IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

"A REVIEW ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM"

[1]Mr. Meherdeep A. Shirbhate, [2] Mr. Nayan N. Bondhare, [3] Mr, Pavan N. Ade [4]Mr. Sankalp K. Jangale

[1]B. Pharmacy, [2]M. Pharmacy(Pharmaceutics), [3]B. Pharmacy, [4]B. Pharmacy

Ishwar Deshmukh Institute Of Pharmacy, Digras,

Maharashtra, India.

ABSTRACT -

Traditional drug delivery methods have been characterised by fast release and frequent dosing of the drug, which may increase the danger of dose fluctuation. As a result, a formulation with controlled release is required in order to maintain a blood level that is almost constant or uniform. Sustain release systems are simple to formulate and independent of the gastrointestinal tract's absorption process after oral administration. They are thought to be a wiser strategy for drugs with short half-lives that need repeated doses. These dosage forms' main goal is to maximise drug delivery in order to achieve some level of therapeutic effect control in the face of variable fluctuations in the in vivo environment where drug release occurs. Systems for sustained release include any drug delivery technique that manages to release the drug slowly over a long period of time. By avoiding the volatility of the therapeutic concentration of the medicine in the body, sustained release is also offering a promising technique to reduce the negative effects of the treatment. The fundamental idea of continuous drug delivery systems is to maximise the medication's biopharmaceutical, pharmacokinetic, and pharmacodynamics qualities in order to minimise its side effects, increase its efficacy, and cure the disease. The main objective of sustained release forms is to enhance medication therapy as determined by the relationship between benefits and drawbacks of using a sustained release system.

Keywords:- Sustained Release, Physiochemical Properties Of Drug, Factors Of Sustained Release Dosage Form, Matrix

INTRODUCTION:

These are the kinds of controlled drug delivery systems that continuously release the drug using both diffusion- and dissolution-controlled methods. Medications are dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non-swellable hydrophobic materials, or plastic materials to control the release of the medications, which have varying solubility qualities. Direct compression of a mixture of the medication, the retardant material, and the additives to create a

tablet with the drug embedded in a matrix of the retardant is one of the simplest methods for creating sustained release dosage forms.

An alternative is to granulate the medication and retardant mixture before compression. Both hydrophilic and hydrophobic polymers are among the materials utilised most frequently in the manufacture of matrix systems. Frequently accessible Hydrophilic polymers include crosslinked homopolymers and copolymers of acrylic acid as well as hydroxyl propyl methyl cellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), Xanthan gum, sodium alginate, and poly (ethylene oxide). Because tiny particle size is essential to the quick creation of a gelatinous layer on the tablet surface, it is typically supplied in micronized forms. In the sphere of pharmaceutical technology, the introduction of matrix tablets as sustained release (SR) has led to a new breakthrough for novel drug delivery systems (NDDS).

It excludes intricate manufacturing processes like coating and pelletization, and the kind and quantity of polymer employed in the preparations largely determines how much medicine is released from the dosage form. Widespread hydrophilic polymer matrix is employed while creating SR dosage forms.

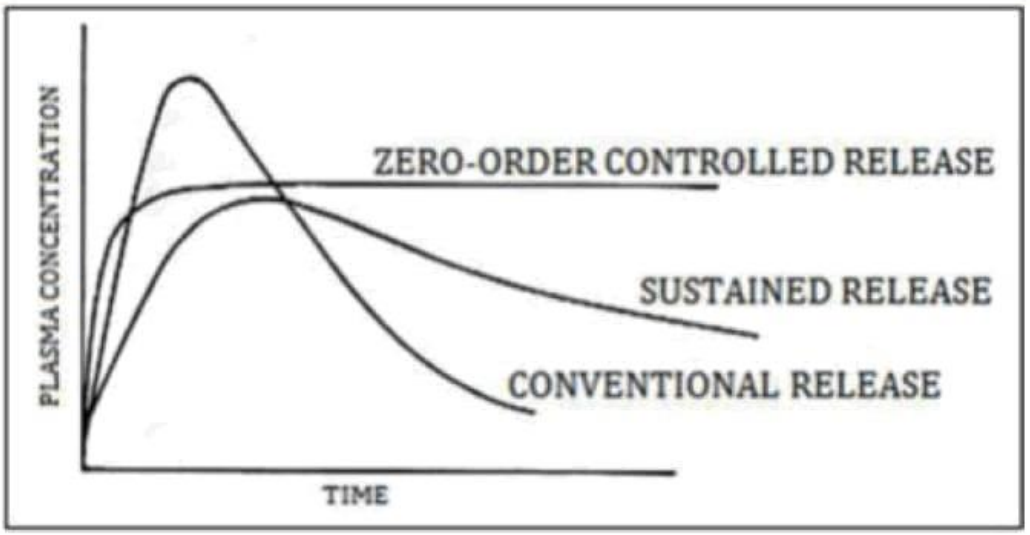

Figure 1. Plasma drug concentration vs. time profile for oral conventional dosing and single oral dose of sustained and controlled release formulation

Conventional Drug Therapy

It is clear from conventional drug therapy that administering a medication intravenously or through an extravascular route, such as orally, intramuscularly, or rectally, does not keep the drug's blood level within the therapeutic range for an extended period of time. The difficulty of standard dose forms to regulate temporal administration is the cause of the brief action. Conventional dosage forms have a number of side effects, including poor patient compliance, unavoidable fluctuations in drug concentration that can result in under- or overdosing as steady state concentration values fall or rise outside of the therapeutic range, and fluctuations in drug levels that can hasten the onset of adverse effects, especially when an overdose of a drug with a low therapeutic index occurs.

Modified -release drug delivery system

Modified release drug delivery systems have been created as a result of many technical breakthroughs to address the shortcomings of conventional drug delivery systems. It is convenient to classify the modified-release delivery systems into four types.

Delayed release System

Drugs from one or more immediate-release units combined into a single dosage form are dosed repeatedly and intermittently in delayed-release systems. Repeat-action tablets and capsules, as well as enteric-coated tablets where timed release is accomplished by a barrier coating, are examples of delayed-release methods.

Sustained release system

Any medication delivery method that accomplishes a slow release of the drug over an extended period of time is considered a sustained-release system. A controlled-release system is one that is capable of exerting some degree of control over the timing, location, or both of drug release in the body. In other words, a controlled-release system is one that is successful at maintaining constant drug levels in the target tissue or cells.

Site -specific Targeting

Site-specific and receptor targeting refer to the direct delivery of a medication to a particular biological site. When an agent is released at a specified location, the target is near or inside the affected organ.

Sustained release drug delivery system

Over the past few years, new and innovative drug delivery technologies have quickly supplanted traditional dosage forms of medications. In contemporary therapies, the controlled release/sustained release dose formulations have proven incredibly popular. In addition to extending the period of drug delivery, the term "sustained release drug administration" also suggests the predictability and reproducibility of drug release kinetics. To maximise the positive clinical response and reduce the occurrence of unfavourable adverse reactions and side effects, drug ingredients' regulated release and efficient delivery to sites of action can be utilized.

ADVANTAGE of Sustained drug delivery

1. Sustained-release tablets can lower local and systemic side effects.
2. It can reduce the dose frequency.
3. It can increase the stability of the drug.
4. It can reduce gastrointestinal irritation.
5. It can reduce drug release fluctuation in different blood concentrations.
6. Easy to manufacture.
7. Can be fabricated in a wide range of Sizes and shapes
8. No danger of dose dumping in case of rupture.
9. It has low cost.
10. Suitable for both non degradable and degradable systems.

Disadvantage of Sustained drug delivery

1. Achievement of zero order release is difficult.
2. More rapid development of tolerance and counselling.
3. Need for additional patient education and Counselling
4. Sometimes it produces poor in-vitro and in-vivo correlation.
5. Poor systemic availability is another disadvantage of it.
6. Requirement for additional patient education for proper medication.
7. Cost of single unit higher than conventional dosage forms.

8. Increase potential for first pass metabolism.
9. Decreased systemic availability in comparison to immediate release conventional dosage form
10. Probability of dose dumping.

Classification of Sustained release

In order to limit the pace at which a drug is released, controlled release systems for oral administration often use solids and are based on one of three mechanisms: diffusion, dissolution, or a combination of both.

1. Continuous Release systems
2. Delayed transit and controlled release systems
3. Delayed release system

Continuous release system

Continuous release methods allow the dosage form to pass through the gastrointestinal tract normally while releasing the medicine over an extended period of time. Following are the several systems included in this category.

A. Diffusion controlled release system
B. Dissolution controlled release system
C. Dissolution and diffusion controlled release system
D. Ion exchange resin drug complex
E. pH -independent formulation
F. Osmotic pressure controlled systems

A. **Diffusion controlled release system**

The rate-limiting stage in these kinds of systems is the diffusion of dissolved drug through a polymeric barrier. Since the diffusional path length lengthens with time as the drug concentration in the insoluble matrix steadily decreases, the drug release rate is never zero order. The foundation of these controlled drug delivery systems is the diffusion of a drug molecule via a polymeric membrane.

The two types of diffusion-controlled release are:

1. Matrix diffusion controlled systems
2. Reservoir devices

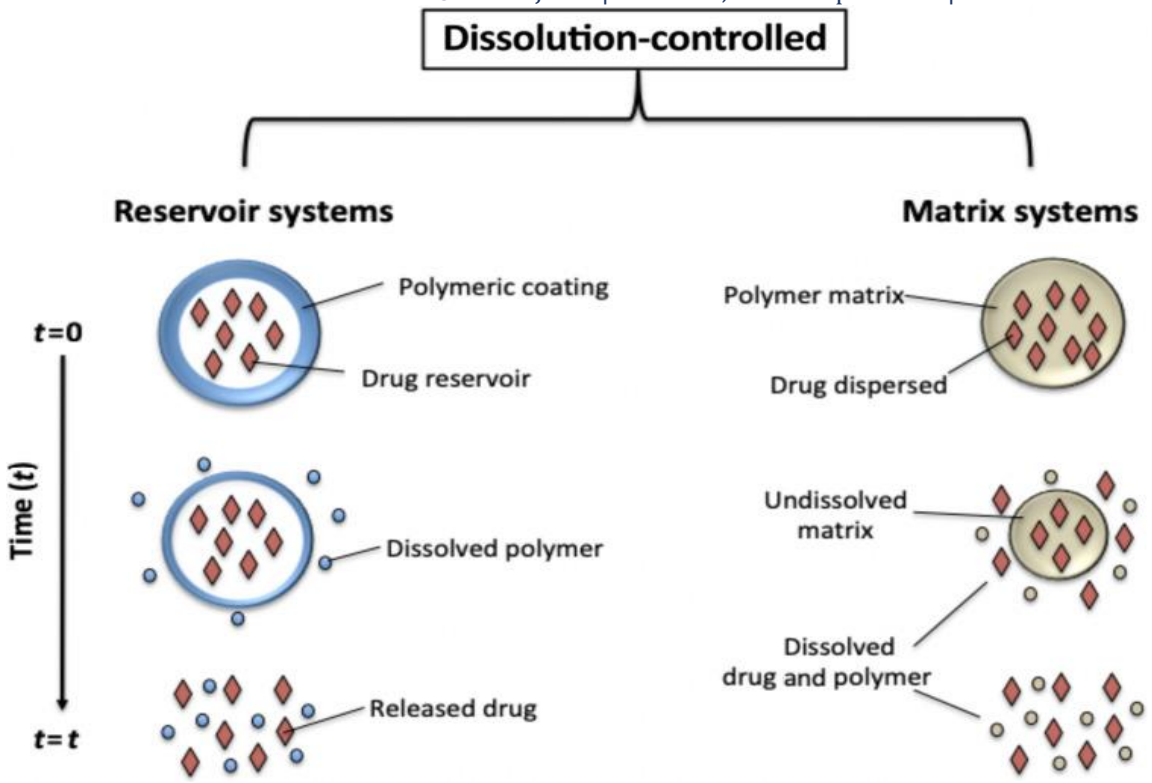

Fig Dissolution-controlled

B. **Dissolution-controlled release systems**

The drug present in such system may be the one:

A.A medication with a high rate of water solubility and dissolution may be present in such a system.

Digoxin and grisofulvin are two examples of drugs that, when they come into touch with GI fluids.

C. Produce slow-dissolving forms due to their naturally slow rate breakdown.

the drug's dissolution rate in an insoluble polymer and coat the drug's rate of dissolution in GI media by integrating particles or granules with polymeric material of different densities.

Dissolution and diffusion controlled release systems

Such systems have a membrane that is only partly soluble around the drug core. Pores are subsequently produced as a result of the membrane's partial disintegration, allowing aqueous medium to enter the core and, as a result, the diffusion of dissolved drugs out of the system.

Ion exchange resin-drug complexes

It is based on how drug resin complexes are made. When ionic resins are in constant touch with an ionic solution. The medication from this complex undergoes modifications in the gastrointestinal system and is released with an excess of Na+ and Cl- that is present there. The resin component of an insoluble cross-linked polymer is often used in this method. They have recurring salt-forming function groups on polymer chains.

pH independent formulation

The release from sustain release formulations is pH dependant, and the majority of drugs are either weak bases or weak acids. However, a buffer, such as tartaric acid, amino acid, or citric acid salt, can be added to the formulation to help maintain a consistent pH and slow pH-independent drug release. A basic or acidic medicine is combined with one or more buffering agents, then is granulated with the proper excipients and coated with a film-forming polymer that is permeable to

gastrointestinal fluids. This formulation is known as a buffer sustain release formulation. In order to maintain a consistent rate of drug release, the buffering agent adjusts the fluid inside to a proper constant pH when gastrointestinal fluid passes through the membrane.

EFFECT OF VARIOUS PARAMETERS ONDRUG

Drug distribution within the matrix, drug/polymer ratio, system shape (cylinder, sphere), polymer swelling, polymer erosion, drug dissolution/diffusion properties, and drug release kinetics are just a few examples of the many variables that might effect drug release kinetics.

- **Drug Solubility**

Another crucial element that is taken into account in the release of drugs from polymeric matrices that control swelling and erosion is the solubility of the drug in water and the size of the molecules. medications with a decent level of aqueous solubility are released by dissolving in an infiltrating medium, while medications with a low level of aqueous solubility are released by both dissolving the drug and releasing drug particles through erosion of the matrix tablet.

- **Polymer hydration**

The maximum number of polymers and polymeric combinations should be studied in terms of polymer hydration/swelling. The absorption or adsorption of water at more accessible locations, the breaking of polymer-polymer kings with the simultaneous formation of water-polymer linking, the separation of polymeric chains, the swelling, and finally the dispersion of polymeric chains are the more crucial steps in polymer dissolution.

- **Polymer diffusivity**

When a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant, the diffusant molecules move to a successive series of equilibrium positions. This process is energy activated and depends on the length of the polymer chain segment, crosslinking, and crystallinity of the polymer.

- **Thickness of polymer diffusion path**

Fick's law of diffusion effectively governs the controlled release of a drug from matrix-type polymeric drug delivery systems:

$$JD = D\, dc/dx$$

Where, JD = flux of diffusion across a plane Surface of unit area

D = is diffusibility of drug molecule

Dc/dx = is concentration gradient of drug molecule Across a diffusion path with thickness dx.

- **Thickness of hydrodynamic diffusion layer**

The hydrodynamic diffusion layer's thickness fluctuation on the surface of matrix-type delivery devices affects the drug release profile. The magnitude of drug release value decreases as hydrodynamic diffusion layer thickness rises.

- **Drug loading dose**

Loading dose of the medicine has a substantial impact on the release kinetics. In the case of medications that are poorly water soluble, the impact of initial drug loading on the tablets' subsequent release kinetics is more complicated; as initial drug loading increases, the relative release rate initially declines and then increases, whereas the absolute release rate increases monotonically. The porosity of the matrix rises with increased initial drug loading in the case of readily water soluble medicines.

- **Surface area**

It has been found that the surface area of the dosage form influences both the in vitro and in vivo rates of drug release. Small tablets release drugs more quickly than giant cylindrical ones tablets.

- **Effect of diluent**

The type of diluent determines the effect of the filler or diluent. While insoluble diluents like calcium phosphate impede Fickian diffusion and speed up matrix relaxation (erosion), water-soluble diluents like lactose induce a noticeable increase in drug release rate and shift the release mechanism towards it.

This is because watersoluble filler in matrices encourages water penetration into the interior of the matrix due to an increase in hydrophilicity of the system, which causes rapid drug diffusion and an increase in drug release rate.

FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGN

Two factors involved in oral sustained-release dosage form design

1. Biological Factors
2. Physicochemical Factors

1.**Biological Factor**

A. Biological half life

An oral SR product's primary objective is to sustain therapeutic blood levels over a longer length of time. Drugs must enter the circulation at a rate that is about equal to their rate of elimination in order to do this. The half-life (t1/2) provides a numerical description of the elimination rate. Each drug has a unique characteristic elimination rate, which is the total of all processes that permanently remove the drug from the bloodstream, including metabolism, urine excretion, and all other processes. Short-half-life therapeutic substances are typically a great candidate for SR formulation since it can lower dose frequency. Levodopa and furosemide are examples of medications whose half-lives are less than two hours, making them poor candidates for SR preparation. Substances with lengthy half-lives, more than Additionally, because their effects are already prolonged, 8 hours are typically not used in sustaining form. Examples include digoxin and phenytoin[5, 20].

B.Absorption

The rate of release must be substantially slower than the rate of absorption because the goal of creating an SR product is to exert control over the delivery system. The device will exit the potential absorptive regions before the drug release is finished if the transit period of most medications in the GI tract is assumed to be between 8 and 12 hours. As a result, the maximum half-life for absorption should be about 3 to 4 hours. Thus, to achieve 80–95% over this time period, an apparent absorption rate constant of 0.17–0.23 h-1 must be the minimum. Consequently, it makes the assumption that the medicine should be absorbed at a roughly constant pace along the entire small intestine. This is not accurate for many substances. SR preparation might hinder absorption if a medicine is absorbed through active transport or if transport is restricted to a particular area of the intestine. Trying to keep compounds in the stomach is one way to create sustaining mechanisms of distribution for compounds. The medicine can then be released gradually and travel to the absorptive location.

C. **Metabolism:**

Drugs that are considerably metabolised in the intestine's tissue or lumen prior to absorption may have decreased bioavailability when taken in slower-releasing dose forms. A medicine can be produced in SR dose form even if it has poor water solubility. To do this, the drug's solubility must be enhanced using the appropriate method before being synthesised in the SR dosage form. However, this is the time when drug crystallisation, which occurs as the drug enters the systemic circulation, should be avoided, and caution should be exercised.

2.Physicochemical Factors

A. Partition Coefficient

A medicine must pass through several different biological membranes after being given to the GI tract in order to have a therapeutic impact elsewhere in the body. Since it is usual to assume that these membranes are lipid, the partition coefficient of medications that are oil-soluble plays a crucial role in determining how well they penetrate membrane barriers. Compounds with high partition coefficients that are lipophilic in nature are poorly soluble in water and stay in the lipophilic tissue for a prolonged period of time. Compounds with an extremely low partition coefficient have a difficult time penetrating membranes, which reduces their bioavailability.Furthermore, diffusion through polymer membranes is not affected differently by partitioning effects. The drug's partitioning properties must be a major factor in the selection of diffusion-limiting membranes.

B.Dose size

For systems that are taken orally, the bulk size of the dose that can be given has a maximum. A traditional dosage form's maximum single dose is typically between 0.5 and 1.0 g. For a sustained release dose form, the same is true. It is occasionally possible to administer several doses of liquid formulations or substantial doses of certain substances.

The safety margin associated with administering a big dose of a medication with a limited therapeutic window is another factor.

C. Stability:

Acid-base hydrolysis and enzymatic breakdown are also possible outcomes of oral medication administration.

Drugs in the solid state will degrade more slowly, making them the preferable composition of delivery for challenging cases. Systems that postpone release until the dosage form reaches the small intestine are also advantageous for dosage forms that are unstable in the stomach. When taken from a sustained-release dose form, substances that are unstable in the small intestine may exhibit lower bioavailability. This is because more medications are administered in the small intestine, where they are therefore prone to breakdown. Examples of such drugs are propentheline and probanthine.

D.Ionization, pka and aqueous solubility:

Most medications are really weak bases or acids. A drug's unaltered form preferentially passes across lipid membranes, thus it's crucial to understand how the compound's pka and the absorptive environment interact. It is beneficial for drug penetration to present the drug unaltered. The fact that the drug's water solubility would typically be lowered by conversion to unaltered form unfortunately adds to the complexity of the situation. The solubility of the drug in aqueous solutions is also a requirement for delivery systems that rely on diffusion or dissolution.

These dosage forms must work in a pH-changing environment, with the stomach being acidic and the small intestine being more neutral. It is important to understand how pH affects the release process. Very low solubility compounds (0.01 mg/ml) are intrinsically maintained since the drug's dissolution will limit their release during the period of a dose form in the GI tract. Therefore, it follows that compounds with low solubility will be poor candidates for medications that are only marginally soluble since they will have low concentrations in solution, which are the driving force for diffusion.

VARIOUS MECHANISMS OF MEDICAMENT RELEASE

1. Diffusion is rate limiting

The migration of drug molecules from a high concentration in the tablet to a lower concentration in gastrointestinal fluids is caused by a process called diffusion. This movement is determined by the system's diffusion coefficient, diffusion pathway, drug concentration gradient, and surface area exposed to stomach fluid. In practice, we can follow either of the two methods.

- The medicinal product is contained in an insoluble matrix, which the gastric juice penetrates to dissolve and release the medication through diffusion
- In order to maintain a steady medication level in the blood, the drug particles are coated with polymer of a specific thickness.

2. Dissolution is rate limiting

The BCS classes 2 and 4 medications, which have weak water solubility, naturally come in sustained release versions. While it is feasible to use a water insoluble carrier while using pharmaceuticals that are soluble in water to slow down the breakdown of the drug particles coated in this sort of substance, such as polyethylene glycol. To encourage delayed release, disintegrating agent usage is optional.

3. Osmotic pressure is rate limiting

Osmosis is a phenomena whereby liquid moves from a lower concentration to a higher concentration across a semipermeable barrier that only permits liquid transfer. The entire medication is covered in a semi-permeable membrane, with a laser-made hole in one end of the tablet. The medicine is solubilized by the gastric fluid as it passes through the membrane, which increases internal pressure and forces the drug solution through the aperture and into the stomach. As long as the pill has enough medication, the delivery rate remains constant. However, it diminishes to zero as the concentration falls below saturation.

4. Release is controlled by ion exchange

Ion exchangers are resinous materials that are insoluble in water and contain anionic or cationic salt-forming groups. In the production process, resin is combined with the medication solution. And dried to create tableted beads. That drug Release is reliant on a significant amount of charged ions. The stomach and intestines, where the medication molecules are Shared with each other and diffused from the resin into the Fluid in the vicinity. This process is dependent on ionic Resin environment, not pH or enzyme, influences absorption Site.

CRITERIA TO BE MET BY DRUGPROPOSED TO BE FORMULATED INSUSTAINED RELEASE DOSAGEFORMS

1. Desirable half-life.
2. High therapeutic index
3. Small dose
4. Desirable absorption and Solubility characteristics.
5. Desirable absorption window.
6. First past clearance

1. **Desirable half-life**

A drug's half-life is a measure of how long it stays in the body. A prohibitively high amount of the drug may be present in the dosage form if the substance has a short half-life (less than 2 hours). However, when taken in non-conventional dose

forms, drugs with an elimination half-life of eight hours or longer are appropriately sustained in the body, negating the need for a sustained release drug delivery method. The medication should ideally have a half-life of three to fourhours.

2. **High therapeutic index**

Drugs with a low therapeutic index should not be included in formulations for sustained release. If the body's system malfunctions, dose dumping may take place and result in fatalities, as with digital toxin.

3. **Small dose**

The suitability of a medicine as a candidate for sustained release is seriously unknown if the dosage is high for the drug in its traditional dosing form. This is mostly due to the fact that a unit dose continuous release formulation would grow too large to administer easily.

4. Desirable absorption and Solubility characteristics

Poorly water soluble drugs frequently have slow absorption rates. Therefore, it would be unreasonable to include such compounds in continuous release formulations, which could also lower overall absorption efficiency.

5. **Desirable absorption window**

When taken orally, some medications are only absorbed from a particular region of the gastrointestinal system. The 'absorption window' is the name given to this area. Drugs with an absorption window, such as fluorouracil and thiazide diuretics, are inappropriate if they are given in sustained release dose forms.

6. **First pass clearance**

The delivery of the medication to the body in the desired concentrations is significantly impeded when given in sustained release forms for pharmaceuticals that are experiencing severe hepatic first pass metabolism, as was previously addressed in the disadvantages of sustained delivery systems.

CONCLUSION:

The description above makes it clear that sustained-release formulations serve to increase the effectiveness of the dose while also boosting the patient's compatibility. It is possible to create Matrix tablets, which release the medicine in a controlled manner, using matrix forming polymers. The tailoring of release kinetics to delivery requirements is made simple by preparatory operations. This versatility of matrix forming polymers in the production of different drug delivery systems demonstrates the value of these specialised excipients in pharmaceutical applications. For various oral delivery issues such varying medication plasma levels, limited bioavailability, more frequent dose administration, etc., they stand as the go-to solution. Therefore, the aforementioned issues with conventional oral drug delivery can be resolved with matrix tablets.

Reference :

1. Mohammed AD, James LF, Michael HR,John EH and Rajabi- Siahboomi AR.Releaseof propranolol hydrochloride From matrixtablets containing sodium Carboxyl methylcellulose and Hydroxypropyl methylcellulose, Pharmaceutical Development and Technology. 1999;4(1):313-324.

2. Basak SC, Reddy JBM and Lucas ManiKP.Formulation and release behaviour Of sustained release ambroxol hydrochloride HPMC matrix tablet. Indian Journal of Pharmaceutical Sciences. 2006;5(68):594-598

3. Harnish Patel, Dhrupesh R. Panchal,Upendra Patel, TusharBrahmbhatt andMayurSuthar.Matrix Type Drug DeliverySystem: A Review. Journal ofPharmaceutical Sciences and BioscientificResearch. 2011;1(3):143-151

4. Loyd V, Allen. JR, Nicholas GP andHoward C Ansel: Ansel's Pharmaceutical dosage Forms and drug delivery system, 8thed. 2011:260-263.

5. Vidyadhara S, Rao PR and Prasad JA.Indian Journal of .Pharmaceutical Sciences.2004;66:188-192.

6. **6.**Aulton ME: Pharmaceutics: The Science of Dosage Form Design. 2nd ed, London:Churchill livingstone. 2005:296-298.

7. **7.**Brahmankar DM and Jaiswal SB.Biopharmaceutics and Pharmacokinetics:Pharmacokinetics, 2nd ed. Delhi: VallabhPrakashan. 2009:399-401

8. Lachman L, Liberman HA. Nicholas Gl. Sustained release dosage forms. 2nd ed. Varghese Publishing house; 1987. PMCid:149289

9. Varshosaz J, Tavakoli N, Kheirolahi F. Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. AAPS Pharm sci Tech 2006;

10. Mandal U, Gowda V, Ghosh A, Selvan S, Solomon S, P al TK. Formulation and optimization of sustained release matrix tablet of metformin HCl 500 mg using response surface methodology. Yakugaku. Zasshi 2007; 127: 1281-90.

11. Pundir S., Badola A.,Sharma D.,Sustained release Matrix technology and recent advance in matrix drug Delivery system : a review. International Journal of Drug Research andTechnology,3(1):12-20, (2013).

12. Moghal M, Islam M, Ahmed I, Islam M, Rahman H, Development and optimization of sustain release matrix tablet of Ambroxol Hcl using central composite design,IJPER 44(1):28-35,2010

13. Prasad A, Issac J, Verma A K Development of Sustained Release Cefpodoxime Matrix Tablets: An Investigation on Effects of Combination of Hydrophilic and Hydrophobic Matrix Formers. Inventi Impact: NDDS.1(2),2010

14. Madgulkar A.R., Bhalekar M.R., Warghade N.S., Chavan N.S., Preparation and Evaluation of Sustained Release Matrix Tablet of Nateglinide Effect of Variables. Inventi Rapid: NDDS.2 (1):2011

15. Metrohm AG. Accurate Detection of API Release from Sustained-Release Tablets Using Near-Infrared Spectroscopy[J]. News-Medical, 2020.

16. Daniel M J, Axel Z. A Review of Disintegration Mechanisms and Measurement Techniques[J]. Pharmaceutical Research, 2017, 34: 890-917

17. Liebermann, H.A., Lachman, L. and Schwartz, J.B. 2001. Pharmaceutical Dosage Forms: Tablets. Marcel Dekker, New York, pg no. 201-243

18. British Pharmacopoeia, Published in the recommendations of the Medicines Commission pursuant to the Medicines Act, London, Vol.I, 33, (1968), 1998.

19. Gambhire MN, Ambade KW, Kurmi SD, "Development and in vitro evaluation of an oral floating matrix tablet formulation of diltiazem HCl",AAPS Pharm Sci Tech, 2007, 8 (3), E1-E9.

20. Jantzen GM and Robinson JR, Sustained and controlled-release drug delivery systems, In Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Ed., Revised and Expanded, Drugs and The Pharmaceutical Sciences, vol 72. Marcell Dekker, Inc., New York, 1995, 575-609.