A REVIEW ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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Abstract: The most popular method for administering different medications is oral drug delivery, out of all drug delivery systems. By maximizing the drug's pharmacokinetic and pharmacodynamic qualities, sustained release solutions offer advantages over traditional dosing forms. By keeping the drug's therapeutic concentration in the body from fluctuating, the sustained release formulation offers a crucial means of reducing adverse effects. Extended release, targeted release, delayed release, and prolonged action dosage forms are offered for these formulations. The formulation design for sustained release is influenced by various aspects such as molecular size, diffusivity, pKa-ionization constant, release rate, stability, dosage, duration of action, absorption window, therapeutic index, protein binding, and metabolism. This article discusses many kinds, assessments, and elements that influence sustained release formulation design.

Keywords: Sustained Release, controlled release system, Factors of Sustained Release Dosage Form.

INTRODUCTION

Because oral drug delivery offers the greatest active surface area of any drug delivery system for the administration of different medications, it is the most convenient and favored alternative. Its benefits include unit dosage form, low cost, and least expensive packaging. One of the most reliable and often used oral dose forms is the tablet. Tablets continue to be a widely used dosage form due to the benefits they provide to patients as well as pharmaceutical makers. Reducing the frequency of dosing or increasing the drug's effectiveness by localizing the medication at the site of action, lowering the dosage needed, and ensuring consistent drug delivery are the main objectives of building sustained or controlled delivery systems. One kind of customized drug delivery system that can be employed in place of a traditional drug delivery system is the sustained release system. These systems prolong the drug's release, keep its plasma concentration within the therapeutic window barring fluctuations, and boost the medication's therapeutic efficacy. They demonstrate their efficacy by eschewing dosage peaks and troughs and exhibiting a steady plasma drug concentration during the therapeutic window. Benefits of a sustained release system include improved plasma drug concentration, avoidance of numerous doses, patient compliance, avoidance of side effects, and resolution of issues with traditional systems. Oral administration is thought to be the most extensively used method due to its easy production, compact size, and ease of self-administration (Sastry et al., 2000; Seager et al., 1998). Still, it's likely that at least 90% of all medications used to manufacture the oral route is used to administer systemic effects (Fig 1).
In recent years, in correlation with advancement and creativity in pharmaceutical technology, there has been a growing endeavor to create sustained release dose variations for numerous medications. The main goal of this system is to guarantee security and enhance medication effectiveness in addition to patient adherence. This is accomplished by improving plasma medication control, levels and less doses administered. According to pharmacokinetic theory, having zero-order absorption is the most effective way to lower the ratio of plasma maximum concentration (Cmax) to plasma minimum concentration (Cmin). As long as absorption continues, the drug concentration in plasma remains constant once steady state is reached in these circumstances. An extended-release formulation's successful commercialization is typically difficult and requires careful consideration of a few elements, including the drug's physiochemical qualities, physiological considerations, and production variables.

Terminology

Four useful categories can be used to group modified release distribution systems.

A) Delayed Release:

These techniques include administering a medication infrequently and repeatedly from one or more combined into a single dose form are units of instant release. Instances of postponed releases Enteric-coated tablets with timed release and repeat action pills and capsules are examples of such systems. is accomplished using a barrier layer.

B) Sustained release:

furthermore, utilized in veterinary goods These devices can also deliver a prolonged, gradual release of the medication. give some control over the release of drugs, either in terms of timing, space, or both. The body, or the system, is effective at preserving steady drug levels in the intended tissue or cells.

i) Controlled Release: These systems encompass any medication delivery method that accomplishes a gradual release of the drug over a prolonged duration.

ii) Extended Release: Medication dosage forms that must double the frequency of doses by releasing the substance at a predetermined rate and slower than usual.
C) Site specific targeting:

These systems discuss administering a medication directly to a certain biological site. The target in this instance is inside the sick tissue or organ, not next to it.

D) Receptor targeting:

These systems discuss administering a medication directly to a certain biological site. Here, the specific drug receptor found in a certain organ or tissue is known as the target. Systems for site-specific targeting and receptor targeting are regarded as sustained drug delivery systems since they fulfill the spatial requirement of drug delivery.

Principle of Sustained Release Drug Delivery System

The active chemicals in conventional dose forms are released instantaneously into an absorption pool. The basic kinetic scheme that follows serves as an illustration of this. The drug's solution at the absorption site is represented by the absorption pool, which also contains the first order rate constants for drug release, absorption, and total elimination, respectively, Kr, Ka, and Ke. When a drug is released from a typical dose form immediately, it is implied that Ka>>>Kr. The rate-limiting phase for non-immediate release dosage forms is the drug's release from the dosage form, or Kr\Ka. The following equation illustrates zero-order kinetics for the drug release from the dose form:

\[ Kr^0 = Ke.Cd.Vd = \text{Rate In} = \text{Rate Out} \]

Where,

Kr^0: Zero-order medication release rate constant: quantity/time
Ke: The first-order rate constant for the total drug elimination period;
Cd: The amount/volume of the desired drug level in the body
Vd: Volume area where the medication is dispersed in the form of litter

Objectives of oral sustained released dosage form

• To keep the drug's concentration at steady state for the intended amount of time.
• To lower the dosage frequency administered in contrast to traditional dose format.
• It ought to send an active entity straight to the location of action, reducing or getting rid of side consequences body parts.
• Strong medications can have a safety margin of grew.
• Prevalence of detrimental local and systemic effects adverse effects in patients who are susceptible can be minimized

Advantage of Sustained Release Drug Delivery System

1. The frequency of doses can be decreased.
2. It might make the medication more stable.
3. It lessens discomfort to the gastrointestinal tract.
4. It can lessen variations in medication release between blood concentrations.
5. Local and systemic side effects may be reduced by sustained-release tablets.
6. Simple to produce.
7. May be produced in a variety of forms and sizes.
8. In the event of a rupture, there is no risk of dose dumping.
9. It is reasonably priced.
10. Fit for systems that are both degradable and non-degradable.
Disadvantage of Sustained Release Drug Delivery System

1. Counseling and tolerance will grow more quickly.
2. The requirement for more patient counseling and education
3. In some cases, it results in poor correlation between in vitro and in vivo.
4. Another drawback of it is low system availability.
5. The need for further patient education in order to administer medication correctly.
6. Single unit costs are more than those of traditional dosage forms.
7. It is challenging to achieve zero order release.
8. Boost the first pass metabolism's potential.
9. Reduced systemic availability as compared to standard dose forms with quick release.
10. The likelihood of dosage dumping.

Drug selection for Sustained Release Drug Delivery System

Table 1 Parameters for drug selection parameter preferred value

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight/size</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>Solubility</td>
<td>&gt;0.1 mg/ml ph 7.8</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>High</td>
</tr>
<tr>
<td>General absorbability</td>
<td>From all GI segments</td>
</tr>
<tr>
<td>Release</td>
<td>Should not be influenced by ph and enzyme</td>
</tr>
</tbody>
</table>

Drugs must be evaluated biopharmaceutically for possible use in controlled release drug delivery systems. This involves understanding the drug's molecular weight, general absorbability, solubility at various pH levels, and apparent partition coefficient. It also requires knowledge of the drug's absorption mechanism from the gastrointestinal tract.

Table 2 Pharmacokinetic parameters for drug selection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half life</td>
<td>Preferably between 0.5 to 8h</td>
</tr>
<tr>
<td>Total clearance</td>
<td>Should not be dose dependent</td>
</tr>
<tr>
<td>Elimination rat constant</td>
<td>Required for design</td>
</tr>
<tr>
<td>Apparent volume of distribution Vd</td>
<td>The larger Vd and MEC, the larger will be required dose size</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>Should be 75% or more</td>
</tr>
<tr>
<td>Intrinsic absorption rate</td>
<td>Must be greater than release rate</td>
</tr>
<tr>
<td>Therapeutic concentration C_{ss}</td>
<td>The lower C_{ss}, av and smaller Vd loss among of drug required</td>
</tr>
<tr>
<td>Toxic concentration</td>
<td>Apart the value of MTC and MEC, safer the dosage form. Also suitable for drug with very short half-life.</td>
</tr>
</tbody>
</table>
Classification of oral sustained/controlled release systems

1. Diffusion controlled Systems
   (A) Reservoir devices:
   They are distinguished by a polymeric membrane encircling a drug core (reservoir). The rate at which drugs release is determined by the composition of the membrane. The traits of diffusion systems in reservoirs are twelve.
   - Drug release with zero order is feasible.
   - The kind of polymer determines the release rate.
   - Delivering high molecular weight molecules through the device is challenging.

   (B) Matrix devices:
   It is made up of medication evenly distributed within a matrix. The matrix's properties Diffusion systems are
   - It is not possible to achieve a zero order release.
   - Producing reservoir devices is more difficult.
   - Through the gadget, high molecular weight molecules are supplied.

2. Dissolution controlled systems
   (a) Systems with matrix dissolution control:
   These include spherical agglomeration, congealing, and aqueous dispersions.
   (b) Encapsulation dissolution-controlled systems:
   Methods like microencapsulation can be used to coat particles, seeds, and granules.

3. Diffusion and dissolution-controlled systems:
   The medicine is uniformly distributed throughout a bioerodible matrix and is released through an enzymatic assault, hydrolysis, or swelling-controlled process.

Factor Controlling the Design of Sustained Release Dosage Form

A. Physicochemical Factors
   Molecular Size and Diffusivity:
   Throughout its journey through the body, a medication needs to permeate through a number of biological membranes. Drugs in many extended-release systems have to permeate across a polymeric membrane or matrix in addition to these biological membranes. Diffusion coefficient D, which measures a drug's diffusivity in polymers, is dependent on the drug's molecular weight.

   pKa – ionisation constant:
   A measure of an acid's or base's strength is the pKa. The drug molecule's charge at any particular pH can be ascertained thanks to the pKa. Only the undissociated and unionized states of the drug molecule are active. Compared to ionized species, a unionized molecule traverses these lipoidal membranes far more quickly. The medication's dissociation constant and the fluid's pH at the absorption site determine how much of the drug is present in unionized form. A medicine needs to be in unionized form at the absorption site in order for it to be absorbed. Pharmaceuticals that are ionized at the site of absorption are not good candidates for controlled or sustained release dosage forms.

B. Biological Factors
   Duration of Action:
   The length of time that the blood level stays over MEC and, more precisely, within the therapeutic window, below MSC levels, is known as the duration of action. Long-acting drugs are not good candidates for formulation into SR or CR formulations. Certain parameters, including as receptor occupation, tissue binding,
half-life, metabolism, partition coefficient, and irreversible cell binding, are accountable for the prolonged effects of medications.

Absorption Window:

Certain medications exhibit region-specific absorption, which is associated with varying drug solubility and stability in various GIT areas due to pH variations in the surrounding environment, enzyme degradation, etc. These medications identify the absorption window, or the part of the gastrointestinal tract where absorption happens most frequently. After the absorption window, drugs released from sustained or controlled release systems are wasted with minimal absorption. Therefore, the absorption window is crucial to the creation of medications with controlled or sustained release.

Therapeutic Index:

It is most frequently used to calculate a drug's margin of safety. TI equals TD50 divided by ED50.
It is not a good idea to formulate drugs with very low therapeutic index values into sustained release products. If a drug's T.I. value is more than 10, it is deemed safe; the higher the TI value, the safer the medicine.

Metabolism:

Medication that undergoes substantial pre-absorption metabolism in the intestinal lumen or tissue may exhibit reduced bioavailability. Most enzyme systems in the gut wall are saturable. Since the medication is introduced into these areas more gradually, less of the total drug is exposed to the enzymatic activity at any given time, allowing for a more thorough conversion of the drug into its metabolite.

Protein Binding:

Certain medications, like albumin, have a propensity to bind with plasma proteins, which can lead to drug retention in the vascular region. Electrostatic, hydrogen bonding, and Vander wall forces are the primary forces of attraction that cause binding. Because of the electrostatic effect, charged compounds often have a stronger ability to bind a protein than uncharged compounds.

Absorption:

When thinking about the formulation of a medication for a controlled-release system, the pace, extent, and homogeneity of the drug are crucial considerations. Since the release of a drug from a dosage form is the rate-limiting stage in drug delivery from a controlled release system, the system's success depends more on the drug's absorption than on its release. Pharmaceuticals that are absorbed through specific gastrointestinal tract sites (absorption window) and by a particular transport pathway (carrier mediated) are not good candidates for continuous release.

Evaluation of Sustained Release Dosage Form

These dose forms are evaluated in two different methods.

1) Evaluation of granules
2) Evaluation of tablets

Future Prospective

Sustained-release products have a bright future, particularly in the following domains where they show great potential and acceptability:
Particulate systems:

For the delivery of peptide medications, which are typically not administered orally, the microparticle and nanoparticle approach which uses biodegradable polymers—that delivers intact drug-loaded particles via Peyer's patches in the small intestine may prove beneficial.

Chronopharmacokinetic systems:

Pulsatile release regimens combined with oral continuous drug delivery could be an effective way to administer medications where they are needed to fight naturally occurring processes like parasite and bacterial development patterns.

Targeted drug delivery:

Certain disease states may be effectively treated with oral controlled drug delivery, which targets specific GI tract regions and releases medications only upon reaching that place (e.g. colon-targeted delivery of Antineoplastics in the treatment of colon cancer).

Mucoadhesive delivery:

This is a promising method of delivering drugs sublingually and buccally, as it avoids the liver's first-pass processing, which can result in a faster start of action and better bioavailability than simple oral delivery.

CONCLUSION

From the foregoing explanation, it is clear that prolonged release formulations aid to improve patient compatibility and boost dosage efficiency. Creation of an oral sustained release dosage form that will relieve patient discomfort and extend medication release, hence reducing plasma peak. Sustained release tablets/capsules have the advantage of maintaining a constant medication level in plasma and allowing for less frequent use than their regular form. It is possible to extend the drug delivery system's residence period in the GIT by a number of methods. Zero order release, or the drug's gradual release over time regardless of concentration, is different from other controlled releases. However, medication release is prolonged in sustained release dose forms. These days, the oral mode of administration for sustained release drug delivery systems has drawn more interest since it offers more patient compliance, flexibility, and fewer dose frequency. The physicochemical characteristics of the drug, the kind of delivery system, the disease being treated, the patient's condition, the length of the treatment, the presence of food, gastrointestinal motility, and the co-administration of other medications are some of the elements that influence the design of an oral sustained release drug delivery system. From the explanation above, we can also draw the conclusion that oral sustained release drug delivery systems are easier to replace than oral conventional drug delivery systems due to their affordable price.

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