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Innovative Approaches in Sustained Release Matrix Tablets: A Review

Parag S. Khandave*[1], Nayan D. Jadhav[2], Durgesh D. Ghule[3], Dr. Khanderao R. Jadhav[4], Dr. Sujit A.Jadhav[5]

Department of Pharmaceutics, KCT's Ravindra Gambhirrao Sapkal College of Pharmacy, Anjaneri, Nashik-422213 (M.S.), India.

Corresponding Author: Parag S. Khandave

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ABSTRACT: The significance of sustained release drug delivery systems is emphasized, highlighting their ability to enhance therapeutic effectiveness by providing controlled and targeted drug delivery. The main aim is to maintain the desired drug concentration at the specific site in the body. The advantages of such systems include improved patient compliance, consistent drug levels, reduced medication toxicity, and enhanced bioavailability. However, challenges such as complex formulation, potential dose dumping, and the need for careful consideration of drug properties and physiological factors are also highlighted. The research underscores ongoing efforts to overcome these limitations to maximize therapeutic efficacy, representing a significant advancement in pharmaceutical technology.

KEYWORDS: Sustained Release, Drug Delivery Systems, Therapeutic Effectiveness, Controlled Delivery, Targeted Delivery, Patient Compliance, Drug Concentration, Medication Toxicity, Bioavailability, Formulation Complexity, Dose Dumping, Drug Properties, Physiological Factors, Pharmaceutical Technology.

I. INTRODUCTION

The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration.[1]The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time.[2]Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now a days the technology of sustained release is also being applied to veterinary products also.[3]

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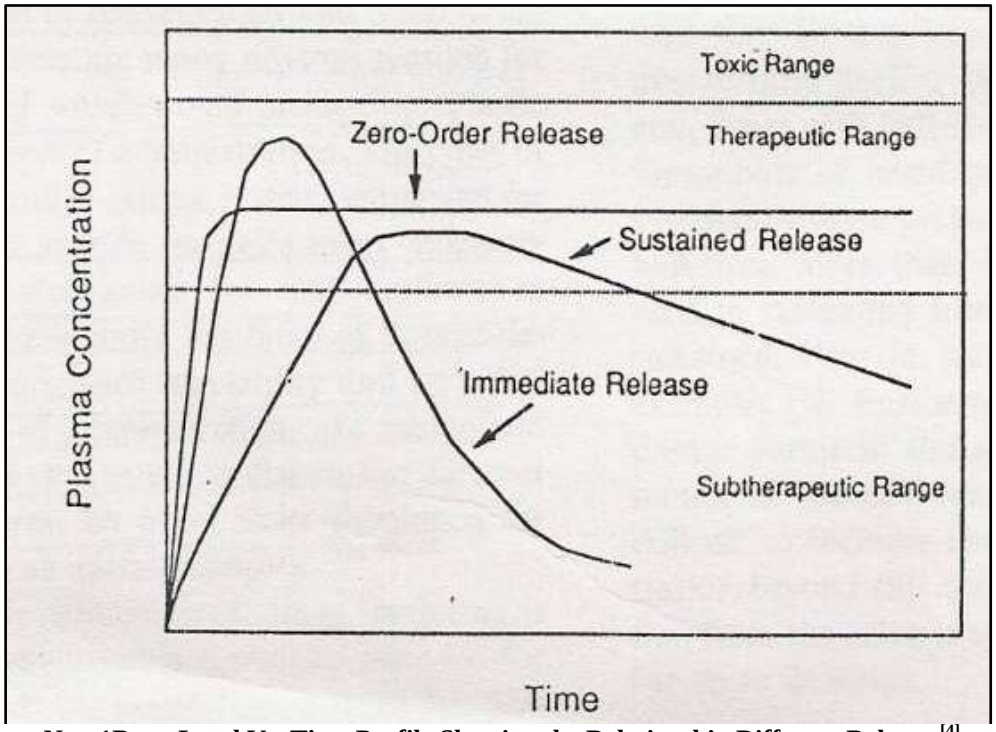

Figure No.: 1Drug Level Vs. Time Profile Showing the Relationship Different Release.[4]

A. ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

1. Less frequent drug administration.
2. Better patient compliance
3. Less fluctuating blood drug levels
4. Less overall drug use compared to conventional treatment
5. Less drug accumulation with long-term therapy
6. Reduction in systemic and local medication toxicity
7. Stabilization of medical state (due to more consistent drug levels)
8. Enhanced bioavailability of some drugs due to spatial control
9. Economical for both the patient and the healthcare professionals.[5][6][7][8][9]

B. DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY SYSTEMS:

1. A delayed onset of action of the drug.
2. It a formulation approach in poor, there may be a chance of dose dumping.
3. Enhanced first-pass metabolism capacity
4. A greater reliance on the dosage form's GI residence duration.
5. In some situations, it may be possible to modify the dose less accurately may be possible dosage is higher compared to conventional doses.
6. Not all medications can be made into ER dose forms.
7. Poor correlation between in vitro and in vivo.
8. It can be challenging to retrieve a medication in cases of toxicity, poisoning, or hypersensitivity reactions.
9. Reduced possibility for dose adjustments for medications that are typically given in different strengths.[9][10][11][12]

II. DRAWBACK OF CONVENTIONAL DOSAGE FORM

1) Poor patient compliance: Chances of missing of the dose of a drug.
2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.
4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.[13][14][15]

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III. SELECTION OF DRUGS FOR THE ORAL DRUG DELIVERY PROGRAM

The biopharmaceutical evaluation of a drug that may be used in a controlled drug delivery system requires information on how to absorb the form of the G-form drug. I., normal absorption, drug molecular weight, pKa, melting at different pH and apparent partition coefficient.[16]

Table No.:1 Parameter for Drug Selection.

PARAMETERS	PREFERRED VALUE
Molecular Weight/Size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to 7.8
Pka	Non ionized moiety > 0.1% at pH 1 to 7.8
Apparent Partition Coefficient	High
Absorption Mechanism	Diffusion
Absorbability	From all G.I. segments
Release	Should not be influenced by pH and Enzyme

Table No.:2Pharmacokinetic Parameters for Drug Selection.

PARAMETER	COMMENT
Elimination half-life	Between 2 to 8 hrs
Absolute bioavailability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution(Vd)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form.[17][18][19]

IV. CLASSIFICATION OF SR FORMULATION

The methods used to achieve sustained release of orally administered drugs delivery systems are as follows:[20]

Diffusion System

- Reservoir Device
- Matrix Device

Dissolution System

Osmatic System

Ion-exchange Resin

Swelling and Expansion System

Floating System

Bioadhesive or Bucoadhesive or Mucoadhesive system

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V. MATRIX SYSTEM

The matrix device, as the name implies, contains a substance dispersed in the same manner throughout the polymer matrix. In the model, the outer layer exposed to the bath solution dissolves first and then disperses out of the matrix. This process continues with the interface between the solvent solution and the solvent-soluble solution, apparently, in order for the system to control the dispersion, the rate of dissolution of the drug particles within the matrix must be too fast for the dispersal to consume the dissolved drug leaving the matrix.[21]

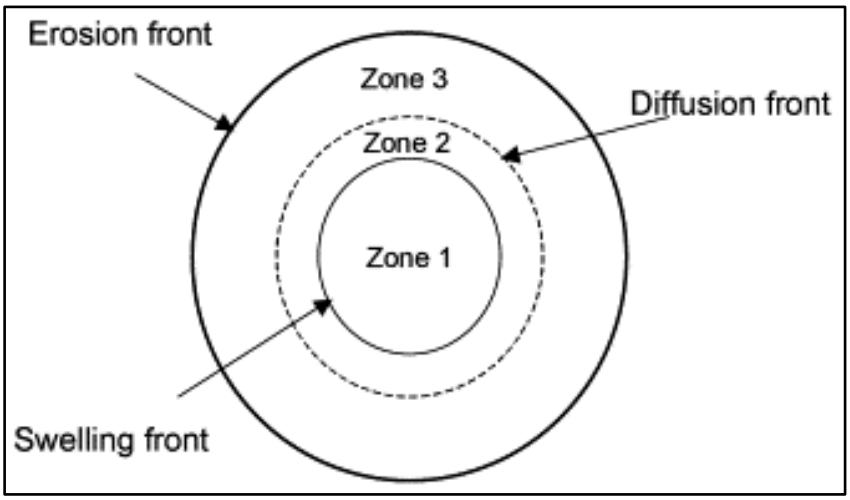

Figure No.: 2Sustain Release Matrix System.

A. ADVANTAGES OF MATRIX TABLET

1) Easy to manufacture.
2) Versatile, effective and low cost.
3) Can be made to release high molecular weight compounds.
4) The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
5) The use of sustain release formulations avoids the high blood concentration.
6) Sustain release formulations have the potential to improve the patient compliance.
7) Reduce the toxicity by slowing drug absorption.
8) Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
9) Minimize the local and systemic side effects.
10) Improvement in treatment efficacy.
11) Minimize drug accumulation with chronic dosing.
12) Usage of less total drug.
13) Improvement the bioavailability of some drugs.
14) Improvement of the ability to provide special effects.

Ex: Morning relief of arthritis through bed time dosing.

15) Very easy to fabricate in a wide range of shape and size.
16) Suitable for both non degradable and degradable system.
17) No danger of dose dumping in case of rupture.
18) Versatile, effective and low cost.
19) Can be made to release high molecular weight compounds.[22][23]

B. DISADVANTAGES OF MATRIX TABLET

1) The remaining matrix must be removed after the drug has been released.
2) High cost of preparation.
3) The release rates are affected by various factors such as, food and the rate transit through the gut.
4) The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in any applications are indistinguishable from zero-order.
5) Achievement of zero order release is difficult.
6) The remaining matrix must be removed after the drug has been released.

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7) The drug release rates vary with the square root of time.
8) Not all drugs can be blended with a given polymeric matrix.[22][23]

VI. CLASSIFICATION OF MATRIX TABLETS

- **On the Basis of Retardant Material Used:**

Matrix tablets can be divided in to 5 types.[24][25][26]

A. Hydrophilic Matrix Tablet: Hydrophilic matrix generally used to control the release rate of drug. The matrix can be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. Water is required for the hydrophilic matrix to activate the release mechanism and explore several advantages, which includes simplicity of manufacture and excellent uniformity of matrix tablets. Use of matrix building material with fast polymer hydration capability is a best choice for formulation of a hydrophilic matrix tablet. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is suitable for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow:
1) Cellulose derivatives: Hydroxyethylcellulose, Hydroxypropymethylcellulose(HPMC) 25,100,4000and15000cps, sodium carboxy methyl cellulose and Methylcellulose 400 and 4000 cps.
2) Non-cellulose natural or Semi-synthetic polymers: Agar-agar, Carob Gum, Alginates, Polysaccharides of mannose and Galactose, Chitosan and Modified starches.
3) Acrylic acid polymer: Carbopol 934 Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums.

B. Fat-Wax Matrix Tablet:Various technique used for incorporation of drug into fat wax granulation which involve spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray drying Technique. Bulk congealing method, a suspension of drug and melted fat wax is allowed to solidify and then comminuted for sustained-release granulations. Mixing of active ingredients waxy materials and fillers when the mixing is over this mixture converted into granule by compacting with s compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. The drug which is embedded into a melt of fats and wax released by leaching and hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GI tract. Addition of various surfactants to the formulation can also influence both the release rate of drug and the total drug proportion that can be incorporated into a matrix.

C. Plastic Matrix Tablet (Hydrophobic Matrices): Sustained release tablets based upon an inert compressed plastic matrix have been used widely. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,
1) The solid drug which is mixed with plastic powder and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
2) An organic solvent which is used for dissolution of drug in the plastic and granulated upon evaporation of the solvent.
3) Using latex or pseudo latex as granulating fluid which is used to granulate the drug and plastic masses. Example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

D.Biodegradable Matrices: These consist of the polymers which comprised of monomers linked to each other by functional groups and have unstable linkage in the backbone. It is 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. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

E. Mineral Matrices: Mineral matrices consist of polymers which are obtained from various species of seaweeds. Example: Alginic acid which is a

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hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

- **On The Basis of Porosity of Matrix: Matrix System is Also Classified According to Their Porosity.**

A. Macro-Porous Systems: In such systems the diffusion of drug occurs through pores of matrix which are of size range 0.1 to 1 μm. This pore size is larger than diffusion molecule size.

B. Micro-Porous System: Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusion Molecules size.

C. Non-Porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

D. Hybrid System: System in which the drug in matrix of release retarding material is further coated with increase controlling polymer membrane.

VII. POLYMERS USED IN MATRIX TABLET

- **Hydrogels:**Polyhydroxyethylemethylacrylate (PHEMA), Crosslinked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene-oxide (PEO), Polyacrylamide (PA).[27]
- **Soluble Polymers:**Polyethyleneglycol (PEG), Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC). Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides.[28]
- **Non-Biodegradable Polymers:**Polyvinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyetherurethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).
- **Mucoadhesive Polymers:**Polycarbophil, Sodium carboxy methyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Xanthan gum, Guar gum, Karaya gum, Locust bean gum.[29]

VIII. BIOLOGICAL FACTORS AFFECTING DESIGN OF ORAL SUSTAINED RELEASE DOSAGE FORM[30][31]

1)Biological Half-Life: Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However, this is limited in that drugs with very short biological half-lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limiting large. In general drug with short half-life than 2 hrs. are poor candidates of sustained release systems.

2)Absorption: The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into an extended release system. The most critical in case of oral administration is Kr<<<Ka. Assuming that the transit time of drug through the absorptive area if gastrointestinal tract is between 9-12 hours, the maximum absorption half-life should be 3-4 hours. This corresponds to a minimum absorption rate constant Ka value of 0.17-0.23/hr. necessary for about 80-95% absorption over a 9-12 hr. transit time. For the drugs with very slow rate of absorption (Ka<<0.17/hr.), the first order release rate constant Kr less than 0.17/hr. results in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drug will be difficult to be formulated into extended release systems where the criterion Kr<<<Ka must be met. If the drug absorbed by active transport or transport is limited to specific region of GIT this drug are poor candidates for sustained release systems.

3)Metabolism: Metabolism leads to either inactivation of an active drug moiety or activation of an inactivedrug molecule. Metabolic alteration of a drug mostly occurs in the liver. Metabolism isreflected in the elimination constant of a drug or by the appearance of metabolite, providedthe rate and extent of metabolism are predictable, this properly can be incorporated into theproduct design, although complex metabolic patterns make the design more difficult,particularly when biological activity is due to a metabolite. If the drug on chronicadministration induces or exhibits enzyme synthesis, it will make a poor candidate forsustained release product because of difficulty of maintaining uniform blood level.

4)Therapeutic Index: It is most widely used to measure the margin of safety of a drug.

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TI = TD50 /ED50 The longer the value of T.I the safer is the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its T.I value is greater than 10.

IX. PHYSIOLOGICAL FACTORS AFFECTING DESIGN OF ORAL SUSTAINED RELEASE DOSAGE FORM.[30, 31]

1) Molecular Size and Diffusivity: For the drug absorption it required to diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many controlled-release systems must diffuse through a rate-controlling polymeric membrane or matrix. The drugs with molecular weight 150-400 are good candidates for sustained release dosage forms. For drugs with a molecular weight greater than 500Da, their diffusion coefficients in many polymers are frequently so small that they are difficult to quantify.

2) Dosage Size: In general, conventional dosage forms, dose size 500-1000 mg is maximum which is also applicable to sustained release dosage forms.

3) Aqueous Solubility: The fraction of drug absorbed into the blood is a function of the amount of drug in the solution in the G.I tract, i.e., the intrinsic permeability of the drug. For a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and the partition into the absorbing membrane. Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems. The lower limit of solubility of drug is 0.1 mg/ml for sustained releases system. Drugs with good aqueous solubility are good candidates for oral sustained release formulation.

4) Partition Coefficient (K): Drugs with extremely large values of K are very oil-soluble and will partition into membranes quite readily and localize in body for long period of time. The values of K larger than the optimum result in poorer aqueous solubility but enhanced lipid solubility and the drug will not partition out of the lipid membrane once it gets in. The value of K at which optimum activity is observed is approximately 1000/1 in n-octanol /water. Drugs with a partition coefficient that is higher or lower than the optimum are, in general, poor candidates for formulation into extended release dosage form.

5) Drug Stability: For those drugs that are unstable in the stomach the most appropriate controlling unit would be one that releases its contents only in the intestine. The release in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling such as in this case would be one that releases its contents, only in the stomach. So, drugs with significant stability problems in any particular area of the G.I. tract are less suitable for formulation into controlled release systems that deliver the contents uniformly over the length of GIT.

X. CONCLUSION

Sustained release drug delivery systems offer numerous advantages, including improved patient compliance, stabilized drug levels, and enhanced bioavailability. However, they also present challenges, such as the complexity of formulation and potential for dose dumping. The research highlights the necessity of considering various factors like drug properties, therapeutic index, and physiological factors to design effective and safe sustained release systems. Overall, sustained release drug delivery systems represent a significant advancement in pharmaceutical technology, with ongoing research aimed at overcoming existing limitations to maximize therapeutic efficacy.

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