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SUSTAINED RELEASE MATRIX TECHNOLOGY: A REVIEW

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Abstract: Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed.

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INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

MODIFIED RELEASE SYSTEM:

To overcome the potential problem associated with conventional drug therapy, modified release systems were developed and may be divided into different categories.

- Delayed release
- Sustained release.
- Controlled release.
- Prolonged release.
- Site specific release
- Receptor release

1. Delayed release system

Delayed release systems are those are that use, repetitive intermittent dosage form.

2. Sustained release system

Sustained release systems are those, which achieves slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response.

3. Controlled release system

An ideal controlled drug delivery system is that which delivers the drug at predetermined rate, locally or systemically for the predetermined period of time.

4. Prolonged release system

Prolonged release system, prolongs the duration of action without maintaining a constant drug blood level.

5. Site specific and receptor release system

Site specific and receptor release and targeted release system refers to targeting of the drug directly to a certain biological location.

SUSTAINED DRUG DELIVERY SYSTEM:

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.

With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced, patient's compliances can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing form of conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients.

Overall, increased administration of sustained release dosage form gives increased reliability. Not all the drugs are the suitable candidates for the sustained release dosage form.

Ideal characteristic of the drug for the sustained release dosage form are:

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.
- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

Rationale of sustained and controlled drug delivery:

The basic rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a desing property of a rate controlled dosage form and less or not at all a property of the drug molecules inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs.

Potential advantage of sustained release dosage form:

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.
- Employ a less total drug.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Obtained less potential of reduction in drug activity with chronic use.
- Improved efficiency in treatment

- Cure or control condition more promptly.
- Improved control of condition i.e. reduced fluctuation in drug level.
- Improved bioavailability of some drugs.
- Make a use of special effects, e.g sustained release aspect for relief of arthritis by dosing before bedtime.
- Economy.
- Overall, administrations of sustained release form enable increased reliability of therapy.

Recent trends in sustained drug delivery system:

Sustained release dosage forms are categorized as:

I) Single unit dosage form.

II) Multiple unit dosage form.

I) Single unit dosage form:

These refer to diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film.

II) Multiple unit dosage forms:

It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are inevitable in a single unit dosage form.

MATRIX SYSTEM:

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters

that differentiate it from other controlled release dosage forms. Hence the following must be considered.

- The chemical nature of support (generally, the support are formed by polymeric net)
- The physical state of drug (dispersed under molecular or particulate form or both)
- The matrix shape and alteration in volume as a function of time.
- The route of administration (oral administration remains the most widely used but other route are adaptable)
- The release kinetic model.

Advantages of matrix system:

The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out.

- With proper control of manufacturing process, reproducible release profiles are possible.
- There is no risk of "dumping" of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable.
- Their capacity to incorporate active principle is large, which suits them to delivery of large dosage

Classification of matrix system:

1. Hydrophobic Matrices (Plastic matrices):

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices:

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxy; Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxy methyl cellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid: Carbopol-934, the most used variety.

4. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymetic process in to oligomers and monomers that can be metabolized or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

1. 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 diffusant molecule size.

2. 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 diffusant molecules size.

3. 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.

Swellable matrices as system for oral delivery:

Monolithic devices or matrices represent a substantial part of drug delivery systems.

Matrices containing swellable polymers are referred to as

- Hydrogel matrices
- Swellable control release systems.
- Hydrophillic matrix tablet

Swellable matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic microparticulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablets. They are constituted of a blend of drug and one or more hydrophilic polymers.

The release of drug from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug –polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree. The central element of the mechanism of drug release in the gel layer (rubbery polymer), which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration.

Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer.

Mechanism of drug release from matrix devices:

I) Dissolution controlled release:

Sustained release oral products employing dissolution as the time limiting step are simplest to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution.

In the dissolution process if the dissolution process is diffusion layer control, the rate of diffusion of drug from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting step. In this case the dissolution process at steady state would be described by Noyes-Whitney equation

$$d_c/d_t = K_D A (C_s - C) \text{----------(1)}$$

Where,

d_c/d_t is dissolution rate.

K_D is dissolution rate constant.

C_s is saturation solubility of drug.

C is the concentration of drug in bulk of the solution.

In relation to diffusion expression, that

$$K_D = D/v*I \text{ ----------(2)}$$

Where,

D is dissolution coefficient

V is volume of dissolution media

I is the thickness of unstirred liquid film.

From the above expression it can be seen that the rate of dissolution i.e. availability is approx. proportional to the solubility of the drug in the dissolution media i.e. (C_s) provided a constant area and diffusional path length are maintained. This equation predicts constant dissolution rate as long as enough drug is present to maintain C_s constant, provided surface area does not change.

Dissolution control formulations are categories as

- Encapsulation dissolution control
- Matrix dissolution control

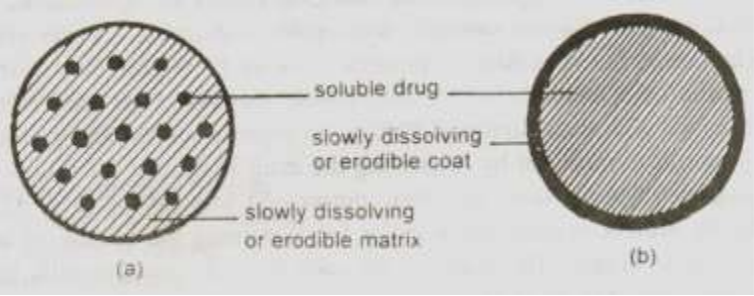

Fig No.2: Schematic representation of dissolution controlled release systems –(a) matrix system, and (b) coated/encapsulated system.

a). Encapsulation dissolution control:

This method involves coating individual particles or granules of drug with slowly dissolving material. The coated particles can be compressed directly into tablet as in spacetabs or placed in capsule as in spansule products.

b). Matrix dissolution control:

This method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophilic and the wettability of the tablet and particle surface.

II) Diffusion controlled release:

These systems are of two types

A). Encapsulation diffusion control:

In this system water –insoluble polymeric material encases a core of drug. Drug will partition into the polymer membrane and exchange with the fluid surrounding the particle or tablet.

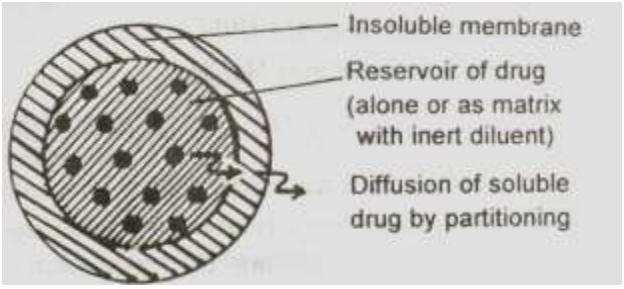

Fig: Drug release of diffusion across the insoluble membrane of reservoir device.

The rate of drug release is given by the equation.

$d_m/d_t = Adk\triangle c$----------(3)

Where,

A is area

D is diffusion coefficient

K is the partition coefficient of the drug between the membrane and the drug core

I is the diffusional path length

$\triangle c$ is the concentration difference across the membrane.

An important parameter in the above eq (3) is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration if the drug in core.

B). Matrix diffusion control.

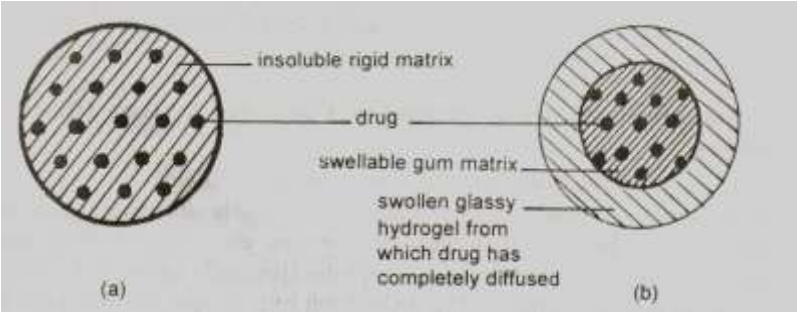

Fig no.3 Diffusion controlled devices – (a) rigid matrix, and (b) swellable matrix.

In this system, a solid drug is dispersed in lipophillic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

Material use as retardants in matrix tablet formulation:

These classes of retardant materials are used to prepare matrix tablet formulations.

1. Water insoluble inert materials:

e.g. polyethylene, polyvinyl chloride, methyl acrylate, methacrylate copolymer, ethyl cellulose.

2. Insoluble, erodable materials

e.g. Steryl alcohol, stearic acid, polyethylene glycol, carnauba wax, caster wax, polyethylene glycol monosterate, triglycerides.

3. Hydrophillic materials:

e.g. Hydroxy propyl methylcellulose, sodium CMC, methylcellulose, hydroxy ethyl cellulose.

Natural gums: Galactomannose (guargum), chitosan, gum acacia, locust bean gum, sodium alginate, karaya gum, pectins, xanthan gum.

4. Natural polymers:

Ispaghula husk, tamarind seed polymer.

Advantages of hydrophilic matrix tablets:

1. With proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is slightly less than that characterizing coated release form

2. Structure allows an immediate release of small amount of active principle there is no risk of dose dumping.

3. Their capacity to incorporate active principle is large, which suits them to delivery of large doses.

4. The manufacturing processes are notably simple. Tablet formulation can be done via direct compression or by wet granulation techniques.

5. Large variety of non expensive gelling agents is approved for oral use by the competent official organization.

6. The safety margin of high-potency drugs can be increased.

7. The drug release from hydrophilic matrices show a typical time dependent profile i.e. decreased drug release with time because of increased diffusion path length.

Factors influencing the drug release from matrix:

- Choice of matrix material.
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic material in aqueous system at a fixed concentration.
- Drug: matrix ratio
- Tablet hardness, porosity, and density variation.
- Entrapped air in tablets.
- Tablet shape and size.
- Drug particle size.
- Solubility of drug in aqueous phase
- Surfactants and other additives

Tablet manufacturing methods:

Tablets are manufactured by wet granulation, Dry granulation or direct compression method.

1] Wet Granulation:

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets.

2] Dry granulation:

In this technique, there is no use of liquids. The process involves the formation of slugs. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

3) Direct compression:

The term direct compression is used to define the process by which tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity & forms a firm compact.

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