Design and In Vitro Evaluation Of Controlled Release Matrix Tablets Of Prazosin

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ABSTRACT

Treatment of hypertension with conventional dosage forms is not effective as the drugs do not reach the site of action in appropriate concentration and it is also requiring dosing. Thus, an effective and safe therapy of hypertension disorder using specific drug delivery system is a challenging task to the pharmaceutical technologists. Most commonly used method of modulating the drug release is to include it in a matrix system, because of their flexibility, hydrophilic polymer matrix system is widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. In present study we have prepared matrix tablet formulations using Prazosin as model drug and Ethyl Cellulose, Two grades of Hydroxy propyl methyl cellulose- HPMC-K4M & HPMC-K100M as polymers in different ratios. The developed matrix tablets were evaluated for different physical chemical evaluations like drug content, hardness, friability, swelling index etc. All the formulations had shown the results within prescribed limits. The In vitro drug release study indicates that formulation F7 containing EC, HPMC K100M in 1:2 ratio shown good release pattern for 14 hours compare to other formulations. The short-term stability study proven no change in the formulation upon ageing and it indicates good stability.

Keywords: Prazosin, Matrix tablets, Ethyl Cellulose and HPMC-K4M & K100M.
INTRODUCTION

Matrix drug delivery systems:
The dictionary meaning of matrix is a) Content or framework and b) The rock in which fossils or pebbles are embedded. The active pharmaceutical ingredient is embedded or entrapped in a network formed by polymers called matrix. Within the scope of this general term, there are a variety of controlled-release devices. Included among these are dissolved systems that are prepared from matrix containing a drug at or below its saturation solubility in the polymer and dispersed systems that contain the drug within a matrix at a concentration that greatly exceeds the saturation solubility of the drug in the polymer. Other controlled-release devices include reservoir dispersed matrix systems, which are analogous to the dispersed system except that barrier layer is present at the surface of such device.

Mechanism of drug release from matrix-drug delivery system.

Dissolution of the drug on the surface

Depletion of the drug closer to the surface by diffusion

Elution of the drug present in the next layer by diffusion through the matrix

The release of a drug from matrix devices is governed mainly by diffusion of the solute within the matrix phase. The development of appropriate release-rate equation is generated via Fick’s first law of diffusion.

Matrix Tablets.
In these systems the drug is homogenously dispersed in the polymeric matrix, mixed along with other excipients and compressed into tablets. A variety of polymers like hydrophilic, hydrophobic, waxes, gums etc. could be incorporated alone or in combination in order to prolong the drug release.

There are three types of matrix tablets i.e.1. Hydrophilic matrices
2. Fat-wax matrices
3. Plastic matrices

Examples of different types of matrices

| Types of matrices            | Examples                                          |
|------------------------------|---------------------------------------------------|
| Hydrophobic matrices         | Polyvinylchloride, Ethyl cellulose, Methyl \copolymers, polyethylene |
| (Plastic matrices)           |                                                   |
Lipid matrices | Stearyl alcohol, stearic acid, triglycerides, carnauba wax, polyethylene glycol
---|---
Hydrophilic matrices | Methylcellulose, Carboxy polymethylene, hydroxyl propyl methylcellulose (HPMC).

Requirements of matrix material:
The matrix materials must comply with the following conditions
- They must be non-toxic.
- They must be completely inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices when compressed either directly or more often granules prepared by the addition of binding agent.

a) **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 controlled release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Controlled release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compactable 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.

b) **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 release formulations.

c) **Hydrophilic Matrices:**
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 drug with gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

**Prazosin**
Prazosin acts by inhibiting the postsynaptic alpha (1)-adrenoceptors on vascular smooth muscle. This inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation.

Disposition in the body

Animal studies indicate that prazosin hydrochloride is extensively metabolized, primarily by demethylation and conjugation, and excreted mainly via bile and faeces. Less extensive human studies suggest similar metabolism and excretion in man.

Materials and Method

Prazosin is obtained from Sun pharmaceuticals Mumbai. HPMC K4M, K100M is obtained from Rolex chemical industries Mumbai. Ethyl cellulose and Methanol is obtained from Karnataka fine chem. Bangalore. Aerosil is obtained from Evonik Degussa Mumbai. Dibasic Calcium phosphate anhydrate is obtained from SD Fine Chem Ltd Mumbai. Talc, Magnesium Stearate, Sodium hydroxide, Potassium chloride solution, Hydrochloric acid, Disodium hydrogen phosphate is obtained from SD Fine Chem Ltd Mumbai.

Preparation of the standard calibration curves of Prazosin

Standard calibration curves of Prazosin in pH 1.2 buffer and volume was made up to 100ml in volumetric flask using pH 1.2 PBS. From this stock solution aliquots of 2.5, 5, 7.5, 10, 12.5 and 15ml were withdrawn and diluted up to 50ml in volumetric flask to give concentration of 5, 10, 15, 20, 25 and 30µg/ml. Absorption of each solution was measured at 329 nm using Evolution 201 UV spectrophotometer and pH 1.2 buffer as a reference standard.

Standard calibration curve of Prazosin in Simulated intestinal fluid (SIF) pH 6.8

Prazosin was dissolved in 20 ml SIF (pH 6.8 buffer) and volume was made up to 100ml in volumetric flask using SIF (pH 6.8 buffer). From this stock solution aliquots of 2.5, 5, 7.5, 10, 12.5 and 15ml were withdrawn and diluted up to 50ml in volumetric flask to give concentrations of 5, 10, 15, 20, 25 and 30µg/ml. Absorption of each solution was measured at 329nm using Evolution 201UV/V is a double beam spectrophotometer and SIF phosphate buffer (pH 6.8) as a reference standard.

Preparation of matrix tablets of Prazosin:

Matrix tablet containing 12mg of Prazosin along with various amounts of polymers such as HPMC (Various grades), Ethyl cellulose, and other excipients (such as magnesium stearate, dibasic calcium phosphate anhydrate and aerosil) were used and tablets were prepared by direct compression technique. Ethyl cellulose and HPMC were passed through mesh No.40. In the first step, the drug and ingredients with the exception of magnesium stearate was blended in a V-Cone
blender for 5 minutes. Then magnesium stearate was added and formulation was mixed for an additional 2 minutes. Desired amount of blend was directly compressed into tablets using rotary tablet compression machine. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate.

All the preparations were stored in airtight containers at room temperature for further studies.

**Composition of matrix tablets of Prazosin.**

| Systems                  | Ratio       | Formulation code |
|--------------------------|-------------|------------------|
| DRUG: EC: HPMC K4M       | 1:1.5:2     | F1               |
| DRUG: EC: HPMC K4M       | 1:1.5:2.5   | F2               |
| DRUG: EC: HPMC K4M       | 1:1.5:3     | F3               |
| DRUG: EC: HPMC K4M       | 1:1.5:3.5   | F4               |
| DRUG: EC: HPMC K100M     | 1:1.5:2     | F5               |
| DRUG: EC: HPMC K100M     | 1:1.5:2.5   | F6               |
| DRUG: EC: HPMC K100M     | 1:1.5:3.5   | F7               |
| DRUG: EC: HPMC K100M     | 1:1.5:3.5   | F8               |

**Formulation of matrix tablets of Prazosin**

A total of 8 formulations had been prepared and each formulation type contains 12mg of drug, common filler such as dibasic calcium phosphate anhydrate. The formulae are as follows:

Formulation of matrix tablets containing HPMC K4M, HPMC K100M and Ethyl cellulose as Sustained release polymer

**Formulation of matrix tablets**

| Ingredient (mg)      | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|----------------------|----|----|----|----|----|----|----|----|
| Prazosin             | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Ethyl Cellulose      | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| HPMC K4M             | 24 | 30 | 36 | 42 | ---| ---| ---| ---|
| HPMC K100M           | ---| ---| ---| ---| 24 | 30 | 36 | 42 |
| Dibasic Calcium Phosphate | 93 | 87 | 81 | 75 | 93 | 87 | 81 | 75 |
| Magnesium Stearate   | 1.5| 1.5| 1.5| 1.5| 1.5| 1.5| 1.5| 1.5|
| Aerosil              | 1.5| 1.5| 1.5| 1.5| 1.5| 1.5| 1.5| 1.5|

**EVALUATION**

**Micrometric properties.**

a) **Angle of repose.**

The angle of repose of powder was determined by the fixed funnel method. The accurately weighed powder was taken in a funnel. The powder was allowed to flow through funnel freely onto the surface in such a way that tip of funnel does not touch the heap of powder. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

\[
\tan \theta = \frac{h}{r}
\]
b) **Bulk density.**
Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 100ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted and calculated by using formulas.

\[
\text{Bulk density} = \frac{\text{weight of powder}}{\text{bulk volume of powder}}
\]

Tapped density=weight of powder/tapped volume of powder

c) **Compressibility index and Hausner’s ratio.**
The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the hausner’s ratio are determined by measuring both the bulk volume and the tapped volume of a powder.

\[
\text{Compressibility Index (\%)} = \frac{(\text{TBD} – \text{LBD}) \times 100}{\text{TBD}}
\]

\[
\text{Hausner’s ratio} = \frac{\text{TBD}}{\text{LBD}}
\]

II) **Physicochemical parameters:**

a) **Tablet hardness**
The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.

b) **Tablet thickness**
Thichness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauge on 3 randomly selected samples.

c) **Friability**
Friability is the measure of tablet strength. Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 min dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, the tablets were re-weighed and the percentage loss in tablet weight was determined.

\[
\% \text{ Loss} = \frac{\text{initial wt. of tablets} – \text{final wt. of tablets}}{\text{initial wt. of tablets}} \times 100
\]

d) **Weight variation**
Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated.
e) Uniformity of drug content

Ten tablets were weighed and average weight is calculated. All tablets were crushed and Powder weight equivalent to 12 mg drug was dissolved in phosphate buffer pH 6.8 and the volume was made up to 10 ml with phosphate buffer pH 6.8 from the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with phosphate Buffer pH 6.8. Further 0.1 ml pipetted and made up to 10 ml with phosphate buffer pH 6.8. Solution was filtered and absorbance was measured spectrophotometrically at 329 nm against phosphate buffer pH as a blank. Amount of drug present in one tablet was calculated.

g) Drug release kinetic from the sustained release matrix tablet dosage forms

Drug release from matrices usually implies water penetration in the matrix, hydration, swelling, and diffusion of the dissolved drug. Several kinetics models relating to the drug release from matrices, selected from the most important mathematical models done here. However, it is worth to mention that the release mechanism of a drug would depend on the dosage from selected, pH, nature of the drug and polymer used.

h) Stability studies

Stability testing of drug products begins as a part of drug discovery and ends with the Demise of the compound or commercial product. The stability studies were carried out of the most satisfactory formulation. The most Satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 40±2°C/75±5% RH for three months. At the end of studies, samples were analyzed for the drug content and

g) Swelling characteristics of matrix tablets

The swelling properties of matrix tablets were determined by placing the tablet in the dissolution medium at 37±0.5°C.

The tablets were removed periodically from dissolution medium. After draining off the free water from the surfaces, they were measured for weight gain. Swelling characteristics of matrix tablets were expressed in terms of percentage water uptake (WP %) it is calculated by using the equation, 

\[ \text{WU\%} = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of tablet}}{\text{Initial wt. of tablet}} \times 100 \]

Uniformity of drug content.

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 329nm after suitable dilution using a UV/Visible Spectrophotometer.

h) In-vitro Dissolution studies
The developed formulations of Prazosin were subjected in vitro dissolution studies using USP-Type I dissolution apparatus with a paddle speed of 50rpm. The dissolution study was carried out in 900ml of two different dissolution media i.e. first 2hrs in pH 6.8 buffer maintained at 37±0.5°C. At suitable time interval, 10ml sample were withdrawn and replaced with equivalent amount of fresh medium to maintain sink conditions. Samples withdrawn were filtered and analyzed at 329nm using a UV spectrophotometer. After analyzing the drug content in the dissolution samples plot of cumulative percentage of drug release versus time was plotted.

Figure 1 Standard plot of Prazosin

Figure 2 FTIR of pure Prazosin
Figure 3 FTIR of pure Prazosin with excipients

Table 1 Pre-compressive parameters of prepared formulations

| Formulation Code | Angle of repose | Loose Bulk density (g/cc) | Tapped Density (g/cc) | Hausner’s ratio | Carr’s index (%) | Drug content (%) |
|------------------|-----------------|---------------------------|-----------------------|----------------|-----------------|-----------------|
| F1               | 23°.26'         | 0.4457±0.005               | 0.5903±0.0041         | 1.182±0.023    | 18.367±1.81    | 92.87           |
| F2               | 22°.36'±0.015   | 0.4367±0.0068              | 0.5832±0.0045         | 1.198±0.05     | 16.396±1.41    | 90.24           |
| F3               | 22°.33'±0.020   | 0.441±0.0037                | 0.5886±0.005          | 1.206±0.05     | 21.898±1.57    | 94.45           |
| F4               | 24°.36'±0.065   | 0.433±0.0045                | 0.5841±0.005          | 1.227±0.05     | 20.32±0.89     | 89.68           |
| F5               | 21°.91'±0.033   | 0.4323±0.0045               | 0.5886±0.0049         | 1.244±0.04     | 19.516±1.49    | 93.22           |
| F6               | 23°.95'±0.045   | 0.4389±0.005                | 0.6019±0.0052         | 1.186±0.02     | 18.257±1.10    | 91.87           |
| F7               | 26°.07'±0.041   | 0.4345±0.007                | 0.5900±0.0028         | 1.234±0.12     | 19.174±0.89    | 90.02           |
| F8               | 22°.91'±0.041   | 0.4225±0.007                | 0.5803±0.061          | 1.256±0.01     | 20.574±1.05    | 94.58           |

Table 2 Post-compressive parameters of prepared formulations

| Formulation Code | Thickness (nm) | Hardness (Kg/cm²) | Weight variation (% devn.) | Friability (%) |
|------------------|----------------|-------------------|----------------------------|---------------|
| F1               | 3.00±0.18      | 7.36±0.24         | 1.157±0.126                | 0.516±0.092   |
| F2               | 2.97±0.22      | 6.74±0.23         | 1.478±0.216                | 0.384±0.046   |
| F3               | 3.00±0.18      | 7.25±0.23         | 1.534±0.156                | 0.486±0.087   |
| F4               | 3.10±0.20      | 7.34±0.20         | 1.614±0.412                | 0.268±0.028   |
| F5               | 3.00±0.18      | 7.67±0.06         | 1.524±0.624                | 0.387±0.022   |
Table 3 Swelling indices of matrix tablets of Prazosin

| Formula Code | Initial weight (mg) | Final weight (mg) | Swelling Index (%) |
|--------------|---------------------|-------------------|--------------------|
| F1           | 156.21              | 230.47            | 67.77              |
| F2           | 155.34              | 229.54            | 67.67              |
| F3           | 154.89              | 228.43            | 67.80              |
| F4           | 155.11              | 227.82            | 68.80              |
| F5           | 156.14              | 233.45            | 66.88              |
| F6           | 154.98              | 228.67            | 67.76              |
| F7           | 155.27              | 221.23            | 69.95              |
| F8           | 155.21              | 223.23            | 69.52              |

Table 4 Coefficient of determinations for prepared matrix tablets of Prazosin

| Formulation Code | Coefficient of Determined (R²) | Zero Order | First Order | Higuchi square root | Korsmeeyer |
|------------------|--------------------------------|------------|-------------|---------------------|------------|
| F1               | 0.9837                         | 0.9565     | 0.9364      | 0.8196              |
| F2               | 0.9939                         | 0.9287     | 0.9235      | 0.9412              |
| F3               | 0.9930                         | 0.8882     | 0.9122      | 0.8534              |
| F4               | 0.9958                         | 0.9238     | 0.9149      | 0.9050              |
| F5               | 0.9760                         | 0.9726     | 0.9406      | 0.8387              |
| F6               | 0.9952                         | 0.982      | 0.9230      | 0.8633              |
| F7               | 0.9894                         | 0.9624     | 0.9387      | 0.8698              |
| F8               | 0.9953                         | 0.9585     | 0.9244      | 0.8955              |

SUMMARY

In the present investigation, efforts were made to develop controlled release matrix tablets of Prazosin. Physical properties like bulk density, compressibility index and angle of repose were determined. Tablet formulations for Prazosin 12mg matrix tablets were developed using three polymers and were evaluated for pharmacopoeia tests. Tablets were prepared with different concentration of polymers like EC, HPMC, K4M, HPMC, K100M and Sodium alginate in order to optimize one final formula for matrix tablets. Suitable analytic method was developed to estimate the drug content of prazosin using UV-Visible spectroscopy. FT-IR spectra showed no interfere with the excipients used. Direct compression method was used to prepare tablets for matrix tablets in-vitro release was carried out in phosphate buffer solution, pH 6.8 for 12hours using USP type II apparatus at 50rpm. Swelling index and stability studies were performed on optimized formulations of Prazosin 12mg matrix tablets were carried out at 40±2°C and 75±5% RH for one month.

Tablets were evaluated for pharmacopoeia tests and were found to be within the prescribed limits. Drug release from the formulations was found to be zero order. Formulation was found to be
reproducible and stable for one month under accelerate stability condition. Formulation F7 was selected as optimized formulation based on in vitro release profiles. Hence it was concluded that matrix tablets of Prazosin can prepared for uniform release of the dug for treatment of hypertension.

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