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An Overview on Sustained Release Matrix Type Drug Delivery System

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ABSTRACT

Over the past decade, there has been much interest in replacing conventional drug administration with delivery systems that release effective doses at controlled rates over extended periods from a protected supply. An appropriately named controlled-release drug delivery system could represent a major advance in solving the problems associated with the targeted delivery of drugs. It acts on human organs or tissues to control the rate of drug delivery to target sites. Due to their simplicity, patient compliance, etc., matrix systems are preferred over conventional drug delivery (TDS), which has many drawbacks such as repeated dosing, and fluctuations in blood levels. The development of sustained and constant release rate oral matrix tablets has always been a challenge for pharmacologists. Most drugs have a slightly faster release of the drug if not properly prescribed, which can result in toxic concentrations of the drug when administered orally. Hydrophilic polymers have become the products of choice as key ingredients in the formulation of sustained-release formulations.

1. INTRODUCTION:

The oral route is the most popular route used for the administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexible dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended-release, or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period after administration of a single dose. The matrix system is broadly used for sustained release. It is the release system that prolongs the release of the drug that is dissolved or dispersed. In fact, matrix is defined as well mixed composite of one or more drugs with gelling agent which is a hydrophilic or hydrophobic polymer.

The main aim of preparing sustained-release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery. During the last 2-3 decades there has been a remarkable increase in interest in sustained-release drug delivery systems. This has been due to various factors viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, the discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating microparticles of varying sizes so that the rate of dissolution can be controlled. Oral drug delivery is the most extensively utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been discovered for systemic delivery of drugs via pharmaceutical products of the different dosage form. Oral route is considered the most natural, uncomplicated, convenient and safe [in respect to the Parenteral route] due to its ease of administration, patient acceptance and cost-effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for the immediate release of drugs for rapid absorption.

ADVANTAGES OF MATRIX SYSTEM:

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.

Better control of drug absorption can be attained since the high blood level peaks that may be observed after administration of a dose of a high-availability drug can be reduced.

- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus:

· Maximizing availability with minimum dose

· Minimize or eliminate local side effects

· Minimize or eliminate systemic side effects

· Minimize drug accumulation with chronic dosing.

- Safety margins of high-potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.

· Cure or control condition more promptly

· Improve control of the condition

· Improve the bioavailability of some drugs

- Economy

DISADVANTAGES OF THE MATRIX SYSTEM:

- Probability of dose dumping
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first-pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor in vitro and in vivo correlations.

CLASSIFICATION OF MATRIX SYSTEM:

Matrix systems can be classified into the following types:

[A] On the basis of retardant material used:

a] Hydrophilic matrices – These matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost efficiency, and broad regulatory acceptance. The hydrophilic matrix may be formulated by a wet granulation of the drugs and hydrophilic matrix material or by direct compression of a mixture of API and hydrophilic carriers.

The polymers used in the preparation of hydrophilic matrices are of three types as:

i] Cellulose derivative: Methylcellulose 400 and 4000cPs, Hydroxypropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), Hydroxypropylmethyl cellulose, HPMC 25, 100, 4000 and 15000cPs, Ethyl hydroxycellulose (E-HEC), Sodium carboxymethyl cellulose. (Na-CMC).

Among all these HPMC is the one most widely used as a drug-release retardant polymer in a hydrophilic matrix.

ii] Noncellulose natural or semisynthetic polymers – Guar gum, Agar-Agar, Carob gum, Sodium, Alginates, Xanthan gum, Carrageen, galactose, mannose, chitosan, pectin and modified starches.

iii] Polymers of acrylic acid: Carbopol-934, the mainly used polymer

b] Hydrophobic Matrices- In this system the use of polymer is not essential to provide sustained drug release. In this formulation the drug release mechanism is diffusion and the rate-controlling step is a penetration of liquid into matrix. Examples- Ethylcellulose, polyvinyl acetate, cellulose acetate etc.

c] Lipid Matrices-These matrices are 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 released 10 formulations.

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

e] Mineral Matrices-The mineral matrices can be obtained from the different species of weeds and seaweeds. Examples- Alginic acid which is a hydrophilic carbohydrate obtained from brown seaweeds by the use of dilute alkali.

[B] On the basis of the porosity of matrices it is divided into three types:

a] Macro porous system: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1µm. This pore size is larger than the molecule size.

b] Micro porous system: In such system diffusion occurs through the pores, pore size ranges between 50-200 A°.

c] Non-porous System: There is no pores in this system and the molecules diffuse through the network like meshes. No pore phase is present only polymeric phase is present.

***[C] On the basis of the way of matrix preparations*:**

a] Floating matrix system

In this type of matrix system, the bulk density of the matrix is lower than the gastric fluid in the stomach. After creating buoyancy in the stomach, the release of drug molecules from the matrix can occur slowly, which prolongs gastric residence time and thereby increases the bioavailability of fast-release drug molecules.

b] pH sensitive matrix system

In this type of matrix system, an enteric coating of the matrix system can protect the drug from the harsh acidic media of the stomach. Thus, low pH-sensitive drug molecules can reach the small intestine and colon safely. This matrix system works by releasing the enteric-coated drug at a specifically high releasing the enteric-coated drug at a specifically high pH value in the GIT, where drug absorption can occur in the right location. PH-sensitive polymers such as HPMC- phthalate or cellulose acetate phthalate can be used in this type of matrix system.

c] Mucoadhesive matrix system

Mucoadhesive matrix systems are designed to enable prolonged retention in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability. In this type of matrix system, the release of the drug is controlled over some time. The targeted tissues can be gastrointestinal, ocular, nasal, respiratory, rectal, urethral and vaginal tissues. In addition, this type of matrix system can be applied to any mucosal tissue in the body. The used materials in this system are swellable hydrophilic polymers that can interact with the glycoproteins available in the mucous layer of the gut.

GENERAL MECHANISM OF DRUG RELEASE FROM POLYMER

There are three primary mechanisms by which active agents can be released from a delivery system namely,

Diffusion

Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues its rate normally decreases with this

type of system since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. In these systems, the combinations of polymer matrices and bioactive agents have chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.

Degradation

Biodegradable polymer degrades within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after the release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds. For some degradable polymers, most notably the poly anhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system.

Swelling

They are initially dry and when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.

MECHANISM OF DRUG RELEASE FROM MATRIX TABLET

The drug in the external layer showing to the bathing solution is dissolved first and then diffuses out of the matrix. This procedure continues with the interface between the bathing solution and the solid drug moving near the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

A. Pseudo-steady state is maintained during drug release,

B. The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

C. The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:

$$dM/dh = Co.\ dh - Cs/2 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, dM = Change in the amount of drug released per unit area dh = Change in the thickness of the zone of matrix that has been depleted of drug Co = Total amount of drug in a unit volume of matrix Cs= Saturated concentration of the drug within the matrix. Additionally, according to diffusion theory:

$$dM = (Dm.\ Cs / h)\ dt \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, Dm = Diffusion coefficient in the matrix. H = Thickness of the drug-depleted matrix dt = Change in time. By combining equation 1 and equation 2 and integrating:

$$M = [Cs.\ Dm\ (2Co - Cs)\ t]^{1/2} \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

When the amount of drug is more than the saturation concentration then:

$$M = [2Cs.Dm.Co.t]^{1/2} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Equations 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from the porous from monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [Ds.\ Ca.\ p/T.\ (2Co - p.Ca)\ t]^{1/2} \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Where, p = Porosity of the matrix t = Tortuosity Ca = solubility of the drug in the release medium Ds = Diffusion coefficient in the release medium. T = Diffusional path length

For pseudo steady state, the equation can be written as:

$$M = [2D.Ca.\ Co\ (p/T)\ t]^{1/2} \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

The total porosity of the matrix can be calculated with the following equation:

$$p = pa + Ca/\rho + Cex/\rho ex \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Where, p = Porosity, ρ = Drug density, pa = Porosity due to air pockets in the matrix ρex =Density of the water-soluble excipients, Cex = Concentration of water-soluble excipients.

For data treatment, equation 7 can be reduced to: $M = k.\ t^{1/2}$ …… (8)

Where, k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

• Initial concentration of drug in the matrix • Porosity •Tortuosity • Polymer system forming the matrix • Solubility of the drug.

CHARACTERS THAT MAKE THE DRUG SUITABLE FOR SUSTAINED RELEASE MATRIX

(A) Biological characteristics

1. Biological Half-Life

Active therapeutic drugs with short half-lives are excellent candidates for sustained-release formulations since this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release formulations. Drugs with long half-lives, more than 8 hours, are also generally not used in sustained-release formulations, since there effect is already sustained.

2. Absorption

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Drugs that demonstrate true lower absorption rate constants will be poor candidates for sustaining the system.

3. Distribution

Drugs with a high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidates for oral sustained release formulations e.g. Chloroquine.

4. Metabolism

Metabolism of drugs before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, the less total drug is presented to the enzymatic process during a specific period, allowing a complete conversion of the drug to its metabolites.

(B) Physicochemical characteristics

1. Dose size

In general, a single dose of 0.5-1.0 gm is considered maximal for a conventional dosage form to be administered orally. This also holds for sustained-release dosage forms.

2. Aqueous solubility

Drugs with very low solubility (less than 0.01mg/ml) are inherently sustained. 0.1 mg/ml is considered the lower limit for the solubility of a drug to be formulated in a sustained-release system, therefore the solubility of the drug will limit the choice of mechanism to be employed in the sustained delivery system.

3. Partition coefficient

In the period between drug administration and its elimination from the body, the drug must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. Drugs with low partition coefficients easily permeate through biological membranes. While drugs with high partition coefficients will either readily penetrate into membrane producing an accumulation in body tissue with subsequent slow elimination.

4. Stability Drugs administered orally can be subject to both acid-base hydrolysis and enzymatic degradation. Systems that prolong delivery over the entire course of transits in the GI tract are beneficial for drugs that are unstable in the stomach. Drugs that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more amount of drugs are delivered in the small intestine and, hence, is subject to degradation.

5. Protein binding

Many drugs can bind to plasma proteins with concomitant influence on the duration of drug action. Binding of drug to the protein can serve as the depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

POLYMERS USED IN SUSTAINED-RELEASE MATRIX TABLET

A. Hydrophobic Polymers: Ethyl Cellulose, Cellulose Acetate

B. Enteric Polymers: Cellulose Acetate Phthalate, Hypromellose Acetate Succinate, Hypromellose Phthalate**,** P

C. Hydrophilic Polymer:

i) Cellulosic Hydrophilic Polymer: Methylcellulose, Hydroxypropyl methylcellulose, Hydroxypropyl Cellulose

ii) Non-Cellulosic Hydrophilic Polymer: Carbomers, Xanthan Gum, Chitosan Alginate, Pectin, Guar Gum

D. Hydrogel Material: Cross-linked Polyvinyl alcohol, Polyethlene oxide, Polycrylamide

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

1. Biological half-life

Drugs with a biological half-life of 2-8 hours are considered good candidates for sustained-release dosage forms as they can be administered less frequently. However, drugs with very short biological half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effects, limiting the size of the dosage form itself. There are restrictions on points. In general, drugs with short half-lives of 2 hours are poor candidates for sustained release systems.

2. Absorption

The rate, extent, and uniformity of drug absorption are important factors when considering formulation in sustained-release systems. The most important for oral administration is Kr<< Assuming a drug transit time of 9-12 hours through the absorption region of the gastrointestinal tract, the maximum absorption half-life is 3-4 hours. This corresponds to a

minimum absorption rate constant Ka value of 0.17-0.23/h required for approximately 80-95% absorption in a run time of 9-12 hours. For drugs with very slow absorption rates (Ka << 0.17/h), first-order release rate constants Kr < 0.17/h lead to unacceptably low bioavailability in many patients. Therefore, it is difficult to formulate a slowly absorbed drug into a sustained release system with a criterion Kr<1. << If drugs absorbed by active transport or transport are restricted to specific regions of the GIT, these drugs are poor candidates for sustained release systems.

Metabolism

Metabolism results in the inactivation of active drug moieties or the activation of inactive drug molecules. Changes in drug metabolism occur primarily in the liver. Metabolism is reflected in the drug's excretion constant or appearance of metabolites. However, if the rate and extent of metabolism can be predicted, this can be properly incorporated into product design, but complex metabolic patterns complicate design. Metabolite. If a drug induces or exhibits enzymatic synthesis when administered chronically, it is difficult to maintain stable blood levels and is not a candidate for a sustained-release product.

Therapeutic index

Most commonly used to measure the margin of safety of a drug. TI = TD50 / ED50 The longer the value of T.I, the safer the drug. Drugs with very low therapeutic index values are not suitable for formulation into sustained-release products. A drug is considered safe if its T.I value is greater than 10.

PHYSIOCHEMICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET

Dose size:

For oral administration systems, there is an upper limit to the dose that can be administered. Generally, for conventional dosage forms, a single dose of 0.5 to 1.0 g is considered the maximum. This also applies to sustained-release dosage forms. Compounds that require large doses can be administered multiple times or formulated in a liquid system. Another consideration is the margin of safety associated with administering large doses of drugs with narrow therapeutic ranges.

Ionization, pka, and water solubility:

Most drugs are weak acids or weak bases. Because the unchanged drug preferentially crosses lipid membranes, it is important to consider the relationship between the compound's pKa and the absorption environment. Administering the drug in its intact form favors drug permeation. Unfortunately, the situation is complicated by the fact that the water solubility of drugs is generally reduced upon conversion to the unchanged form. Delivery systems that rely on diffusion or dissolution also depend on the drug's solubility in the aqueous medium. These dosage forms need to function in changing pH environments. The stomach is acidic and the small intestine is more neutral, and the action of the Phone release process must be defined. Compounds with very low solubility (<0.01 mg/mL) are inherently preserved because drug dissolution limits release during formulation in the gastrointestinal tract. Therefore, it is clear that compound solubility is a poor choice for poorly soluble drugs because the driving force for diffusion, which is the concentration of the drug in solution, is small. Partition coefficient: When a drug is administered to the gastrointestinal tract, it must cross various biological membranes to produce a therapeutic effect in another area of the body. It is common to assume that these membranes are lipidic. Therefore, the partition coefficient of oil-soluble drugs becomes important in determining their efficacy to permeate membrane barriers. Lipophilic compounds with high partition coefficients are difficult to dissolve in water, Stays longer in lipophilic tissue. Compounds with very low partition coefficients have a very difficult time permeating membranes, resulting in low bioavailability. Furthermore, dispersion effects apply equally to diffusion through polymer membranes. The choice of the diffusion-limiting membrane should be highly dependent on the distribution properties of the drug.

Stability

Orally administered drugs can undergo both acid-base hydrolysis and enzymatic degradation. Degradation occurs at a reduced rate for solid-state drugs. Therefore, this is the preferred delivery format in case of problems. For dosage forms that are unstable in the stomach, systems that prolong delivery during gastrointestinal transit are advantageous. This also applies to systems that delay the release until the dosage form reaches the small intestine. Compounds that are unstable in the small intestine may exhibit reduced bioavailability when administered from sustained-release dosage forms. This is because more drug is released into

the small intestine, where it is more easily broken down. Propenterine and propanhin are representative examples of such drugs.

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