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A Review on Controlled and Sustained Release System

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Abstract: *Oral sustained and controlled release drug delivery systems are developed to maintain stable therapeutic drug levels, minimize dose frequency, and enhance patient compliance. These systems rely on appropriate drug selection, considering solubility, stability, partition coefficient, absorption, metabolism, and biological half-life. Release mechanisms include diffusion, dissolution, ion-exchange, osmotic systems, and water-penetration control. Natural, biodegradable, and synthetic polymers play a crucial role in achieving predictable and prolonged drug release. SR/CR systems ultimately improve therapeutic efficiency, reduce side effects, and optimize treatment outcomes.*

Keywords: Oral drug delivery, Sustained release, Controlled release, Diffusion, Dissolution, Polymers

I. INTRODUCTION

Oral route of drug delivery is the most preferred route of the various drug molecules among all other routes of drug delivery because of ease of administration, patient compliance, and flexible design of dosage form.(1) All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release).(2)

Controlled release drug delivery systems:- The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is in variant with time.(3) The purpose of designing controlled release dosage forms is to maintain relatively constant concentration of the drugs in the blood, tissues or target organs.(4) **Sustained release drug delivery system:-** The drug is released slowly at a rate governed by the delivery system.(5) It includes any drug delivery system achieves release of drug over an extened period of time, which not depend on time.(6)

II. THE RATIONALE FOR DEVELOPING SUSTAINED RELEASE(7,8)

- Formulation of SRDDS minimizes dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drug molecule.
- To extend the duration of action of the drug.
- To minimize the fluctuation in plasma level.
- To reduce the frequency of dosing.
- Improved drug utilization.
- Less adverse effects.
- To reduce cost of treatment by reducing number of dosage requirement.
- To minimize toxicity due to overdose which is often in conventional dosage from.
- To enhance the activity duration of a drug possessing short half-life.

III. ADVANTAGES AND DISADVANTAGES OF SUSTAINED/CONTROLLED RELEASE DOSAGE FORMS

Advantages of Sustained/Controlled Release Dosage Forms(9)

- Reduction in dosing frequency.

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- Reduced fluctuations in circulating drug levels.
- Avoidance of night time dosing.
- Increased patient compliance.
- More uniform effect.

Disadvantages of Sustained/Controlled Release Dosage Forms[10]

- Unpredictable or poor in vitro-in vivo correlation.
- Dose dumping.
- Reduced potential for dosage adjustment.
- Poor systemic availability in general

IV. DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

Parameter	Preferredvalue
Molecular weight/ size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to pH 7.8
P_{ka}	Non ionized moiety > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Table 1- Parameter for drug selection.[11]

Parameter	Comment
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Table 2- Pharmacokinetic parameter for drug selection.[12]

V. CLASSIFICATION OF SUSTAINED AND CONTROLLED DRUG DELIVERY SYSTEM

A. **Diffusion system:-** In diffusion release models, the diffusion of dissolved drug through a polymeric membrane is a rate limiting step. In this system, the drug release rate never follows zero-order kinetics, because the diffusional path length increases with time as the insoluble matrix is drug depleted.[13]

The mechanism of diffusion process shows the movement of drug molecules from a region of a higher concentration to region 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.

$$J = -D \frac{dc}{dx}$$

where,

J = flux of the drug across a membrane in the direction of decreasing conc.,

D = Diffusion coefficient of the drug, and

dc /dx = Change in the concentration of the drug in the membrane,

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Whereas when drug present in a water insoluble membrane, it must diffuse through the membrane. The drug release rate dm/ dt is given by

dm/ dt= ADKΔ C/L

where,

A = Area,

K = Partition coefficient of drug between the membrane and drug core,

L = Diffusion path length (i.e. thickness of coat),

ΔC = Concentration difference across the membrane.[14]

a) Reservoir Type:- Delivery systems akin to reservoirs are manufactured. This guarantees that the medication exits the delivery vehicle gradually. The partitioning of the drug molecules within the polymeric membrane is the rate-limiting step during the release process in various kinds of delivery systems.[15]

b) Matrix Type:- In a matrix system, the drug is dispersed as solid particles within a porous matrix formed of a water-insoluble polymer. The drug particles located at the surface of the release unit will be dissolved first and drug release rapidly.[16]

B. Dissolution System:- These systems are easy to formulate. Drug which are formulated using system have slow dissolution rate, produce slow dissolving forms with gastric intestinal fluids and the drugs which are having high aqueous solubility and dissolution rate.[17] The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by following equation:

dm/dt =ADS/h

Where,

A = Surface area of the dissolving particle or tablet

D = Diffusivity of the drug

S = Aqueous solubility of the drug

h = Thickness of the boundary layer.[18]

a) Reservoir Type:- The drug is coated with a given thickness coating, which is slowly dissolved in the contents of GI tract. By alternating layers of the drug with the rate controlling coats, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.[19]

b) Matrix Type:- In this system an alternative approach is to compress the drug with a slow dissolving carrier. Here the rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wet ability of system and surface of particle.[20]

C. Mechanism using Ion exchange:- Resins are the materials which are insoluble in water. Resin contains anionic groups such as amino or quaternary ammonium groups and cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the chain. A drug–resin complex is formed by prolonged exposure of drug to the resin. 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.[21]

D. Methods using Osmotic Pressure:- In this method, the release controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the

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compartment. This technology provides zero order release used for hydrophilic drugs. Drug may be osmotically active or combine with osmotically active salt eg. NaCl.[22]

E. Water penetration-controlled systems:-he systems functions by penetrating water into the system. These systems come in two main categories: swelling CRDDS and osmotically CRDDS. At first, swelling CRDDS systems are dry; however, upon entering the body, they take up water or other body fluids, allowing the drug to permeate the surrounding area through the swelled network.[23]

VI. PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF CONTROLLED/SUSTAINED RELEASE

Physicochemical properties of controlled/sustain release:-

a) Aqueous solubility and pKa:- The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration solution and hence the driving force for diffusion across membrane.[24]

b) Drug stability:- The important factor in oral dosage forms is the loss of medication in the GI tract by means of acid hydrolysis and/or metabolism. While a drug undergoes degradation in solid states at a much slower rate than a suspended or solution substance. It is possible to significantly improve the relative bioavailability of a medication that is toxic in the stomach; the most effective control unit would be one that activates its substance only in the intestine.[25]

c) Partition coefficient (P (o/w)):- Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition co-efficient are also not suitable for oral SR drug delivery system.[26]

d) Protein Binding:- There are some drugs which having tendency to bind with plasma proteins (eg. Albumin) and causes retention of the drug in the vascular space. If a drug with protein then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein.[27]

e) Molecular size and diffusivity:- Diffusivity depends on size & shape of the cavities of the membrane. The diffusion co efficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6-10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.[28]

Biological properties of controlled/sustain release:-

a) Absorption:- The rate, extent, and uniformity of absorption of a drug are important factors when considering its formulation into an extended release system. For a drug with slow rate of absorption (K_a<<0.17/hr), the first order release rate constant K_r less than 0.17/hr results in unacceptably poor bioavailability in many patients.[29]

b) Distribution:- Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor for oral SR drug delivery system e.g. Chloroquine.[30] Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue is that in plasma at the steady state called T/P ratio.[31]

c) Metabolism:- Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.[32]

d) Biological half-life:- 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.[33] Therapeutic compounds with short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. Drugs with long half-life, more than 8 hrs., are also generally does not be used in sustaining forms, since their effect is already sustained.[34]

VII. POLYMERS USED FOR CONTROLLED RELEASE SYSTEMS

Characteristics of Ideal polymer system.[35]

An ideal polymer system should possess the following characteristics:

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1. It should be inert and compatible with the environment.
2. It should be non-toxic.
3. It should be easily administered.
4. It should be easy and inexpensive to fabricate.
5. It should have good mechanical strength.

POLYMERS

a.) Natural Polymers:- These are derived from biological sources and are often biodegradable, biocompatible, and non-toxic, making them ideal for many pharmaceutical applications.[36] Natural polymers are often biocompatible, meaning they are well-tolerated by the human body and do not trigger adverse immune responses or toxicity.[37]

b.)Biodegradable polymers:- These polymers break down into harmless byproducts in the body over time, gradually releasing the drug. include polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer poly (lactic-co-glycolic acid) (PLGA).[38]

c.) Synthetic Polymers in Controlled drug delivery system:- Synthetic polymers offer better control over drug release, higher stability, and modifiability. They can be tailored for different routes and rates of release.[39]

VIII. CONCLUSION

Sustained and controlled release drug delivery systems are developed to maintain consistent therapeutic drug levels, minimize fluctuations in plasma concentration, and improve patient compliance by reducing dosing frequency. These systems rely on well-understood physicochemical and biological properties of drugs, along with suitable polymers that regulate release through mechanisms such as diffusion, dissolution, ion exchange, osmotic pressure, and water-penetration processes. While these dosage forms offer significant advantages—including extended drug action, reduced side effects, and improved clinical efficiency—they also present limitations such as dose dumping, reduced dose adjustment, and variable in vitro–in vivo correlation. Overall, sustained and controlled release systems provide an effective and reliable approach to optimizing drug delivery when drugs are appropriately selected based on their pharmacokinetic and physicochemical characteristics

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