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A COMPREHENSIVE REVIEW ON: SUSTAINED RELEASE MATRIX TYPE DRUG DELIVERY SYSTEMS

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ABSTRACT

The review of the matrix tablets seems to be most promising when developing an oral controlled release formulation. Matrix tablets are most commonly used methods to modulate the release profile of drugs. They are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system.

Keywords: Matrix tablets, Hydrophilic polymers, sustained release formulations.

INTRODUCTION

Oral route is the oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance [1]. Approximately 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the predominant route for drug delivery [2-4]. Tablets are the most commonly and widely used dosage form. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. Such immediate release products results in relatively rapid drug absorption and onset of accompanying pharmacodynamics effects. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administration of another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations In recent years, pharmaceutical industries and academic

laboratories have been focused on establishment of novel drug delivery system/modified release/sustained release or the controlled-release drug delivery system rather investigation and development of new drug due to investigation cost of a new drug [5-8].

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in a narrow range, above the minimum effective level and below toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained release dosage form with good release profile precision [9]. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and palletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, drug and retardant blend may be granulated prior to compression [10-13].

The major Drawbacks Associated with Conventional Dosage Forms are

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur [14].

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to tissue. Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release

2) Sustained release

3) Site-specific targeting

4) Receptor targeting

More precisely, controlled delivery can be defined as: Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects [15,16].

Matrix Systems

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a hydrophobic polymer or hydrophilic polymer. In this sense, the term "matrix" indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation [17].

Advantages offered by matrix tablets:

1. Improved patient compliance.
2. Avoids the high blood concentration.
3. Reduction in toxicity by slowing drug absorption.
4. Minimize the local and systemic side effects.
5. Improvement in treatment efficacy.
6. Better drug utilization.
7. Minimize drug accumulation with chronic dosing.
8. Can be made to release high molecular weight compounds.
9. Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
10. Reduction in health care cost.

11. Usage of less total drug.
12. Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
13. Maintains therapeutic concentrations over prolonged periods.
14. Easy to manufacture, versatile, effective and low cost

Disadvantages of Matrix Tablets:

1) Achievement of zero order release is difficult.
2) Greater dependence on GI residence time of dosage form.
3) Increased potential for first-pass metabolism.
4) Delay in onset of drug action.
5) Release rates are affected by food and the rate transit through the gut.
6) Release rate continuously diminishes due to increased diffusional resistance and decrease in effective area at the diffusion front.
7) The remaining matrix must be removed after the drug has been released.
8) Not all drugs can be blended with a given polymeric matrix [18-20].

Mechanism of Drug Release from Matrix System

1) Diffusion method

In this method 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 towards 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.

2) Bimodal release

In certain system there is a bimodal release of the active ingredients. In this system there is diffusion. The extended release drug may become hydrated and begins to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusion path length undergoes change due to polymer dissolution.

3) Higuchi model

The drug release from Higuchi model is much slower than zero – order profile. When a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablet superficial layer and consequently, the release rate is fast. As the time passes, the external layers of the tablet become depleted of the drug and water molecule must travel through long, tortuous channels to reach the drug remaining in the deeper layer of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for continuously decreasing rate of the drug release is more than the matrix swells, the longer the diffusion path length required for the drug to come out [18, 21-22].

Polymers used in matrix tablets:

There are number of polymers which may be used to formulate matrix tablets depending on the physicochemical properties of the drug substance to be incorporated into matrix system and type of drug release required [23]. Polymers used for matrix tablets may be classified as:

1. Hydrogels: Poly hydroxyl ethyl methylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Poly acryl amide (PA).

2. Soluble polymers: Poly ethylene glycol (PEG), polyvinyl alcohol (PVA), Poly vinyl pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC).

3. Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Poly anhydrides, Polyorthoesters.

4. Non-biodegradable polymers: Polyethylene vinyl acetate (PVA), Poly dimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

5. Mucoadhesive polymers: Poly carbophil, Sodium carboxy methyl cellulose, Poly acrylic acid, tragacanth, Methyl cellulose, Pectin

6. Natural gums: Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

Classification of Matrix Tablets:

On the Basis of Retardant Material Used:

Matrix tablets can be divided in to 5 types

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 formulations.

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[24-26].

4. Biodegradable Matrices:

These systems are 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 olegomers and monomers that can be metabolized or excreted [27].

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 (Phaeophyceae) by the use of dilute alkali [28].

Components of Matrix Tablet:

These include:

- ✓ Active drug
- ✓ Release controlling agent(s): matrix formers
- ✓ Matrix Modifiers, such as channelling agents and wicking agents
- ✓ Solubilizers and pH modifiers
- ✓ Lubricants and flow aid
- ✓ Supplementary coatings to extend lag time further reduce drug release etc.

Matrix formers:

Hydrophobic materials that are solid at room temperature and do not melt at body temperature are used as matrix formers. These include hydrogenated vegetable oils, cotton seed oil, soya oil, microcrystalline wax and carnauba wax. In general, such waxes form 20-40% of the formulation.

Channelling agents:

These are chosen to be soluble in gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channelling agent but a water soluble pharmaceutical acceptable solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. This choice will depend on the drug and desired released characteristics. These agents can be 20-30% of the formulation.

Solubilizers and pH modifiers:

It is often necessary to enhance the dissolution of drug. This may be achieved by the inclusion of solubilising agents such as PEGs, polyols and surfactants. If the drug is ionisable then the inclusion of buffers or counter ions may be appropriate. On occasions the dissolution enhancer may also be the channelling agent.

Anti-adherent or glidants:

Heat is generated during compaction of the matrix can cause melting of the wax matrix forming compounds and sticking to the punches. Something is needed to cope with the sticking; suitable anti adherents include talc and colloidal silicon dioxide. These materials also can act as glidants and improve the flow of formulations on the tablet machine. The typical amounts used will depend on the antiadherent used, for example 0.5-1% for colloidal silicon dioxide and 4-6% for talc. Magnesium stearate, if added, can also act as an antiadherent [29].

Method of Preparation of Matrix Tablet

A. Wet Granulation Technique

- Milling and mixing of drug, polymer and excipients.
- Preparation of binder solution.
- Wet massing by addition of binder solution or granulating solvent.
- Screening of wet mass.
- Drying of the wet granules.
- Screening of dry granules.
- Blending with lubricant and disintegrant to produce "running powder"
- Compression of tablet [30].

B. Dry Granulation Technique

- Milling and mixing of drug, polymer and excipients.
- Compression into slugs or roll compaction.
- Milling and screening of slugs and compacted powder.
- Mixing with lubricant and disintegrant
- Compression of tablet [31].

C. Sintering Technique

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled. The changes in the hardness and disintegration

time of tablets stored at elevated temperatures were described as a result of sintering. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release [32].

Factors Influencing Release from Matrix Tablet:

Biological Factors Influencing Drug Release from Matrix Tablet

A Biological half-life

B. Absorption

C. Metabolism

D. Distribution

E. Protein binding

F. Margin of safety [33, 34]

Physicochemical Factors Influencing Drug Release from Matrix Tablet

A. Dose size

B. Ionization, *pka* and aqueous solubility

C. Partition Coefficient

D. Stability [35,36]

Effect of Release Limiting Factors on Drug Release:

A. Polymer hydration

B. Drug solubility

C. Solution solubility

D. Polymer diffusivity

E. Thickness of polymer diffusional path

F. Thickness of hydrodynamic diffusion layer

G. Drug loading dose

H. Surface area and volume

I. Diluent's effect

J. Additives [37, 38]

Evaluation of Matrix Tablet:

Precompression characterization:

- ✓ Bulk Density
- ✓ Granule Density
- ✓ Tapped Density
- ✓ Compressibility Index
- ✓ Angle of Repose

Post Compression Characterization:

- ✓ Weight Variation Test
- ✓ Friability Test
- ✓ Hardness Test
- ✓ In- Vitro Drug Release profile [39, 41]

Table 1: List of drugs formulated using different polymers and methods

DRUGS USED	CATEGORY	METHOD USED	POLYMER USED
Zidovudine	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934
Venlafexine	Anti-depressant	Wet Granulation	Beeswax, Caranuaba wax
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Alfuzosin	Alfa-adrenergic Agonist	Direct Compression	HPMC-K15M, Eudragit
Minocycline	Antibiotic	Wet Granulation	HPMC-K4M, K15M, EC
Ibuprofen	Anti-inflammatory	Wet Granulation	EC, CAP
Metformine HCL	Anti-diabetic	Direct Compression	HPMC-K100M, EC
Propranolol HCL	Beta-adrenergic blocker	Wet Granulation	Locust bean gum, HPMC
Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin, Xanthan gum
Acarbose	Anti-diabetic	Direct Compression	HPMC, Eudragit

Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Ambroxol HCL	Expectorant, Mucolytic	Direct Compression	HPMC-K100M,
Aspirin	Anti-inflammatory	Direct Compression	EC, Eudragit-RS100, S100
Diclofenac Na	Anti-inflammatory	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Diethylcarbamazepine citrate	Anti-filarial	Wet Granulation	Guar gum, HPMC-E15LV
Diltiazem	Ca+2 channel blocker	Direct Compression	HPMC-K100M, K4M, Karaya gum, Locust bean gum, Sod.CMC
Enalpril meleate	ACE inhibitor	Direct Compression	HPMC-K100M, K4M,
Flutamide	Anti-androgen	Direct Compression	HPMC-K4M, Sod.CMC, Guar gum, Xanthan gum
Indomethacin	Anti-inflammatory	Direct Compression	EC, HPMC
Chlorphenarimine meleate	H1 antagonist	Melt-extrusion	Xanthan gum,Chitoson
Losartan potassium	Anti-Hypertensive	Direct Compression	HPMC-K100M, K4M, EC
Metoclopromide	Anti-emetic	Direct Compression	HPMC-K100M, K4M, Eudragit
Naproxen	Morphine antagonist	Direct Compression / Wet Granulation	HPMC, CMC, EC, SSG
Ondansertan	Anti-hypertensive	Direct Compression / Wet Granulation	HPMC-K100M, K4M, K15M
Phenytoin Na	Anti-epileptic	Direct Compression	Tragacanth, Acacia, Guar gum,
Ranitidine HCL	H2 antagonist	Wet Granulation	Chitoson, Carbopol-940
Theophylline	Respiratory depressant	Wet Granulation	Carbopol-934P, HPMC-K100M, K4M,
Tramadol	B2 blocker	Wet Granulation	HPMC-K4M, Karaya gum, Carrageenam gum

Verapemil	Ca+2 channel blocker	Direct Compression	HPMC-K100M, K4M, K15M
Amlodipine	Anti-arrythmatic	Direct Compression	HPMC, EC

CONCLUSION

The focus of this review article has been on the formulation of sustained-release matrix tablets, advantages and disadvantages and various polymers used to design such system. Above discussion concludes that matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design.

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