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Sustained Release Drug Delivery System: A Comprehensive Review

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Abstract:
Due to their inherent benefits, pharmaceutical companies are currently focusing on the development of sustained release formulations. Sustained release dosage forms are made to release a drug at a set rate while keeping the drug level constant for a set amount of time with the fewest side effects possible. A sustained-release drug delivery system's fundamental premise is to maximise a drug's biopharmaceutical, pharmacokinetic, and pharmacodynamic properties while minimising its side effects and working toward a cure for the disease. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of a potent drug, reduction in healthcare costs through improved therapy and shorter treatment period.

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I. INTRODUCTION

In a sustained release formulation, the active pharmaceutical component has a rapid ascent and long-lasting maintenance of a therapeutic blood level. Because the qualities of polymers impact drug release, which is reliant on polymer properties, the application of polymer properties can result in well-characterized formulations. Because the release from a formulation for controlled release is independent of the amount of medicine in the formulation, it differs from sustained release. Sustained release medications take longer to start working gently.[1]

Merits of sustained and controlled release dosage forms

- A decrease in dosage frequency as a result of prolonged medication release. This is incredibly helpful for treating chronic illnesses that call for a therapeutic plasma concentration of the medication.[2]
- Because of high plasma concentrations or dosage dumping, side effects are reduced or eliminated.
- The patient finds this dose form convenient since he is not frequently disturbed, even when sleeping, which leads to improved patient compliance.
- Economical production since fewer pills are needed for each patient. Sustained and controlled release formulations have various drawbacks, much as all other dosage forms.
- The production cost is high because some formulations for prolonged and controlled release need specialised equipment and inert components.
- Crushing or chewing is not possible as it might lead to two important issues include loss of 'slow release' characteristics and toxicity.[3]

MATRIX TABLETS IN SUSTAINED DRUG DELIVERY

Incorporating the medication into a matrix system is the most often used method to deliver the prolonged release. In a homogenous matrix formulation, the drug and the polymer have been extensively combined, and the release diffusion is carried out either via the pores or the polymer chains. Due to its cost-effectiveness, favourable drug release profile, and patient compliance over traditional medication administration, matrix formulations are favoured.[4]

They may be classified as monolithic matrix systems, reservoir matrix systems, and osmotic pump systems based on how long the medication is released after they are taken.

1. Reservoir matrix systems

In this system the drug release is controlled by a membrane. Diffusion of the drug eventually occurs all the way through the polymeric membrane.

2. Osmotic pump formulations

These formulas rely on osmotic force to function. A semi-permeable membrane with a hole encloses the core tablet of an osmotic tablet, which is made up of two layers called the active layer and push layer. The push layer houses the osmotic agent, whereas the active layer houses the drug particle. The medication is dissolved and suspended when water enters via the semi-permeable membrane. The osmotic agents are also dissolved, which increases the osmotic pressure and pumps the drug out through the delivery orifice. The two factors that can change the rate of drug delivery are the size of the delivery aperture and the thickness of the semipermeable membrane.[5]

3. Monolithic matrix formulations

These formulations integrate or encapsulate the medication. Diffusion matrix systems are divided into three categories based on the kind of retarding agent and polymeric material: hydrophilic matrix systems, hydrophobic matrix systems, and fat wax matrix systems.

Hydrophilic matrix system

Hydrophilic matrix technologies are widely employed in controlled drug delivery due to their repeatability and affordable price tag for drugs with desirable pharmacological profiles. Drugs are released from several sources, not just one front.

Method Using A Fat Wax

For integrating the medication into the matrix, three different techniques were used: spray drying, spray congealing, and mix congealing.

Water-Repellent System

Drugs with high solubility are typically included in hydrophobic matrix systems, which are mostly made of waxes. Although the hydrophobic matrix systems are effective at controlling the release of the medication, the technology is not cost-effective for producing sustained release formulations since it requires particular heat treatments.[6]

Drug release Kinetics

The diffusion and erosion of the outer hydration of the polymer on the matrix surface determines how quickly the active medicinal component is released from formulations with hydrophilic matrixes. If the medicine is extremely soluble, there will occasionally be an initial burst. The gel layer thickens as more water enters, acting as a barrier to diffusion, but as the outer layer becomes more hydrated, erosion takes place. Gel strength, interactions between polymers and solvents, and erosion are significantly influenced by these factors. Swellable matrices release kinetics depend on the gel layer's thickness.

FACTORS AFFECTING FORMULATION OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Molecular Size and Diffusivity:

Various biological membranes must allow a medicine to diffuse across them as it moves through the body. Drugs in many extended release systems must diffuse through a polymeric membrane or matrix in addition to these biological membranes. The term "diffusivity" (also known as the "diffusion coefficient D") refers to a drug's capacity to diffuse in a polymer and is a function of the molecular weight of the medication.

Biological Half-Life

An oral sustained-release product's primary objective is to sustain therapeutic blood levels over an extended period of time. The half-life quantitatively describes the elimination rate. Each medication has a unique characteristic elimination rate, which is the total of all processes that permanently remove the drug from the circulation, including metabolism, urine excretion, and all other processes.

Short half-lives of therapeutic compounds make them ideal candidates for sustained release formulations, which can lower dose frequency. This is constrained, though, because medications with extremely short half-lives may need excessively high doses of the medication in each dosage unit to ensure sustained efficacy, leading the dosage form to grow to an unacceptably large size. Drugs having half-lives less than two hours are generally not good candidates for sustained-release formulations. Since their effects are already maintained, compounds having half-lives longer than 8 hours are likewise often not employed in sustaining forms.[7]

Therapeutic Index:

It is most frequently used to calculate a drug's safety margin. TD50 / ED50 = TI Drugs with very low therapeutic index values make poor candidates for formulation into products with prolonged release. If a drug's T.I value is larger than 10, it is considered to be safe; the higher the value of TI, the safer the medicine.[8]

Metabolism:

Drugs with considerable pre-absorption metabolization in the intestine's tissue or lumen may have lower bioavailability. The majority of gut wall enzymes are saturable. Due to the slower rate of drug release in these areas, less total drug is exposed to enzymatic processes over the course of a given time, allowing for a more thorough conversion of the drug to its metabolite.

Plasma concentration response relationship

In most cases, plasma drug concentration rather than dosage is more important for pharmacological action. However, medications with pharmacological action unrelated to plasma concentrations are poor candidates for oral SR drug delivery systems. [9]

Dependence on drug transfer for concentration

Such medications are poor candidates for oral SR delivery systems if the drug is transferred from one compartment to another according to a zero order kinetic mechanism. It ought to be kinetically first order.

Aqueous Solubility

The majority of medications are weak bases or weak acids. It will be challenging to include drugs with limited water solubility into sustained release mechanisms. It might be challenging to slow the dissolving rate of a medication with a high solubility and quick dissolution rate. When compared to a medicine that is less soluble in water, a drug with a high water solubility readily dissolves in water or digestive fluid, tends to release its dose form all at once, and is absorbed quickly. This causes the blood drug concentration to rise sharply. When the dose is high, it is sometimes challenging to combine a highly water soluble medicine in the dosage form and delay the drug release. Due to the fluctuating pH in the gastrointestinal system and the variability in the dissolving rate, the pH dependent solubility, particularly in the physiological pH range, would be a concern for sustained release formulation. The three main parameters that impact oral absorption—solubility, dissolution, and intestinal permeability—can be estimated using the biopharmaceutical categorization system (BCS). Drugs from Classes III (High solubility- Low permeability) and Class IV (Low solubility- Low permeability) are poor candidates for sustained release dosage forms because compounds with solubility less than 0.1 mg/ml face significant solubilization challenges, and compounds with solubility greater than 10 mg/ml frequently present challenges to solubilization dosing formulation. Highly soluble medications should generally not be formulated into a product with sustained release.[10]

Partition coefficient (P (o/w))

The ratio of the medication in an oil phase to that in an adjacent aqueous phase is known as the partition coefficient. Due to the lipophilic nature of biological membranes, drugs that pass through them have very high bioavailability if the partition coefficient of the drug impacts this. Because they won't partition out of the lipid membrane once they enter it, medications with lower partition coefficients are not acceptable for oral CR drug delivery systems, while drugs with larger partition coefficients are likewise not suitable for oral SR drug delivery systems.

Drug stability

When taken orally, drugs are subject to enzymatic and acid/base hydrolysis deterioration. Drugs that are unstable in the stomach benefit from prolonged administration to the entire GI tract since the rate of degradation will be decreased if the medication is in the solid state. Drugs that are unstable in the small intestine may exhibit lower bioavailability if they are delivered in prolonged release dose forms. This happens because more medication is transported to the small intestine, where it is prone to more breakdown.

pka – ionisation constant:

The strength of an acid or base is determined by its pKa value. At any given pH, the pKa allows one to determine the charge on a drug molecule. Only the undissociated and unionised states of the drug molecule are active. Ionised species take far longer to traverse these lipodial membranes than unionised molecules do. The Pharma Innovation Journal website states that the dissociation constant of a medication and the fluid's pH upon absorption determine how much of a drug is present in unionised form. A medication has to be in unionised form at the absorption site in order for it to be absorbed. Drugs that are ionised at the point of absorption are poor candidates for dosage forms with sustained or controlled release.[11]

DRUG RELEASE MECHANISM FROM MATRIX SYSTEMS

Zero Order Kinetics

A zero order release would be predicted by the following equation,

$Q_t - Q_0 = K_0t$

Where, Q_t = Amount of drug release dissolved in time‘t’.

Q_o = Initial amount of drug concentration in solution.

K_0t = Zero order rate constant.

The data obeys zero order kinetics with a slope equal to Ko when the data is displayed as cumulative% drug release vs time and the plot is linear. To provide the sustained pharmacological activity, this model reflects the optimal release profile.

First Order Kinetics
A first order release would be predicted by the following equation
Log Q_t = Log Q_o - $K_1t/2.303$
Where, Q_t = Amount of drug released in time't'.
Q_o = Initial amount of drug concentration in solution.
K_1t = First order rate constant.

A straight line results from plotting the data as log cumulative% medication remaining vs time, which shows that first order kinetics governs the release. Slope values may be multiplied to find the constant K.

Higuchi's Model

The Higuchi's Diffusion equation has been used to characterise drug release from the matrix device through diffusion
$f_t = Q = \sqrt{D\delta/\tau}\ (2C- \delta Cs)Cst$
Where, Q = Amount of drug released in time't'.
D = Diffusion coefficient of the drug in the matrix.
Cs = Solubility of the drug in the matrix.
δ= Porosity of matrix.
τ= Tortuosity.
t = Time (h).
The equation may be simplified then equation becomes;
$f_t = Q = K_H X t^{1/2}$
Where, K_H = Higuchi dissolution constant.
When data was plotted according to this equation, i.e., cumulative drug released verses square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.[12]

Peppas Korsmeyer Equation
When diffusion is the primary drug release mechanism, Korsmeyer et al. (1983) devised a straightforward semi-empiric model that exponentially relates drug release to time. (t).
$A_t/A_\infty = kt^n$
Where, k = Constant.
n = Release.
t = Time.
A_t and A_∞= Absolutecumulative amount of drug released at time't'.

When more than one sort of release phenomena may be present or when the release mechanism is not fully understood, this is employed.

Hixon-Crowell Formula

Hixon-Crowell's equation for diffusion has been used to explain drug delivered from the matrix device;

$W_0^{1/3} - W_t^{1/3} = Kt$
Where, W0 = Initial amount of drug.
W_t = Remaining amount of drug.
t = Time.
K= Constant (Kappa).
This expression is applicable to pharmaceutical dosage forms like tablets, where the dissolving happens in planes parallel to the drug surface, provided that the tablet dimensions are reduced proportionally in a way that maintains the initial geometric shape over time.[13]

II. CONCLUSION

Patient compliance, dosage effectiveness, and dose safety are all greatly enhanced by the seeeeeeeeeeeeeee medication delivery method. The oral mode of administration for Sustained release drug delivery systems has lately drawn greater interest because to its enhanced flexibility, lower dose frequency, and improved patient compliance. The physical-chemical properties of the drug, the type of delivery system, the condition of the patient, the length of the treatment, the presence of food, gastrointestinal motility, and the

coadministration of other medications are some of the factors that affect the formulation of an oral sustained release drug delivery system. We can infer from the discussion above that the affordable price of oral sustained release drug delivery systems has made it easier for them to replace oral conventional drug delivery systems in the market.

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