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Sustained Release Tablet: A Review

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ABSTRACT:-
These days, not many pharmaceuticals emerge from research and development, and those that do have resistance issues stemming from their overuse—particularly antibiotics, which are used erratically—are the result. Therefore, by slightly altering the medication distribution, a modification in operation is an appropriate and optimal technique to make some drugs more effective. Because sustained release keeps the therapeutic concentration of the medicine from fluctuating inside the body, it is also a viable method of reducing adverse effects. The fundamentals of sustained-release formulation and its various varieties are covered in this article.
Keywords.:-Matrix system, Controlled drug delivery, Polymers.

I. INTRODUCTION[1,2,3]:-

These are the kinds of controlled drug delivery systems that employ diffusion control and dissolution control processes to continuously release the drug. The medications are dispersed in swellable hydrophilic substances, an insoluble matrix of stiff non-swellable hydrophobic materials, or plastic materials to control the release of the drugs, which have varying solubility qualities. The direct compression of a mixture of medication, retardant material, and additives to create a tablet with the drug embedded in a retardant matrix is one of the simplest methods for producing sustained release dosage forms. An alternative is to granulate the medication and retardant combination before compression. The most commonly utilized materials in the creation of matrix systems are hydrophilic and hydrophobic polymers.

Drawbacks assiated with convential release tablet:-

Low patient compliance and a higher risk of forgetting to take a medication that needs to be taken often because of its short half-life.Drug overmedication or undermedication may result from the unavoidable changes in drug concentration.The obtained profile of peak-valley plasma concentration-time is normal, which makes reaching a steady-state condition challenging. When overmedication occurs, variations in drug levels can hasten the onset of negative effects, particularly when the drug has a modest Therapeutic Index (TI). To address the shortcomings of the traditional medication delivery system, a number of recent innovations have been introduced. These methods can be used to target the administration of a drug to a specific tissue, maintain the therapeutic activity for an extended period of time, or regulate the pace at which drugs are delivered.

Classifications of Matrix Tablets[5,6,7,12,13] :

A. On the basis of Retardent material used:
1. Hydrophobic matrices(Plastic matrices)
2. Lipid matrices
3. Hydrophilic matrices
4. Biodegradable matrices
5. Mineral matrices

B. On the basis of porosity of matrix
1. Macro porous system
2. Micro porous system
3. Non-porous system

A.On the basis of Retardent material used[8,11,14,16]:

1. Hydrophobic matrices(Plastic matrices)

It was first proposed in 1959 to use hydrophobic or inert materials as matrix materials. This technique compresses the medication into a tablet after combining it with an inert or hydrophobic polymer to provide prolonged release from an oral dose form. The dissolving medication diffuses through a network of channels that are present between compressed polymer particles, resulting in sustained release. Various materials such as polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate polymers and their copolymers have been employed as inert or

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hydrophobic matrices. In these formulations, liquid penetration into the matrix is the rate-controlling step. Diffusion is one potential medication release mechanism in these kinds of tablets. When water and gastrointestinal fluid are present, certain kinds of matrix tablets become inert.

2. Lipid matrices:

These matrices were created using lipid waxes and associated substances. Such matrices allow for both pore diffusion and erosion-mediated drug release. Therefore, release properties are more responsive to the makeup of the digestive fluid than they are to the completely insoluble polymer matrix. For several prolonged release formulations, carnauba wax has been used as a retardant base in conjunction with stearyl alcohol or stearic acid.

3. Hydrophilic matrices:

Hydrophilic polymer matrix systems are extensively employed in oral controlled drug delivery due to their cost-effectiveness, wide regulatory acceptability, and flexibility in achieving a desired drug release profile.In the field of controlled release, hydrophilic polymers with high gelling capabilities are used as base excipients in the formulation of the pharmaceuticals into gelatinous capsules or, more frequently, tablets. Spread an well-mixed mixture of one or more medications and a gelling agent (hydrophilic polymer) is referred to as a matrix. We refer to these systems as scalable controlled release systems. Three broad classes of polymers are utilized in the creation of hydrophilic matrices.

a) Cellulose Derivatives
b) Non Cellulose/Natural/Synthetic Polymers

4. Biodegradable matrices:

These are composed of polymers with an unstable backbone made up of monomers connected to one another by functional groups. Enzymes produced by nearby live cells or by nonenzymatic processes biologically break them down or erode them, converting them into oligomers and monomers that can be digested or eliminated. Examples include modified natural polymers, such proteins and polysaccharides, and synthetic polymers, like polyanhydrides and aliphatic poly(esters).

5. Mineral matrices:

These are made of polymers that come from different kinds of seaweed.Alginic acid, for instance, is an ahydrophilic carbohydrate that is produced by diluting alkali and is derived from some types of brown seaweed (Phaephyceae).

B.On the basis of porosity of matrix:

1. Macro porous system

Within these systems, the medication diffuses through matrix holes with a size range of 0.1 to 1 μm. The size of the diffusant molecule is smaller than this pore size.

2. Micro porous system

In this kind of system, diffusion primarily takes place through pores. The size of pores in micro porous systems is between 50 and 200 A°, which is marginally bigger than the size of diffusant molecules.

3. Non-porous system

Molecules in non-porous systems diffuse over network meshes because they lack pores. In this instance, there is no pore phase present only the polymeric phase.

Effect of Various Parameters On Drug Delivery[18,20,22]:

Numerous parameters, including polymer swelling, polymer erosion, drug dissolution/diffusion properties, drug distribution within the matrix, drug/polymer ratio, and system shape (cylinder, sphere), might influence drug release kinetics.

A. Drug Solubility:

The release of the drug from swelling and erosion-controlled polymeric matrices is influenced by a number of significant factors, including the drug's water solubility and molecular size. medications with a fair level of aqueous solubility are released as water soluble through dissolving in an infiltrating media, while poorly water soluble medications are released through both drug and drug particle breakdown through erosion of the matrix tablet.

B. Polymer Hydration:

Researching the polymer hydration/ swelling process for the greatest number of polymers and polymeric combinations is crucial. The more crucial stages in the dissolution of polymers are the following: the absorption or adsorption of water in more accessible areas; the rupture of polymer polymer linkings, which simultaneously forms water-polymer linkings; the separation of polymeric chains; the swelling; and,

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finally, the dispersion of polymeric chain in dissolution medium.

C. Polymer diffusivity:

The process of small molecules diffusing into a polymer structure is energy-activated. Once the diffusant molecules have acquired enough activation energy for diffusion, they move to successive equilibrium positions. The length of the polymer chain segment, the degree of cross linking, and the crystallinity of the polymer all play a role in this process.

D. Thickness of polymer diffusional path:

The controlled release of a drug from matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

JD=Ddc/dx

Where, JD=flux of diffusion a cross aplane 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.

E. Thickness of hydrodynamic diffusion layer:

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

F. Drug loading dose:

The drug loading dose has a substantial impact on the release kinetics. When it comes to pharmaceuticals that are poorly soluble in water, the impact of the initial drug loading on the release kinetics is more complex. While the absolute release rate increases monotonically, the relative release rate first declines and then increases with increasing initial drug loading. When pharmaceuticals are easily soluble in water, the porosity of the matrix rises as the initial drug loading increases.

G. Surface area:

It has been discovered that the surface area of the dosage form influences both the in vitro and in vivo drug release rates. Small pills deliver the medication more quickly than huge, cylindrical tablets.

H. Effect of diluent:

The type of diluent determines its effect, whether it is filler or diluent. While insoluble diluents like dicalcium phosphate decrease Fickian diffusion and raise the relaxation (erosion) rate of the matrix, water soluble diluents like lactose induce a noticeable increase in drug release rate and release mechanism is also switched towards Fickian diffusion. This is because water-soluble fillers in matrices promote water penetration into the interior section of the matrix, which increases the hydrophilicity of the system and causes the drug to diffuse more quickly, increasing the rate of drug release.

I. Additives:

It has been reported that the addition of non-polymeric excipients to a polymeric matrix increases the pace at which hydrosoluble active principles release. If the excipients are soluble, like lactose, these increases in release rate would be noticeable, and if they are insoluble, like tricalcium phosphate, they would be less significant.

Polymers used in matrix[26,27]:

1. Hydrophilic Polymers:

Xanthan gum, sodium alginate, poly(ethylene oxide), hydroxylpropylmethyl cellulose (HPMC), hydroxylpropyl cellulose (HPC), hydroxylethyl cellulose (HEC), and cross linked homopolymers and co-polymers of acrylic acid are among the materials.

2. Hydrophobic Polymers:

In their formulation, waxes and water insoluble polymers are typically used.

3. Waxes:

waxes such as paraffin, ozokerite, candelilla, microcrystalline, beeswax, and low molecular weight polyethylene.

4. Insoluble Polymers:

Latex dispersion comprising methacryl ester copolymers, ethylcellulose, cellulose acetate butyrate, cellulose acetate propionate, and ammoniomethacrylate co-polymers. (Eudragit RL100, PO, RS100, PO).

Factors Affecting Drug Release form matrix tablets:

A. Swellingcharacteristicsofpolymers
B. Polymererosion
C. Drug loading
D. Drug solubility

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Advantages:

1. Simple to produce.
2. Adaptable and efficient.
3. It is reasonably priced.
4. Has the ability to release molecules with a high molecular weight.
5. Fit for systems that are both biodegradable and no biodegradable.
6. In the event of a rupture, there is no risk of dose dumping.
7. May be produced in a variety of forms and sizes.

Disadvantages:

1. After the medication has been released, the remaining matrix needs to be eliminated.
2. The square root of time affects the medication release rates.
3. Reaching zero order release is a challenging goal.
4. Not every medication can be combined with a certain polymeric matrix.
5. Drugs that dissolve in water have a propensity to leave the body quickly.
6. Insufficient in vivo – in vitro connection.
7. The potential for dosage dumping as a result of dietary, physiological, or formulation factors.
8. Drug retrieval can be challenging in the event of toxicity, poisoning, or hypersensitive reaction.
9. Less opportunity to change the dosage of medications that are often given in different strengths.
10. Issues with stability.
11. A higher price.
12. Faster growth in counseling and tolerance.
13. More patient counseling and education are required.

Criteria to be met by drug proposed to be formulated in sustained release dosage forms.

a) Desirable half-life:

A drug's half-life serves as a gauge for how long it will remain in the body. The dosage form may contain an excessively high amount of the medicine if it has a short half-life (less than two hours). However, when given in an unconventional dosage, drugs with an elimination half-life of eight hours or longer are adequately sustained in the body, and a sustained-release drug delivery method is usually not required in these situations. The drug's half-life should ideally be between three and four hours.

b) High therapeautic index:

It is not appropriate to include medications with poor therapeutic indices in sustained-release formulations. Digitoxin is one example of a dosage dumping that can happen if a mechanism in the body fails.

c) Small Dose:

It is highly uncertain whether a medicine is suitable as a candidate for sustained release if its dose in the normal dosage form is high. This is mostly due to the fact that a unit dose sustained release formulation's size would grow to an unmanageable size.

d) Desirable absorption and solubility characteristics:

Drugs that dissolve slowly often have reduced absorption rates. Therefore, it is unrealistic to include such compounds in sustained release formulations, and doing so could lower overall absorption efficiency.

e) Desirable absorption window:

When taken orally, some medications exclusively absorb from a particular portion of the digestive system. The "absorption window" is the name given to this section. It is not appropriate to use drugs with an absorption window, such as fluorouracil and thiazide diuretics, if they are packaged in sustained release dose forms.

f) First pass clearance:

Delivery of the drug to the body in desired quantities is severely impeded when pharmaceuticals undergoing considerable hepatic first pass metabolism are supplied in sustained release forms, as was previously mentioned in the disadvantages of sustained delivery systems.

Evaluation of sustained release tablets[23,24,25]:

Prior to going on sale, a sustained release product needs to have its strength, safety, stability, and dependability confirmed through correlation studies between in vivo and in vitro analyses. The assessing parameters and processes for sustained release formulations have been covered by a number of publications.

A. In-Vitro methods:

1. Beaker method
2. Rotating disc method
3. Rotating bottle method
4. Rotating Basket method
5. Stationary basket method

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6. Oscillating tube method
7. Dialysis method
8. UPS dissolution method

B. In-Vivo methods:

It becomes vital to perform in-vivo evaluation and establish in-vitro in vivo correlation after a suitable in-vitro profile is reached. The several techniques for in-vivo evaluation are:

1. Clinical response
2. Blood level data
3. Urinary extraction studies
4. Nutritional studies
5. Toxicity studies
6. Radioactive tracer techniques

C. Stability studies:

To guarantee the strength, safety, identity, quality, purity, and in-vitro in-vivo release rates that the medicine and its dosage form claim to have at the time of administration, adequate stability data are necessary. A sustained-release product need to release a fixed dosage of the medication at predetermined intervals, and this dosage ought to remain constant while being stored. A significant departure from the recommended release would make the sustained release product unusable. Temperature and humidity are examples of atmospheric or accelerated variables that can affect the in-vitro and in-vivo release rates of sustained release products. A sustained-release product's stability programs involve storing it at both normal and accelerated temperatures and humidity levels to make sure it can resist these changes.

In Vitro-In Vivo Correlations:

It goes without saying that developing strong in vitro-in vivo correlation is essential to the creation of sustained release delivery systems. In addition to the pharmaceutical aspect of a sustained release drug delivery system, one must take into account the biopharmaceutics and pharmacokinetics of the therapeutic agent in the body following its release from the drug delivery system, as well as the pharmacodynamics of the therapeutic agent at the site of drug action, in order to make a meaningful in-vitro in-vivo correlation. By comparing and studying the mechanism and rate profiles of sustained drug release, a straightforward in vitro-in vitro link can be formed by conducting simultaneous in- vitro and in-vivo studies of candidate drug delivery systems. The in-vitro in vivo correlation factor is obtained when it is demonstrated that the in-vivo drug release mechanism agrees well with that seen in the in vitro drug release experiments. For capsule type drug delivery system the factor can be represented as:

(Q/t)In-vivo
Q=(Q/t)In-vitro

Where, Q/t = release rate.

Drug delivery systems' dependant profiles are represented by "Q" values. Regarding the administration sites and ambient circumstances that the animals encounter while receiving therapy.

Bioavailibility Testing[25,26]:

The velocity and degree of absorption of an undisturbed medication from its application site into the general circulation is known as bioavailability. The phrase "bioavailability" refers to a certain drug moiety, which is typically an active therapeutic entity. This entity can be the unmodified drug or, in the case of a prodrug, a metabolite. On the other hand, the term "absorption" frequently describes the net movement of drug-related mass into the body from the point of application. Therefore, a molecule may be fully absorbed yet only partially accessible, as would happen in the event if inadequate absorption is the cause of poor bioavailability. Pharmaceutical dosage form optimization may be necessary to enhance the drug's absorption properties and, consequently, its bioavailability. Typically, bioavailability studies compare evaluated medicinal products at a single dose to healthy persons who are fasting.

It is preferable to use a crossover design, where each subject receives both the product and reference material on different days. Clinical testing guidelines for multiple dosage trials have been published. To support the claims of sustained release claims, there may need to be a correlation between bioavailability and pharmacological activity or clinical evidence of therapeutic efficacy. Multiple dose experiments are necessary to determine the ideal dosing schedule, even though single dose trials are typically adequate to demonstrate the validity of sustained released dosage form design. They are also necessary in cases when there may be variations in the rate of absorption but not in its extent. When subject-to-subject variance is considerable or when the observed .A single dose, blood levels are too low to be reliably quantified. It takes a sufficient number of doses to achieve blood levels in the steady state. A thorough investigation of sustained release theophylline products revealed, for instance, that encapsulated formulations had less peaking over

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repeated dosages, which improved blood level control within the intended ranges.

II. CONCLUSION:

Drawing from the preceding discourse, it is evident that sustained-release formulations serve to enhance both the patient's compatibility and the dosage's efficiency. It is possible to effectively manufacture Matrix tablets, which release the medicine in a regulated way, using matrix forming polymers. Preparatory steps make it simple to modify release kinetics to meet delivery requirements. The fact that matrix-forming polymers can be prepared for a variety of drug delivery systems validates the significance of these specific excipients in pharmaceutical applications. For numerous oral delivery issues, such as varying medication plasma levels, limited bioavailability, more frequent dose administration, etc., they are the ideal option. Therefore, matrix tablets can solve the issues with traditional oral drug delivery mentioned above.

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