CONTROLLED RELEASE MATRIX TABLET: A SCIENTIFIC VIEW

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ABSTRACT

In past decade great interest got generated on replacing conventional administration of drug by delivery system which would release effective quantities from a protected supply at a controlled rate over a long period of time. An appropriately designated controlled release drug delivery system can be a major advance towards solving problems concerning targeting of a drug to a specific organ or a tissue and controlling the rate of a drug delivery to the target site. Matrix system are favored because of their simplicity, patient compliance etc, than traditional drug delivery(TDS) which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Developing oral controlled release matrix tablet has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating matrix tablets.

KEYWORDS: Matrix tablet, Controlled release, Polymers.

INTRODUCTION

Oral dosage forms has long been the most popular and convenient route of drug delivery various types of modified release formulations have been developed to improve the patient compliance and also clinical efficacy of the drug. The oral dosage form have been demonstrated to improve the therapeutic efficacy by maintaining the steady state drug plasma concentration.

A Matrix tablet is formed when an active pharmaceutical ingredient is homogeneously
dispersed (embedded) in inert material, matrix materials are often swellable hydrophilic or non-swellable hydrophobic polymers. The materials properties affect the rate of drug release through factors including diffusion, permeation and dissolution.

The materials must be widely used in preparing matrix system including both hydrophilic and hydrophobic polymers, commonly available hydrophilic polymers include HPMC, HPC, HEC, xanthum gum, sodium alginate, poly ethyl oxide, cross linked homopolymers, comopolymers and acrylic acid. It is used usually supplied in micronized forms because small particles size is critical to the rapid formulation gelatinous layer on the tablet surface.

The matrix tablet developing for safety and efficient drug delivery system is one of the major challenges in the pharmaceutical industry.

**Objectives**

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral sustain release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate sustain release system for in order to achieve even plasma concentration profile up to 24 hrs.

**Reason for the selection of -API as a model drug**

- Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to sustain the drug release.
- Less risk of dose dumping.
- High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations
- Transport of drug is independent of gastric emptying.
- Bioavailability after oral administration is 20% Silent features to design formulation in sustain release tablets.
- Less inter and intra subject variability
- Drug may reach the site of optimum absorption in areproducible fashion so reproducible bioavailability.
Advantages of matrix tablet

- Easy to manufacture
- Can be made to release high molecular weight compounds
- The use of sustain release formulations avoids the high blood concentration
- Reduce the toxicity by slowing drug absorption
- Minimize the local and systemic side effects
- Minimize drug accumulation with chronic dosing
- Improvement the bioavailability of some drugs
- Versatile, effective and low cost
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods
- Sustain release formulations have the potential to improve the patient compliance
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract
- Improvement in treatment efficacy
- Usage of less total drug
- Improvement of the ability to provide special effects

Disadvantages of matrix tablet

- The remaining matrix must be removed after the drug has been released
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- 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.
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**Type of matrix tablet**
The matrix system can be divided into few categories depending on the type of retarding agents or polymeric materials.
- Hydrophobic matrix system.
- Hydrophilic matrix system.
- Fat-wax matrix system.
- Biodegradable matrix.
- Mineral matrix.

**Mechanism of drug release from matrix tablet**
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.

Derivation of the mathematical model to describe this system involves the following assumptions:
- A pseudo-steady state is maintained during drug release,
- The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,
- The bathing solution provides sink conditions at all times.
- The release behaviour for the system can be mathematically described by the following equation:

\[
dM/dh = Co. dh - Cs/2
\]

Where,
\[
dM = \text{Change in the amount of drug released per unit area}
\]
\[
dh = \text{Change in the thickness of the zone of matrix that has been depleted of drug}
\]
\[
Co = \text{Total amount of drug in a unit volume of matrix}
\]
\[
Cs = \text{Saturated concentration of the drug within the matrix}
\]
Effect of release limiting factor 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[^7]

Biological factors influencing release from matrix tablet

- Biological half-life.
- Absorption.
- Metabolism
- Distribution
- Protein binding
- Margin of safety

Limitations of matrix system

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix based technologies such as layered tablets are required.

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipients in order to achieve release by a continuous leaching of the drug from the inert matrix core. Matrix systems can be divided into three types:

- Monolithic matrix tablets
- Gel forming hydrophilic matrix tablet
- Erodible (hydrophobic) matrix tablet
Methods of preparation

Direct compression
In this process powdered materials are compressed directly without changing the properties of the drug like physical and chemical properties.

Wet granulation
In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant and disintegrant to produce “running powder” tablets are compressed using a single-punch tablet compression machine.

Melt granulation
In this process use of a substance, which melts at relatively low temperature. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binders were tried by using melt granulation technique.

Hot melt extrusion process
In the hot melt extrusion process, a mixture of active ingredients, the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw.

The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

Polymers used in matrix tablets
a) Hydrogels
Polyhydroxyethylmethacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Crosslinked polyvinyl pyrrolidone(PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).

b) Soluble polymers
Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

c) Biodegradable polymers
Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides,
Polyorthoesters

d) Non-biodegradable polymers
Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)
e) Mucoadhesive polymers
Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
f) Natural polymers in sustained release drug delivery
Xanthum Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan

Below table shows the drug to be formulated as the matrix tablets with polymers and methods used for its preparations:

Table 1: Drugs to be formulated as the matrix tablets with polymers and methods used for its preparations.

<table>
<thead>
<tr>
<th>Drugs used</th>
<th>Category</th>
<th>Method used</th>
<th>Polymer used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Anti-viral</td>
<td>Direct compression</td>
<td>Hpmc-k4m, carbopol-934, ec</td>
</tr>
<tr>
<td>Venlafexine</td>
<td>Anti-depressant</td>
<td>Wet granulation</td>
<td>Beeswax, caranuaba wax</td>
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<tr>
<td>Domperidone</td>
<td>Anti- emetic</td>
<td>Wet granulation</td>
<td>Hpmc-k4m, carbopol-934</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>Alfa-adrenergic agonist</td>
<td>Direct compression</td>
<td>Hpmc-k15m, eudragit-rspo</td>
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<tr>
<td>Rasagiline mesylate</td>
<td>Anti parkinson</td>
<td>Wet granulation</td>
<td>Hpmc-k4m, hpmc-k15m, ec</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Anti-inflammatory</td>
<td>Wet granulation</td>
<td>Ec, cap</td>
</tr>
<tr>
<td>Metformin hcl</td>
<td>Anti-diabetic</td>
<td>Direct compression</td>
<td>Hpmc-k100m, ec</td>
</tr>
<tr>
<td>Propranolol hcl</td>
<td>Beta-adrenergic blocker</td>
<td>Wet granulation</td>
<td>Locust bean gum, hpmc</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Anti-diuretic</td>
<td>Direct compression</td>
<td>Guar gum, pectin, xanthan gum</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Anti-diabetic</td>
<td>Direct compression</td>
<td>Hpmc, eudragit</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>Anti-inflammatory</td>
<td>Wet granulation</td>
<td>Hpmc-k4m,k15m, k100m,e15,ec, guar Gum</td>
</tr>
<tr>
<td>Ambroxol hcl</td>
<td>Expectorant, mucolytic</td>
<td>Direct compression</td>
<td>Hpmc-k100m,</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Anti-inflammatory</td>
<td>Direct compression</td>
<td>Ec, eudragit-rs100, s100</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>Anti-inflammatory</td>
<td>Wet granulation</td>
<td>Chitoson, ec, hpmcp, hpmc</td>
</tr>
<tr>
<td>Diethylcarbamazepine</td>
<td>Anti-filarial</td>
<td>Wet granulation</td>
<td>Guar gum, hpmc-e15lv</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Ca²⁺ channel blocker</td>
<td>Direct compression</td>
<td>Hpmc-k100m, hpmc-k4m, karaya gum, Locust bean gum, sod.cmc</td>
</tr>
<tr>
<td>Enalpril meleate</td>
<td>Ace inhibitor</td>
<td>Direct compression</td>
<td>Hpmc-k100m,hpmc k4m,</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Anti-inflammatory</td>
<td>Direct compression</td>
<td>Ec, hpmc</td>
</tr>
<tr>
<td>Drug</td>
<td>Action</td>
<td>Formulation</td>
<td>Excipients</td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td>Chlorpheniramine meleate</td>
<td>H1 antagonist</td>
<td>Melt-extrusion</td>
<td>Xanthan gum, chitoson</td>
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<tr>
<td>Losartan potassium</td>
<td>Anti-hypertensive</td>
<td>Direct compression</td>
<td>Hpmc-k100m, hpmc-k4m, eudragit-Rspop</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Anti-fungal</td>
<td>Direct compression / wet granulation</td>
<td>Pectin, hpmc</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Morphine antagonist</td>
<td>Direct compression</td>
<td>Hpmc-k100m, hpmc-k15m, pvp</td>
</tr>
<tr>
<td>Ondansertan</td>
<td>Anti-hypertensive</td>
<td>Wet granulation</td>
<td>Hpmc-k100m, hpmc-k4m, hpmc-K15m</td>
</tr>
<tr>
<td>Ranitidine hcl</td>
<td>H2 antagonist</td>
<td>Direct compression</td>
<td>Chitoson, carbopol-940</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Respiratory depressant</td>
<td>Direct compression</td>
<td>Carbopol-934p, hpmc-k100m, hpmc-K4m, hpmc-k15m, ec</td>
</tr>
</tbody>
</table>

**Evaluation of matrix tablets**

- **Weight variation:** Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.

- **Hardness:** Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.

- **Friability:** The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.

- **Thickness:** The thicknesses of tablets were determined using micrometer screw gauge.

- **Content uniformity:** Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.

- Kinetic Studies

- **In vitro dissolution study:** Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 37°C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time.

- **Stability studies:** Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.

- **In vivo methods:** Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are:-
a. Clinical response  
b. Blood level data  
c. Urinary excretion studies  
d. Nutritional studies.  
e. Toxicity studies  
f. Radioactive tracer techniques  

CONCLUSION  
The focus of this review article has been on the formulation of 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, matrix tablets trends towards the optimization of the dosage form design.  

REFERENCE  

