2. Compliance with the patient can be improved.

3. More convenient drug administration.

4. Reduction of multiple dosing of conventional dosage forms due to the blood level oscillation characteristic.

5. Controlled drug absorption can be attained. High blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.

6. Reduction of blood concentration variations due to multiple dosing of conventional dosage forms.

7. Reduction of the total amount of drug administered, thus: Maximizing availability with a minimum dose. Minimize or eliminate local side effects. Minimize or eliminate systemic side effects. Minimize drug accumulation with chronic dosing.

8. Safety margins of high potency drugs can be increased.

9. The incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

10. The drug can be more economic than conventional drugs.

Disadvantages of Sustain-Release Matrix Drug Delivery System

1. Dose dumping probability.

2. Reduction of potential for dose adjustment.

3. Cost of single unit higher than conventional dosage forms.

4. Increase the potential for first-pass metabolism.

5. Need to provide additional patient education for proper medication.

6. Probability of decreased systemic availability in comparison to the immediate release of conventional dosage forms.

7. Difficult to have an *in-vitro* and *in-vivo* correlation.

Criteria of a drug to be met to formulate sustained release dosage forms:

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 the amount of residence time of the drug in the body. If the drug has a short half-life (less than 2 hours), than the dosage form may contain a prohibitively of the large quantity of the drug required for the treatment. Ideally, the drug should have a half-life of three to four hours. On the other hand, a drug with an elimination half-life of eight hours or more is sufficiently sustained in the body, when administered in conventional dosage form, and sustained release drug delivery system is generally not necessary in such cases.

(b) High therapeutic index:

Drugs with low therapeutic index are not suitable for formulating in the sustained release dosage formulation. If the system fails in the body, dose dumping may occur, leading to fatalities e.g. 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 challenged. 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 the gastrointestinal tract. This part is referred to as the 'absorption window'. E.g. fluorouracil, thiazide diuretics, if formulated as sustained release dosage forms are unsuitable.

(f) First pass clearance:

Delivery of the drug to the body in the required concentrations is difficult to achieve in case of drugs undergoing extensive hepatic first-pass metabolism when administered in sustained release forms.[22]

MECHANISM OF DRUG RELEASE FROM MATRIX DEVICES

(1) Dissolution controlled release sustained-release oral products employing dissolution as the time-limiting step are the simplest to prepare. For example, if a drug has a rapid rate of dissolution than it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. In the dissolution process, if the dissolution process is diffusion layer control, the rate of diffusion of the drug from the solid surface to the bulk solution through an unstirred liquid film is the rate-limiting step. In this case, the dissolution process at steady state would be described by Noyes-Whitney equation,

$$dc/dt = KDA (Cs-C) \text{ ---------- } (1)$$

Where,

dc/dt = Dissolution rate.

KD = Dissolution rate constant.

Cs = Saturation solubility of the drug.

C = The concentration of drugs in the bulk of the solution.

Dissolution control formulations are categories as

- Encapsulation dissolution control
- Matrix dissolution control

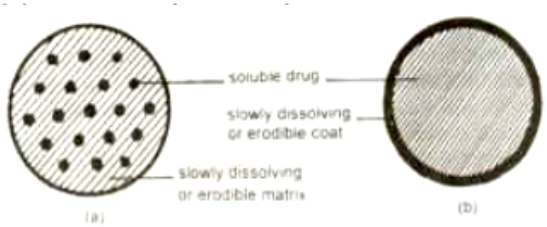

Figure No. 3: Schematic representation of dissolution controlled release systems

a. Encapsulation dissolution control

The encapsulation dissolution control method involves the coating of the individual particles or granules of the drug along with slowly dissolving material. The coated particles can be compressed directly into a tablet or placed in a capsule.

b. Matrix dissolution control

The matrix dissolution control method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This, in turn, can be controlled by the porosity of the tablet matrix, the presence of hydrophilic, and the wettability of the tablet and particle surface.

(2) Diffusion controlled release

Diffusion controlled release system are of two types:

a. Encapsulation diffusion control

In the encapsulation diffusion control system, water-insoluble polymeric material encloses the core of the drug. The drug will partition into the polymer membrane and exchange it with the fluid surrounding the particle or tablet.

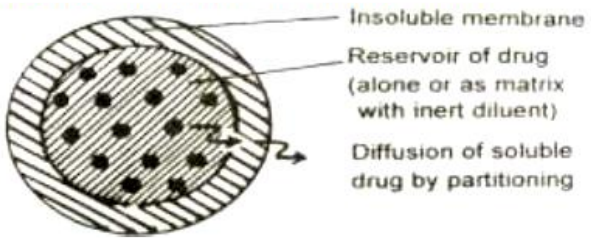

Figure No. 4: Drug release of diffusion across the insoluble membrane of the reservoir device

The rate of drug release is given by the equation.

$$dm/dt = AdK\Delta c \text{---------- (2)}$$

Where,

A = Area

D = Diffusion coefficient

K = The partition coefficient of the drug between the membrane and the drug core

I = The diffusional path length

Δc = The concentration difference across the membrane.

An important parameter in the above eq. (2) is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration of the drug in the core.

b. Matrix diffusion control

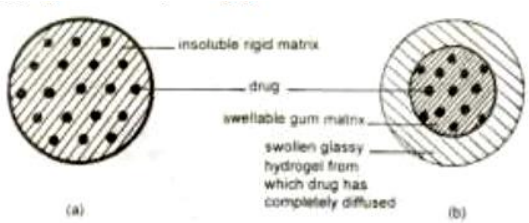

Figure No. 5: Diffusion controlled devices

In matrix diffusion control system, a solid drug is dispersed in lipophilic or a hydrophilic polymer matrix and the rate of release of a drug depends on the rate of drug diffusion and not on the rate of solid dissolution.[23]

CLASSIFICATION OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM[16-29]

According to the mode of drug release, this system has been classified as follows:

A. Continuous Release system

a) Diffusion sustained system

- Reservoir type
- Matrix type

b) Dissolution sustained system

- Reservoir type
- Matrix type

c) Methods using Ion-exchange

d) Methods using osmotic pressure

e) pH-independent formulations

B. Delayed Transit and Continuous Release System: These type systems are designed to prolong their residence in the GIT along with their delayed and continuous drug release.

C. Delayed-Release System: The design of such systems involves the release of a drug only at a specific location in the GIT. The drug contained in such a system is those that are destroyed in the stomach or by intestinal enzymes. These systems are known to cause gastric distress. These systems are absorbed from a specific location in the intestinal site.

METHODS OF PREPARATION[16-29]

1. Direct Compression

In the direct compression process, powdered materials are compressed directly without changing the physical and chemical properties of the drug.

2. Wet Granulation

In the wet granulation method, the weighed quantities of drug and polymer are mixed with a sufficient volume of the granulating agent. After enough cohesiveness has been obtained, screening of wet mass will be done. The granules need to be dried and screening of dry granules, then blending with lubricant and disintegrate to produce “running powder” tablets which will be compressed using a single-punch tablet compression machine.

3. Melt Granulation

In the melt granulation process, the use of a substance, which melts at relatively low temperatures. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binders were tried by using the melt granulation technique.

4. Hot-Melt Extrusion Process

In the hot-melt extrusion process, a mixture of the active ingredients, the thermoplastic polymers, and other processing aids are fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw. The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.[16-29]

FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGN[16-29]

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

A. Biological Factors

B. Physicochemical Factors

A. Biological Factors

1. Biological half-life

The purpose of formulating an oral sustain release product is to maintain therapeutic blood levels over an extended or longer period. To achieve the same, the drug must enter the blood circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$).

Each drug has its characteristic of the elimination rate. Elimination rate is the sum of all elimination processes, including metabolism, urinary excretion, and all over processes that permanently remove the drug from the bloodstream. Therapeutic compounds with a short half-life are generally excellent molecules for sustain release formulation. The reason for the

same is that it can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for sustain release preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form since their effect is already sustained e.g. Digoxin and Phenytoin.

2. Absorption

Since the purpose of forming a sustain release product is to place the control on the drug delivery system, the rate of release must be much slower than the rate of absorption. If it has been assumed that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the formulation will pass out of the potential absorptive regions before drug release completed. Thus, corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h^{-1} to give an 80-95% overtime period. Hence, it has been assumed that the absorption of the drug should occur at a relatively uniform rate over the entire length of the small intestine. For many compounds, absorption of the drug at a relatively uniform rate over the entire length of the small intestine is occurrence is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, sustain release preparation may be disadvantageous to the absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows the slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate a low-density pellet or capsule. Another approach is that of bio-adhesive materials.

3. Metabolism

Those drugs which are significantly metabolized before absorption, either in the lumen of the tissue of the intestine, can show decreased bioavailability from the slower-releasing dosage form. Even a drug that is poorly water-soluble can be formulated in sustain release dosage form. For the same, the solubility of the drug should be increased by a suitable system, and later on, that is formulated in the sustained release dosage form. But during this, the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

B. Physicochemical Factors

1. Partition Coefficient

When a drug enters the GI tract, it must cross a variety of biological membranes or barriers to producing a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic having high partition coefficient are poorly aqueous soluble and retain in the lipophilic tissue for a longer time. In the case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

2. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0gm is considered maximal for a conventional dosage form. This also holds for the sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems.

Another consideration is the margin of safety involved in the administration of a large amount of a drug with a narrow therapeutic range.

3. Stability

Oral administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. The degradation will proceed at a lower rate for drugs in solid-state; hence, this is the preferred composition of delivery for problem cases. For the dosage form that is unstable in the stomach, systems that prolong delivery over the 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 that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because

more amount of drug is delivered in the small intestine and, hence, is subject to degradation e.g. propantheline and propantheline.

4. Ionization, pka and aqueous solubility

Almost all drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to an unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach is acidic and the small intestine more neutral, the effect of pH on the release process must be defined. Compounds with very low solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.[16-29]

CONCLUSION

Despite all advancements made within the field of oral drug delivery, sustained release matrix tablets are popular due to their ease in preparation, scale-up, and versatility. Many new systems are still emerging. But the marketability and feasibility of each new formulation have to be assessed carefully before launching a new product.

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