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Sustained Release Matrix Technology for Cefixime- A Review

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Abstract:
Sustained release drug delivery system is designed to sustain the release of the drug dosage forms at a predetermined rate. Sustained release formulation maintains uniform drug level in therapeutic window, improved efficacy of drug by localization at the site of action with better patient compliance, reducing the dose required, providing uniform drug delivery. The sustained release formulations minimize the frequency of drug administration and do not interfere with the therapeutic action of the drug. The use of sustained release matrix technology for antibiotics is effective in preventing the resistant of antibiotics in body on irrational use. Drug release through matrix SRDDS is determined by Polymer swelling, Water penetration, Drug dissolution, diffusion, Matrix erosion. The present article contains brief review on various formulation approaches for Sustained release drug delivery system, advantages, selection criteria for matrix SRDDS and use of cefixime trihydrate in formulating matrix SRDDS.

Keywords: Sustained release system, Matrix tablet, Half-life, Matrix type system, reservoir system, selection criteria, cefixime trihydrate.

1. Introduction

Drug delivery system (DDS) is a formulation that helps in the introduction of therapeutic drug substance in the body or at targeted site to improve the efficacy and safety of the drug (Bhavani et al., 2021; Li et al., 2019). Oral drug delivery is the most convenient, conventional and preferred route of drug administration as it provides maximum patient compliance, lower cost of manufacturing, cheap packaging, and ease of administration (Alqahtani et al., 2021; Homayun et al., 2019). Tablets and capsules are the most stable form of oral drug delivery system that most of the researchers rely on to deliver drug/therapeutic substance at the targeted site inside the body (Wen et al., 2015; Hua 2020). The advantages offered by oral route of administration can never be neglected and hence it is still used by most of the pharmaceutical manufacturers (Monterio et al., 2022). But the conventional way of delivering the drug orally does not maintain the plasma-drug level within the

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therapeutic level for extended period of time (Singh et al., 2019). The conventional drug delivery systems are associated with several disadvantages such as poor patient compliance, drug concentration fluctuation (Agarwal et al., 2019).

Modified Drug Release System

In order to overcome the drawbacks associated with conventional oral drug delivery systems several advancements have been made in the drug delivery system usually named as modified release drug delivery system (Adepu et al., 2021). Modified release drug delivery system can be categorised into:

a. Delayed release system
b. Sustained release system
c. Site-specific drug delivery system
d. Receptor targeting (Chandana et al., 2020)

Sustained release drug delivery system (SRDDS)

Sustained or controlled drug delivery system is defined as the modified release drug delivery systems that changes or modify the release pattern of the drug depending on the purpose that has to be offered (Patil et al., 2022). The controlled release drug delivery systems successfully maintain the constant drug level in blood or target tissue (Sharma et al., 2019). The sustained release systems are designed in order to slower release of drug over an extended period of time. Sustained release formulation maintains uniform drug level in therapeutic window, improved efficacy of drug by localization at the site of action with better patient compliance, reducing the dose required, providing uniform drug delivery (Parida et al., 2022; Bae et al., 2020; Lowinger et al., 2018). The sustained release formulations minimize the frequency of drug administration and do not interfere with the therapeutic action of the drug (Bhowmik et al., 2018; Karvekar et al., 2017).

Rationale for developing of Sustained Release Drug Delivery System (Mishra, 2019; Lokhande et al., 2019)

The rationale or main objective of formulating SRDDS is:

- To minimize dosing frequency
- To provide availability of drug at targeted action site for extended period of time
- To deliver the drug to specific receptors or to localize to targeted cells or to definite affected areas in the body
- To improve clinical efficacy/efficiency of a drug molecule
- To reduce treatment of cost by reducing number of dosage requirement.
- To minimize toxicity due to overdose which is often in conventional dosage form

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- To enhance the duration of activity for the drugs possessing short half-life
- To maintain the concentration of drug at constant level for a preferred period of time
- The safety margin of potent drugs can be improved
- Incidence of both local and systemic adverse side effects can be reduced in sensitive patient

Principle of developing of Sustained Release Drug Delivery System

The conventional dosage forms usually release the API immediately in an absorption pool. The absorption pool represents a solution of the drug at the site of absorption, K_r, K_a and K_e - first order rate-constant for drug release, absorption and overall elimination respectively (Kumar et al., 2018).

- For Immediate drug release from a conventional dosage form implies that Kr>>>>Ka.
- For non-immediate release dosage forms, Kr<<<<Ka i.e., the release of drug from the dosage form is the rate limiting step.

The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

$Kr° = Rate\ In = Rate\ Out = K_e . C_d . V_d$

Where, Kr°: Zero-order rate constant for drug release-Amount/time

K_e: First-order rate constant for overall drug elimination-time

C_d: Desired drug level in the body – Amount/volume

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

Advantages of SRDDS

Clinical advantages (Karna et al., 2015; Patnaik et al., 2013; Diwedi et al.,2012)

i. Reduction in frequency of drug administration
ii. Improved patient compliance
iii. Reduction in blood-drug level fluctuation and hence more uniform pharmacological response, cure of control of condition more promptly
iv. Reduction in drug accumulation with chronic therapy
v. Reduction in drug toxicity (local/systemic)
   - Better drug utilization
   - Reduction in amount of drug used compared to conventional therapy
   - Improved efficiency in treatment and optimised therapy
vi. Stabilization of medical condition (because of more uniform drug levels)
vii. Improvement in bioavailability of some drugs because of spatial control; For eg., the drugs that degrade enzymatically can be protected by encapsulation by usage of polymer system

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viii. Economical to the health care providers and the patient
ix. Reduction in frequency of intake
x. Uniform release of drug substance over time
xi. Drug administration can be made more convenient
xii. Reduction in blood level oscillation characteristic of multiple dosing in conventional dosage forms
xiii. Better control of drug absorption can be attained
xiv. Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time

Commercial advantages (Hauck et al., 2022; Geraili et al., 2021; Kamaly et al., 2016)

i. Product life-cycle extension
ii. Product differentiation
iii. Market expansion
iv. Patent extension
v. Cost effective

Disadvantages of SRDDS (Hauck et al., 2022)

i. Probability of dose dumping
ii. Toxicity due to dose dumping, rapid release of contained drug (mechanical failure, chewing or masticating, alcohol intake)
iii. Reduced potential for dose adjustment
iv. Risk of side effects or toxicity upon
v. Cost of single unit higher than conventional dosage forms
vi. Increase potential for first pass metabolism/ clearance
vii. Requirement for additional patient education for proper medication
viii. Decreased systemic availability in comparison to immediate release conventional dosage forms
ix. Poor *in vitro* and *in vivo* correlations
x. Increased cost in case of costlier polymers
xi. Delayed onset of action
xii. Greater dependence on GI residence time of dosage form
xiii. Decreased bioavailability compared to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
xiv. Retrieval of drug is difficult in case of toxicity, poisoning (or) hypersensitivity reactions

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Classification of Oral Sustained/ Controlled Release Systems

1. **Diffusion controlled systems**
   a. **Reservoir Devices:** Drug reservoir surrounded by polymeric membrane. The nature of polymeric membrane or the type of polymer determines the rate of drug release. The diffusion reservoir system is zero order release system. The drugs with lower molecular weight are optimum for formulation (Pasha et al., 2021; Jain et al., 2019; Owusu et al., 2019; Manasa et al., 2016).
   b. **Matrix devices:** The drug is dispersed homogenously in polymer matrix. The release pattern is usually first order and are easier to manufacture as compared to reservoir type system. The drugs with higher molecular weight are manufactured in matrix system (Aeila et al., 2020; Reddy et al., 2017).
2. **Dissolution Controlled system**
   a. **Matrix dissolution controlled system:** Matrix dissolution system involves the dissolution of drug present in the matrix which controls the drug release.
   b. **Reservoir dissolution controlled system:** The drug particles are coated with polymer using encapsulation technique (Elahi et al., 2018).
3. **Diffusion and Dissolution controlled system:** The drug is homogenously added in polymer matrix and released by either of the methods, Swelling controlled, hydrolysis or enzymatic attack (Wasilewska et al., 2019).

Matrix Systems

The matrix system involves the embedment of drug in matrix core. The matrix systems are classified on the basis of type of polymer used and porosity (Misa et al., 2013). The matrices classified on type of polymer involve hydrophobic matrix, hydrophilic matrix, lipid matrix, biodegradable and mineral matrix (Patel et al., 2011). The matrices are also classified on the basis of porosity that involves macro porous matrix, micro porous and non-porous matrix system (Shoaib et al., 2006).

Hydrophobic Matrices: When the drug is mixed with inert or hydrophobic polymer such as polyvinyl chloride, polyethylene, ethyl cellulose and acrylate polymers & copolymers; sustained release formulation is obtained called as hydrophobic matrix SRDDS. The drug diffuses through network channels that exist between the compacted polymer matrix and show sustained release pattern (Yadav et al., 2021; Alhalmi et al., 2018).

Lipid Matrices: When the drug is mixed with lipid waxes and related material such as carnauba wax in combination with stearic acid or stearyl alcohol; sustained release formulation is obtained called as lipid matrix

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SRDDS. In this formulation, the drug releases through either of two methods: pore diffusion or erosion (Miyan et al., 2011).

Hydrophilic Matrices: When the drug is mixed with hydrophilic polymer such as cellulose derivates (methyl cellulose, hydroxyethyl cellulose, HPMC, Na CMC), non cellulose natural or semi synthetic derivates (Agar-agar, alginates, polysaccharides of mannose and galactose, chitosan and modified starches); sustained release formulation is obtained called as hydrophilic matrix SRDDS (Palparthi et al., 2013).

Biodegradable Matrices: In forming biodegradable SRDDS, the drug is embedded in polymer matrix comprised of monomers having unstable linkage between functional groups such as proteins, modified natural polymers and synthetic polymers. These polymers are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process into oligomers and monomers that can be metabolized or excreted (Palparthi et al., 2013).

Mineral Matrices: Mineral matrix SRDDS are formed by embedding drug in polymers obtained from seaweeds such as alginic acid obtained from brown seaweeds using dilute alkali (Murari et al., 2019).

Macro porous Matrix System: The diffusion of drug occurs through macro pores of matrix whose size range from 0.1 to 1 µm. The pore size in this system is larger than diffusant molecule size.

Micro porous System: The diffusion of drug occurs through micro pores of matrix whose size range from 50 – 200 A°. The pore size in this system is smaller than diffusant molecule size.

Non-porous System: The diffusion of drug occurs through network meshes as the matrix comprise of no pores for diffusion. In such cases only polymeric phase exist and no pore phase (Siraj et al., 2020).

Criteria for selection of Sustained Release Drug Delivery System (Bose et al., 2013)

A. **Desirable half life:** The drugs with shorter half life can be easily formulated into sustained release drug matrix system so that it can sustain/ retain inside the body for longer period of time.
B. **Therapeutic index:** The drugs with lower therapeutic index cannot be used in matrix system as chances of dose dumping are higher in this case.
C. **Small doses:** The drugs that are required in larger doses are difficult to formulate in matrix system as the higher amount of drug can be difficult to handle in unit dosage form. Hence, only small dose drugs are preferred for sustained release formulations.
D. **Solubility and Absorption:** In case of drugs with poor aqueous solubility, the dissolution becomes the rate limiting step and incorporating poorly soluble drugs in sustained release formulations is practically of no use as overall absorption will further decrease.

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E. **Absorption window:** The drugs such as diuretics that are absorbed only through specific region of body are not suitable for formulation in sustained release formulation as they would undesirably affect the absorption of the drug.

F. **First pass clearance:** The drugs that undergo first pass metabolism are not suitable for sustained drug delivery because the drug delivery is hindered in desired concentration at the targeted site in body.

Drug Profile of Cefixime

Description: Cefixime is β-lactum antibiotic, 3rd generation cephalosporin highly active against Enterobactriaceae and H. influenzae. It is white, practically odourless powder. It is practically insoluble in water but cefixime trihydrate is soluble in water. Cefixime trihydrate is stored in well closed container and should be kept at 20-25°C (Tripathi, 2003).

Pharmacokinetics and Pharmacodynamic (Sirisolla et al., 2015)**:**

Absorption:

Bioavailability is 40-50%, absorb from the GIT.

T max is about 2 to 3 h.

Food: T max increased and C max and AUC are slightly decreased.

Distribution: V_d is 8.8 L.

Protein binding is more than 99.5%.

Metabolism: Completely metabolized by oxidation via CYP-450 2C9. Major metabolites are cyclohexylhydroxymethyl (M1) (about one-third of the activity of the parent) and carboxyl (M2) derivatives.

Elimination: About 60% is excreted in urine and about 40% in faces as metabolites. The half-life is about 3 to 4.2h.

Pharmacology:

Cefixime is used with diet to reduce bacterial infections. Cefixime, an antibiotic, is a third-generation cephalosporin like ceftriaxone and cefotaxime. The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall (Patel et al., 2009).

Uses:

- β-lactum antibiotic to treat bacterial infections.
- Ear: Otitis caused by Haemophilus influenzae, Moraxella atarrhalis and Streptococcus pyongenes.
- Sinuses: Sinusitis.
- Throat: Tonsillitis, pharyngitis caused by Streptococcus pyogenes.
- Chest and lungs: Bronchitis, pneumonia caused by Streptococcus pneumoniae and Haemophilus influenzae.

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Dose: Adults: 200 – 400 mg daily (max 200 mg /day initial dose) with breakfast or the first main meal of the day. Increase by 200 to 400 mg /dose.

Adverse effects: Adverse drug reactions include diarrhea, dyspepsia, nausea and vomiting. Hypersensitivity reactions like skin rashes, urticaria and Stevens-Johnson syndrome have also been reported.

Contraindication: Cefixime is contraindicated in patients with known sensitivity or allergies to cephalosporin class of antibiotics. As Cefixime is a third generation cephalosporin, it is not contraindicated for patients with a true penicillin allergy (Arora et al., 2010).

2. Conclusion

It can be easily concluded by the above discussion that cefixime trihydrate can be easily sustained in its release pattern by using matrix technology. The sustained release matrix technology provide increased bioavailability, reduced number of administration, reduced drug concentration fluctuation, reduced side effects, targeted drug delivery, and improved absorption and distribution of drug with reasonable cost and use of polymers with easy availability. The dosage forms such as tablets, granules can be easily and effectively optimized by sustained released matrix technology. The irrational administration of cefixime trihydrate as an antibiotic usually cause resistance in body and this can be overcome by using matrix SRDDS.

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