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A REVIEW ON MATRIX TYPE CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

The term "sustained release" is known to have existed in the medical and pharmaceutical field for many decades. Sustained release dosage forms are designed to release a drug at a predetermined rate by asserting a constant level of drug for a particular period of time with minimal adverse effects. This type of dosage form is possible only with the combination of suitable polymers. Biodegradable materials uses includes in the field of packing, agriculture, medicine and other areas. Now-a-days it has been an increase in interest in biodegradable polymers. Biodegradable polymers can be classified into two classes, synthetic and natural polymers. These are the polymers derived either from the petroleum resources or from biological sources.

KEYWORDS

Matrix Tablets, Sustained Release, Controlled Release and Polymer.

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INTRODUCTON

Sustained release or controlled release or constant release and depot release are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a extended period of time after administration of single dose of drugs[1]. Matrix tablets are one of the commercially doable sustained action dosage forms that utilize the conventional facilities and accommodate large doses of drug[2]. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. In stomach juices, the entire drug dose releases into the system while the polymer container remains intact, to be later excreted through normal digestion.

In some sustained release formulation, the drug dissolves into the matrix and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface[1]. The advantages of sustained release formulation include:

- Uniform release of drug substance over time.
- Reduction in frequency of intake.
- Adverse side effects can be minimized.
- Improved patient compliance.
- These types of dosage form can also be created using liquid excipients to form either a water insoluble matrix or a hydrophobic film around an active drug.
- Drug administration can be made more convenient as well[3].

Mechanisms of Drug Release Form Matrix Tablets[4-6]

Diffusion

Drug in the outer layer exposed to the bathing solution is dissolved first and then diffuse out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior. To control the diffusion of this system, the dissolution rate of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Osmosis

Under the right circumstances when water is allowed to enter, an osmotic pressure can be created inside the interior of the tablet. Due to this the drug is expelled out of the tablet into the outside through the coating.

Erosion

In some cases matrix can be designed to wear away gradually with time, thus delivering the drug contained within the tablet.

Mathematical model of derivation to describe the matrix system involves the following assumptions: a) 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 solutions that provides sink conditions at all times. The release behavior for the system can be mathematically described by the following equation:

$$dQ/dh = C_0 . dh - Cs/2 \quad \text{..... (i)}$$

Where, dQ = 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

C_0 = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix

Additionally, according to diffusion theory:

$$dQ = (Dm . Cs / h) dt \quad \text{..... (ii)}$$

Where, Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation (i) and equation (ii) and integrating:

$$Q = [Cs . Dm (2Co - Cs) t]^{1/2} \quad \text{.....…… (iii)}$$

When the amount of drug is in excess of the saturation concentration then:

$$Q = [2Cs.Dm.Co.t]^{1/2} \quad \text{…… (iv)}$$

Equation (iii) and equation (iv) relates the amount of drug release to the square-root of time. Therefore, if a system is prevalent diffusion controlled, then it is expected that a plot of the drug release vs. square root of time, gives a straight line. Drug release from a porous matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through convoluted interstitial channels or pores. The volume and length of the pores must be accounted for the drug release from a porous or granular matrix:

$$Q = [Ds . Ca . p/T . (2Co - p.Ca) t]^{1/2} \quad \text{……. (v)}$$

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:

$$Q = [2D.Ca .Co (p/T) t]^{1/2} \quad \text{……. (vi)}$$

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

$$p = pa + Ca/ \rho + Cex / \rho ex \quad \text{…… (vii)}$$

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 the purpose of data treatment, equation is usually reduced to

$Q = k.t^{1/2}$…… (viii)

Therefore, a plot of amount of drug released versus the square root of time should be linear if the drug release from the matrix is diffusion controlled. In the instances one may control the release from a homogeneous matrix by varying the following parameters:

- Loading drug concentration in the matrix system
- Porous membrane of matrix
- Flexibility
- Rate retarding system forming the matrix
- Solubility of the drug

Polymers

The term novel drug delivery system mainly includes two terms i.e, sustained and controlled formulation. The success of this types of formulation is mainly due to the potential role of polymers (Table No.1). Polymers are becoming increasingly important in pharmaceutical products especially in case of drug delivery system. Polymers have application ranging from their uses as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions; can also be used as film coatings;

- to mask the unpleasant taste of a drug,
- to improve drug stability and
- to modify the release characteristics[7].

Hydrophobic Matrices (Plastic matrices)

In this method, the drug is granulated with an iner plastic material such a polyethylene, polyvinyl acetate or polymethacrylate, and the granules are compressed into tablets. The release of drug from the inert plastic matrix occurs slowly by leaching to the body fluids. The compression of the tablet creates the matrix or plastic form that retains its shape during the leaching of the drug and through its elimination from the alimentary tract. The initially released drug is present on the surfaces of the tablet or is only superficially embedded. The primary example of a dosage form of this type is the *Gradumet* (Abbott), which is marketed as an iron preparation. In this case, the matrix reduces the exposure of the irritating drug to the GI mucosal tissues[8]. The matrix is usually expelled unchanged in the faeces after all the drug has been leached out[9] (Table No.2).

Lipid Matrices

These matrices are prepared by the lipids and its derivatives. Release of drug from lipid matrices occurs through pore diffusion or erosion. The release characteristics of drug are therefore more sensitive to composition digestive fluid than to totally insoluble lipid matrix. The combination of carnauba wax and stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation[10] (Table No.2).

Hydrophilic Matrices

These matrices are commonly used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. In a hydrophilic matrix, there are two competing mechanisms involved in the drug release: Fickian diffusional release and relaxation release. Diffusion leads to release of drug from the matrix and the erosion of the matrix following polymer relaxation contributes to the overall release. In this case, release of drug is primarily dependent hydro-solubility of a given drug. If the drug is moderately or highly hydro soluble, the mechanisms governing release will be diffusion. For example, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of drug. Penetration of water into a glassy polymeric matrix leads to swelling of polymer and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium (Table No.2).

- **Cellulose derivatives** Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose, different grades of Hydroxy propylmethyl cellulose (HPMC), and Sodium CMC.

- **Natural or semi synthetic polymers (non-cellulose):** Agar-Agar, Carob gum; Alginates, Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches[11].

Biodegradable Matrices

In this system, the matrix-forming polymer contains hydrolytically or enzymatic ally labile bonds and drug is uniformly dissolved or disperse in this matrix. As the polymer erodes by hydrolysis or enzymatic cleavage, the drug is released to the surrounding environment. The erosion process has a direct effect on drugs. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides[11] (Table No.2).

Mineral Matrices

These types of matrix consists of polymers obtained from various species of seaweeds. For example, Alginic acid which is a hydrophilic carbohydrate obtained from species of Phaephyceae (brown seaweeds) by the use of dilute alkali[11] (Table No.2).

Macro porous Systems

This systems involves diffusion of drug through pores of matrix, which are of size range 0.1 to 1 μm. Usually pore size is larger than diffusant molecule size[12] (Table No.2).

Micro porous System

This systems also involves diffusion of drug through pores of matrix, but pore size ranges between 50 - 200 A°, which is slightly larger than diffusant molecules size[13] (Table No.2).

Non-porous System

Since there is no pore phase in this system, only polymeric phase exists and the molecules diffuses through the network meshes[14] (Table No.2).

Effect of Release Limiting Factor On Drug Release[15,16]

The mechanism of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various role in rate determining in the controlled release of drugs from either capsules or matrix type drug delivery systems.

Polymer hydration

In this, number of polymers or polymeric combinations are with macromolecular network that swells but does not dissolves when brought in contact with water. The swelling of polymers is due to presence of hydrophilic functional group attached to the polymeric network and enables the drug to diffuse out of network.

Drug solubility

Molecular size and water solubility of drug are important determinants in the release of drug either by swelling or erosion of controlled polymeric matrices. For drugs with moderate aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor aqueous solubility, release of drugs occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

Solution solubility

In view of *in vivo* (biological) sink condition maintained effectively simulated in *in-vitro* studies and all the *in vitro* drug release studies should also be conducted under perfect sink condition. This can be done by;

- By maintaining zero concentration in bulk,
- By maintaining higher solution concentration than bulk concentration,
- By use of co-solvent (PEG-400).

It is necessary to maintain a sink condition so that the release of drug is maintained constant for specific period of time is not altered or affected by solubility factor.

Polymer diffusivity

Small molecules of drug diffuses within polymer structure by energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a adequate amount of energy of activation for diffusion has been gained by the diffusant. The extent of polymer diffusivity is also dependent on length of polymer chain segment, cross linking and crystallanity of polymer. The release of drug may be attributed to the three factors which includes,

Polymer particle size

When the content of hydroxyl propyl methylcellulose is higher, the effect of particle size

is less important on the release rate of drugs, the effect of this variable is more important when the content of polymer is low.

Polymer viscosity

Polymers viscosity is an indication of molecular mass of matrix. Increase in the polymer viscosity or molecular mass in the matrix formulation, increases the gel layer viscosity and thus slows drug release. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug release.

Polymer concentration

Viscosity of gel as well as formation of gel layer with a longer diffusional path increases by increasing the concentration of polymer. This could cause a decrease in the effective diffusion coefficient of the drug and can reduce the release rate. The release rate of drug from matrix also changes from erosion to diffusion as the polymer concentration increases.

Thickness of polymer diffusional path

The controlled release of a drug from matrix type of polymeric materials is based on Fick's law of diffusion:

$J_D = D.dc/dx$

Where, J_D= flux of diffusion across a plane surface of unit area

D = diffusibility of drug molecule,

dc/dx = concentration gradient of drug molecule across a diffusion path with thickness dx.

Thickness of hydrodynamic diffusion layer

Since the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix devices, the magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer.

Drug loading dose

The loading dose of drug affects the release kinetics along with drug solubility. In case of water soluble drugs, increase in initial loading dose increases the porosity of matrix which leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs, it has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

Surface area

Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. The release of drug from small tablet is faster than large cylindrical tablets.

Diluent's effect

The effect of diluent or filler depends upon the nature of diluent. Diluents like lactose (water soluble) causes marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while diluents like dicalcium phosphate (water insoluble) reduces the Fickian diffusion and increases the relaxation (erosion) rate of matrix. The cause behind this is that water soluble filler in matrices stimulate the water penetration into inner part of matrix layer, causing rapid diffusion of drug, leads to increased drug release rate.

Additives

The effect of adding excipients (non-polymeric) to a rate retarding materials has a vital role to increase the release rate of water soluble active principles. These increase in release rate would be marked if the excipients are soluble like dextrose or lactose and the release rate also decreases if the excipients are insoluble like tricalcium phosphate.

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET [15,17]

Biological half-life

The aim of an oral SR preparation is to maintain therapeutic blood levels over an prolonged period of time. To achieve this, drug must enter the blood circulation at almost the same rate at which it is eliminated. The elimination rate is described by the term 'half-life' ($t_{1/2}$). Each drug has its specific elimination rate, which includes metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Drugs with short half-life are generally best candidate for SR formulation, and can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide is poor

candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

Absorption

The purpose of formulating a SR product is to release the drug in slower manner than the rate of absorption. If the transit time of drugs at the site of absorption is about 8-12 hours, then the maximum half-life for absorption should be approximately 3-4 hours; if not, the device will pass out of the potential absorptive regions before drug is released completely. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. Since this is not true for many compounds, one method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach and allows slow release of the drug, which then travels at the site absorption. This attempt is made to formulate low density pellet or capsule.

Metabolism

Those drugs which are significantly metabolized before absorption, either in the lumen or by the tissue of the intestine, can show low bioavailability with slow release rate. Hence criteria for the drug to be used for formulating Sustained Release dosage form is, drugs should:

- Have low half-life (<5 hrs.)
- Be freely soluble in water.
- Have larger therapeutic window.
- Be absorbed throughout the GIT

Distribution

Since all drugs have their own characteristics elimination rate, the distribution of drug molecules into the tissue and cells can be the primary factor in particularly drug elimination kinetics. The distribution also includes the binding of the drug to the tissues and blood proteins. Drug molecules that binds to protein are considered to be inactive to permeate biological membranes, and a high degree of protein binding gives prolonged release of drug. The apparent volume of distribution of drugs is the proportionality constant of the plasma concentration of the drug to the total drug amount in the body.

Protein Binding

The Pharmacological response of drug depends on concentration of unbound drug rather than total concentration and all drug bound to some extent to plasma or tissue proteins. Binding of drug to proteins play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

Margin of safety

It is known that, larger the value of therapeutic index safer is the drug. Drugs with low therapeutic index are considered as poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

PHYSICOCHEMICAL FACTORS INFLUENCING RELEASE RATE FROM MATRIX TABLETS[21-23]

Dose size

There is an upper limit for the dose to be administered. A single dose of 0.5 of 1 gm is considered maximum.

Ionization, pKa, and aqueous solubility

The unchanged form of drug species is absorbed more through many body tissues and hence it is important to note the relationship between pKa of the compound and its absorption. The site of maximum absorption is the area in which the drug is least soluble. For conventional dosage forms the drugs fully dissolve in the stomach and absorbed in the alkaline pH of the intestine. For dissolution of diffusion controlled forms, much of drug will arrive in small intestine in solid form. Hence the solubility of the drug is likely to change several times during its release.

Partition coefficient

The compounds having high partition coefficient are lipid soluble and penetrate easily through the membranes resulting in high bio availability. Compounds having low partition coefficient do not penetrate through the membranes resulting in poor

bio availability. Partitioning effects apply equally to diffusion through polymer membranes.

Drug stability

Orally administered drugs can be degraded either by acid-base hydrolysis or enzyme action. Drugs that are unstable in stomach can be formulated with slowly soluble polymers and have their release delayed until they reach the small intestine.

EVALUATION OF SUSTAINED RELEASE PRODUCTS[35]

Rigorous standards based on *in vitro* and *in vivo* data are necessary to assure that the manufactured product gives predictable therapeutic performance.

***In vitro* testing**

In vitro dissolution testing is now widely accepted as a standard method for evaluation of drug release from solid dosage forms and the use of such *in-vitro* test to determine drug product bioavailability or bioequivalence has been emphasized by the drug licensing authorities of many countries.

A meaningful *in vitro* to *in vivo* correlation should be established to obviate the bioavailability studies, which are not always feasible due to high cost, time factor and the human risk involved. It may be categorically stated however, that although *in vitro* testing is an excellent quality control tool, no *in vitro* test is a substitute for the *in vivo* determination of drug bioavailability and sustained action performance.

In *in-vitro* dissolution, the testing procedure involves measuring the drug amount released from the dosage unit at various intervals of time in simulated gastric and intestinal fluids maintained at 37^0C±0.5 under mild agitation.

Several *in vitro* dissolution models for dissolution testing of controlled release dosage forms have been reported. These models include official methods as well as non compendial methods such as modified rotating basket dissolution test apparatus.

USP specifies two apparatus for the dissolution testing of tablets and capsules

Apparatus 1 consists of a rotating cylindrical basket fastened to the bottom of the shaft of a variable speed motor. A single tablet is placed in the basket, which is immersed in the dissolution medium contained in 1000ml cylindrical vessel. The temperature of dissolution medium is maintained at 37±0.50C by a constant temperature bath. The motor is adjusted to turn the basket at the specified speed, and samples of the dissolution fluid are withdrawn at intervals to determine the amount of drug released.

Apparatus 2 consists of the same assembly as apparatus 1 except that a paddle formed from blade and shaft is used as the stirring element and the dosage form is allowed to sink at the bottom of the vessel containing dissolution medium before rotation of the paddle.

Table No.1: Polymers used in matrix tablets[8]

S.No	Polymer Types	Examples
1	Hydrogels	Polyhydroxyethylmethylacrylate (PHEMA), Cross linked polyvinyl alcohol (PVA), Cross linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
2	Soluble Polymers	Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
3	Biodegradable polymers	Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters
4	Non-biodegradable polymers	Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)
5	Mucoadhesive polymers	Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
6	Natural gums	Xanthan gum, Guar gum, Karaya gum, Locust bean gum

Table No.2: Classification of Matrix Tablets

S.No	Based on Retardant Material Used	Based on Porosity of Matrix
1	Hydrophobic Matrices Lipid Matrices Hydrophilic Matrices Biodegradable Matrices Mineral Matrices	Macro porous Systems Micro porous Systems Non-porous Systems

Table No.3: Pharmacokinetic parameters for drug selection[18-20]

S.No	Parameters	Criteria
1	Elimination half-life	Between 2 to 8 hrs
2	Absolute bioavaliability	Should be 75% or more
3	Absorption rate constant (Ka)	Must be higher than release rate
4	Apparent volume of distribution(Vd)	Larger Vd and MEC, Larger will be the required dose
5	Total clearance	Not depend on dose
6	Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required.
7	Toxic concentration	Apart the value of MTC And MEC safer the dosage form

Table No.4: Some of the drugs can be formulated as a matrix tablet with polymer and method used for its preparation

S.No	Drugs	Category	Method	Polymers	References
1	Metoclopromide	Antiemetic	Direct Compression/ Wet Granulation	HPMC, CMC, SSG, EC	24
2	Diltiazem HCl	Ca^{2+} channel blocker	Direct Compression	Rosin	25
3	Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC K100, HPMC K15	26
4	Diclofenac Sodium	Anti-inflammatory	Wet Granulation	HPMC, Cashew nut tree gum, Carbopol	27
5	Valsartan	Antihypertensive	Direct Compression	Guargum, Pectin	28
6	Glipizide	Anti-diabetes	Direct Compression	Eudragit RL-100, EC	29
7	Carbamazepine	Antiepileptic	Solvent Evaporation Method	HPMC, CMC, PVP K90	30
8	Propanolol HCl	β-blocker	Wet Granulation	Guargum, Xanthan gum, Karaya gum, HPMC K100	31
9	Pantoprazole	Proton-pump inhibitor	Wet Granulation	HPMC, Cassava starch, PVP	32
10	Domperidone	Antiemetic	Wet Granulation	HPMC, IM-OR-023, Eudragit RS PM	33
11	Pregabalin		Hot Melt Extrusion	Okra gum, Tragacanth HPMC, HPC	34

CONCLUSION

Formulation of matrix tablets is a promising approach for oral controlled drug delivery system. The release retarding material used in the matrix plays a critical role in controlling drug release from matrix tablets. Though several release retarding materials or polymers are available there is a continued need to develop new, more efficient release retarding materials and polymers for matrix tablets.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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