



Review Article

RECENT RESEARCH ON MATRIX TABLETS FOR CONTROLLED RELEASE – A REVIEW

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Abstract: Formulation and manufacture of matrix tablets is a least complicated approach widely used in industry for obtaining oral controlled release. Matrix tablet formulation needs an efficient release retarding material, which plays a critical role in regulating drug release from matrix tablets. Literature on matrix tablets along with recent research on matrix tablets for controlled release is reviewed in this article.

Keywords: Matrix tablets, Controlled release, Recent research, Polymer

INTRODUCTION

Matrix tablets

Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.¹⁻² One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug release, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the release retardant. Alternatively drug and release retardant blend may be granulated prior to compression. The release retardant materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly used hydrophilic polymers include hydroxy propyl methylcellulose (HPMC), hydroxy propyl cellulose (HPC), hydroxy ethyl cellulose (HEC), xanthan gum, sodium alginate, poly (ethylene oxide) and cross-linked homo polymers and copolymers of acrylic acid. The release retardant materials are usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.³⁻⁵ Introduction of matrix tablet for sustained release (SR) has given a new break through for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the matrix tablets. Hydrophilic polymer matrix is widely used for formulating an SR dosage for.⁶⁻¹⁰

Advantages of Matrix Tablets¹¹⁻¹²

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- No risk of dose dumping

Disadvantages of Matrix Tablet¹¹⁻¹²

- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.
- The release rates are affected by various factors such as, food and the rate transit through the gut.

Classification of Matrix Tablets

On the basis of release retardant material used matrix tablets can be divided in to five types.¹³⁻¹⁵

1. Hydrophobic Matrices (Plastic matrices)¹³

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 Matrices¹⁴

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. In fact 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, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers

Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

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

4. Biodegradable Matrices¹⁵

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 enzymatic 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 Matrices¹⁵

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 (Phaeophyceae) by the use of dilute alkali.

Classification on the Basis of Porosity of Matrix¹⁶⁻¹⁹

Matrix systems 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 Å , 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.

Polymers Used in Matrix Tablets²⁰

Hydrogels

Poly hydroxyl ethyl methylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA) Soluble polymers Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Poly vinyl pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC)

Biodegradable polymers

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyamides, Polyorthoesters

Non-biodegradable polymers

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

Mucoadhesive polymers

Polycarophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin

Natural gums

Xanthan gum, Guar gum, Karaya gum, Locust bean gum

MECHANISMS OF DRUG RELEASE FROM MATRIX TABLETS²¹⁻²³

i) Diffusion

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward 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 dissolved drug leaving the matrix.

ii) 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.

iii) Erosion

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

Factors Effecting Drug Release Rate from Matrix Tablets²⁴⁻²⁵

1. Drug solubility

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

$$J_D = D \frac{dc}{dx}$$

2. Solution solubility

In view of in vivo (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

3. Polymer diffusivity

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer. The release of drug may be attributed to the three factors viz,

- i. Polymer particle size
- ii. Polymer viscosity
- iii. Polymer concentration.

i. Polymer particle size

Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

ii. Polymer viscosity

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii. Polymer concentration

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

4. Thickness of polymer diffusional path

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

Where,

J_D is flux of diffusion across a plane surface of unit area
 D is diffusibility of drug molecule,
 dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx .

5. Drug loading dose

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases.

In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug 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.

6. Surface area and volume

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the in vitro and in vivo rate of the drug release, are observed to be dependent upon surface area of dosage form. Siepman et al. found that release from small tablet is faster than large cylindrical tablets.

7. Diluent's effect

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

CONCLUSION

Formulation of matrix tablets is a promising approach for oral controlled release. 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.

Table-1: Recent Research on Matrix Tablets for Controlled Release

S.No	Drug (Therapeutic category)	Polymers and excipients used	Result	Reference
1	Alfuzocin Hcl (Selective antagonist of post-synaptic alpha 1-adreno receptor)	MCCPH101,HPMCK100 M, Hydrogenated castor oil ,Ethyl cellulose and Lactose monohydrate .	Drug release followed zero order kinetics and by non - fickian diffusion	26
	Nicorandil (Anti angina)	HPMC ,Ethylcellulose,Guar gum,Zanthan gum,PVP	The release data was well fit to Peppas and Hixon crowel release kinetics	27
3	Captopril (Antihypertensive)	HPMC K4M,Ethyl cellulose	Ethylcellulose significantly effected invitro drug release profile.	28
4	Gliclazide (Antidiabetic)	HPMC K4M,HPC75-100cps, Dicalcium phosphate,PVP K 30, Aerosil.	The drug release sustained upto 12 hours and was stable under accelerated conditions of temperature for a period of 6 months.	29
5	Glimepiride (Anti diabetic)	HPMC 15cps,MCC,Ethyl cellulose,HPC	The drug release extended for a period of 12 hours,the release followed first order kinetics.	30
6	Glipizide (Anti diabetic)	HPMC K100M,Eudragit L100,Lactose,Povidone	The release of drug follows zero order release kinetics	31
7	Lithium carbonate (Treatment of manic depression and mania)	Carbopol,Sodium CMC,HPMC,Lactose,MCC, Eudragit,	The matrix tablets exhibited slow release kinetics and uniform absorption characteristics	32
8	Metformine Hydrochloride (Antidiabetic)	Eutragit L- 100 and S-100,Eutragit RLPO and RSPO,MCC.	The drug release mechanism ranges from diffusion controlled to anomalous type	33
9	Minocycline Hydrochloride (Antibiotic).	Eutragit L and S,Poly ethelene oxide.	Matrix tablets produced exhibited pH-independent release profiles.	34
10	Naproxen (NSAID)	Methocel K 15 M CR, Methocel K 100M CR, PVP,MCC,Pregelatinized starch	Showed desired drug release upto 24 hours	35
11	Nifedipine (Antihypertensive)	HPMC K 15M,HPMC E 10PCR premium,sodium alginate,MCC.	Showed gradual sustained release by fickian diffusion process	36
12	Pregabalin (Anti epileptic, Anti convulsant).	HPMC K-100M,PVP K-30,MCC 102,IPA,glyceryl behanate.	Controlled release over an extended period of 8 hours.	37
13	Risperidone (Anti psychotic)	Methocel K 100 LV CR,Ethocel standard 7FP	pH-independent zero order release kinetics for 24 hours.	38
14	Salbutamol (Antiasthamatic)	Xanthum gum ,Carbapol 934,EC.	Fulfills all the requirements for sustained release tablets .	39
15	Theophylline (Respiratory depressant)	HPMC 15 CPS,HPMCP,Eudragit L 100 ,Eudragit RLPO,Polyvinyl acetate, Alginic acid.	Release followed zero order kinetics	40
16	Venlafaxine Hydrochloride (Anti	Eudragit RLPO and RSPO ,Lactose	Sustained release over 24 h was obtained	41

	depressant)			
17	Diclofenac sodium (NSAID)	Gum acacia ,tamarind gum, MCC.	Drug release was sustained for more than 12 hours	42
18	Ambroxol hydrochloride (Mucolytic agent)	MCC,Guar gum	The release was well fit to zero order kinetics.	43
19	Furosemide (Antidiuretic)	Guar gum,Xanthum gum,Pectin.	Controlled drug release over 24 h was obtained .	44
20	Olanzapine (Anti psychotic)	Methocel ® K 100 LV-CR, Ethocel® standard 7 FP	zero –order release kinetics for 24 hours .	45
21	Diclofenac sodium (NSAID)	HPMC K4M, Sodium CMC, Sodium alginate, Stearic acid	Erosion is the release mechanism	46
22	Cavedilol phosphate (Antihypertensive)	Methocel® K4M CR and K 100 M CR, Avicel PH 101, Starch	Release mechanism is diffusion	47
23	Flutamide (Antiandrogen)	HPMC K4M, Sodium CMC, Zanthan and Guar gum, Sodium Lauryl sulphate, Avicel, Lactose	First order release kinetics	48
24	Indomethacin (NSAID)	Hibiscus rosa – sinensis, Microcrystalline cellulose	Controlled drug release over 24 h was obtained	49
25	Mefenamic acid (NSAID)	Sodium hydroxide, Monobasic potassium phosphate, CMC, Starch, Lactose,Methocel	Constant drug release over 24 h	50
26	Stavudine (Antiretroviral)	HPMC K15M, Bees wax, Ethyl cellulose, Lactose	Zero order drug release over 24 h	51
27	Losartan potassium (Antihypertensive)	Eudragit, HPMC	Drug release extended over 12 h	52

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