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# FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF CAPTOPRIL

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**ABSTRACT**

The main objective of the present work was to develop oral sustained release matrix tablets of water soluble captopril using hydrophilic polymer viz. xanthan gum and chitosan. The granules of captopril were prepared by wet granulation method using PVP as binder. To increase the flowability and compressibility of the granules, and to prevent its adhesion to punch and die, magnesium stearate and talc were added to the granules in 1:2 ratios before punching. The matrix tablets were analyzed for weight variation, hardness, thickness, friability, drug content and were subjected to *in vitro* drug release studies. The *in vitro* drug release of matrix tablet showed that formulation M9 has sustained drug release in compare to other formulation. The controlled drug release is due to increased proportion of polymers. The kinetics of drug release was explained by first order equation followed by Higuchi's model. From the Korsmeyer-peppas study, the n value of the formulations show that the release profile obeys non-fickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism. There was no chemical interaction between drug and polymer as been confirmed by FT-IR studies. Thus, it was concluded that the potential controlled and sustained release matrix tablets could be prepared using optimized amount of hydrophilic polymers such as xanthan gum and chitosan.

**Key words**: Captopril, Xanthan gum, Chitosan, Matrix tablets, Kinetics.

## INTRODUCTION

Oral sustained release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages. Introduction of matrix tablet as sustained release has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. It excludes complex production of procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type of proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form [1].

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years [2]. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration [3-5]. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form [6]. Matrix material such as (HPMC) hydroxyl propyl methyl cellulose, ethyl cellulose, PVP, Guar gum and Xanthan gum [7] are used. The drug release for extended duration, particularly for highly water soluble drug using a hydrophilic matrix system is restricted because of the rapid diffusion of the dissolved drug though the hydrophilic network [8].

Captopril is an orally potent and specific angiotensin converting enzyme inhibitor, it inhibits the conversion of angiotensin-I to angiotensin-II. It is used therapeutically to treat hypertension and heart failure. Captopril was chosen as a model drug due to its high water solubility. It was designed to obtain enhanced therapeutic efficacy of this drug through the provision of constant rate input and maintenance of steady state blood levels. The pharmacokinetic studies have established that it has relatively short half life of 1.7 – 1.9 h and 70% of oral bioavilability. It is mainly prescribed for patients who are chronically ill and require long term therapeutic agents. The dose required is 37.5-75mg to be taken three times a day in divided doses. It is considered as an ideal drug candidate for the design of oral controlled release dosage form [9-10].

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Sustained release formulation that would maintain plasma levels of drug for 8 to 12 hours might be sufficient for once daily dosing for captopril. Sustained release are needed for captopril to prolong its duration of action and to improve patient compliance.

Xanthan gum is a commercial hydrophilic polymer, secreted from *Xanthomonas campestris* (a Gram-negative, yellow-pigmented bacterium). In earlier studies, the performance of xanthan gum as a potential excipient for oral controlled release tablet dosage forms was thoroughly evaluated and characterized [11]. Chitosan is a natural polysaccharide obtained from the deacetylated derivative of naturally occurring chitin. Chitosan has been extensively examined in the pharmaceutical industry for its potential use in the development of controlled drug delivery systems [12-13].

The aim of this paper was to investigate the role of hydrophilic polymers such as xanthan gum and chitosan in matrix tablets to provide sustained therapeutic effect of captopril. The matrix tablets were prepared and evaluated for different physiochemical parameters such as weight variation, thickness, hardness, friability, drug content and *in vitro* release. The release kinetics and mechanism of drug release were also investigated by using various release kinetics model equations.

## MATERIALS AND METHODS

### Materials

Captopril was obtained as a gift sample from Akums Pharmaceutical Ltd., Haridwar, India. Chitosan, xanthan gum, MCC, talc and magnesium sterate were purchased and of analytical or reagent grade.

### Methods

### Preparation of Captopril matrix tablets

Matrix tablets of Captopril were prepared by the wet granulation method. A mixture of talc and magnesium stearate (2:1 ratio) was used as lubricant and MCC was used as diluent. Xanthan gum and chitosan were included in the formulation in various proportions. Nine matrix formulations were prepared with xanthan gum and chitosan and were coded as M1 to M9, respectively. The composition of formulations used in the study containing 50 mg of captopril in each case is shown in Table 1. In all the formulations, xanthan gum and chitosan was sieved (<250 µm) separately and mixed with captopril and MCC (<250 µm). The powder mix was granulated with 10% PVP solution in the same mixer. The wet mass was passed through a mesh number 18 and the granules were dried at 50 °C for 2 hr in a tray drier. The dried granules were lubricated with a mixture of talc and magnesium sterate (2:1 ratio). Compression was done on 16 stations multiple tablet compression machine (Cadmach, Ahmedabad, India) using 8 mm flat faced punches.

## EVALUATION OF GRANULES

### Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [14]:

$\tan \theta = h/r$

Where, h and r are the height and radius of the granules cone.

### Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. The bulk density of granules depends mainly on the particle size, particle shape and the trend of particles to adhere to one another. Mathematically bulk density can be represented by Equation [15-16]:

$$\text{Bulk Density } (\rho) = \frac{\text{Weight of powder (w)}}{\text{Bulk volume } (V_b)}$$

Granules were transferred into a 100 ml graduated measuring cylinder and bulk volume was read. Bulk density is then obtained by dividing the weight of the sample in grams by the final volume in $cm^3$ of the sample present in the cylinder.

### Tapped density

Tapped density is determined by mechanically tapping a graduated measuring cylinder containing granules. Mathematically tapped density can be represented by Equation [17]:

$$\text{Tapped Density } (\rho t) = \frac{\text{Weight of powder (w)}}{\text{Tapped volume (V)}}$$

Tapped density of granules was determined by placing a graduated cylinder into a mechanical tapper apparatus (Electrolab, U.S.P). After observing the volume, the cylinder was mechanically tapped for 100 times or until the granules achieves a constant volume.

### Compressibilty index (Carr's index)

Compressibility index is used as an important parameter to determine the flow behaviour of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by Equation[18]:

$$\text{Carr's index } (\%) = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

### Hausner's ratio

Hausner's ratio is used to predict the flowability of the powders. This method is similar to compressibility index. Hausner ratio can be represented by Equation [18]:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

## EVALUATION OF TABLET

### Weight variation

All prepared matrix tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets were randomly selected from each batch individually weigh, to evaluate weight variation among tablets and standard deviation was calculated [19-20].

### Friability

Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Roche friabilator with triplicate readings [19-20].

### Hardness

Hardness of all batches was determined using Digital Force Gauge (Model:EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets[19-20]. The hardness is measured in $kg/cm^2$.

### Thickness

Thickness was measured by digital vernier caliper as per USP XXIV monograph. The readings were carried out in triplicate and average value was noted.

### Drug content

The tablets were powdered, and 50 mg equivalent weight of Captopril in tablet powder was accurately weighted and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 min. then, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed at 203 nm using UV-visible spectrophotometer (Shimadzu UV-1700, Japan). The drug content of the each sample was estimated from their standard curve [21].

### *In vitro* drug release studies

*In vitro* drug release studies of matrix tablets were done in eight-station USP XXII type II dissolution test apparatus( Electro lab TDT-08, India) at 37°C (± 0.5°C) and 50 rpm speed in 900 mL of dissolution medium. Dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 8 hours. Five millitre (5ml) samples were taken by filtration at predetermined time intervals and after each sampling the volume of dissolution medium was replaced with 5ml of phosphate buffer (pH 6.8). The absorbance of samples were measured at 203 nm using UV-Visible double beam spectrophotometer (Shimadzu UV-1700, Japan) and cumulative percentage drug release was calculated.

### Mathematical modeling

The release profile of the drug obtained was analysed using different kinetic models (Table-2) such as zero order, first order, Higuchi and Korsmeyer- Peppas model in order to evaluate the release mechanism from the matrices [22].

### FT-IR *Studies* (*Fourier Transform Infrared*)

The FT-IR spectrum of pure captopril and powdered sample of matrix tablets. Infrared spectrum was taken (Shimadzu FT-IR system, Japan) by scanning the sample in potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually to detect drug-excipients interaction.

### Stability Studies

Stability study was carried out according to ICH guidelines at 40 ± $2^0$ C, 75 % RH for three months by storing the samples in stability chamber to observe the effect of temperature and relative humidity on optimized formulation

## RESULT AND DISCUSSION

The granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table 3. Angle of repose was in the range of 26.49±3.15 to 30.53±0.61 which indicates excellent flow of the granules for all formulations. The bulk density of the powder formulation was in the range of 0.29 ± 0.00 to 0.41± 0.00 g/ml; the tapped density was in the range of 0.33 ± 0.00 to 0.48 ± 0.00 g/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 12.12 ± 0.00 to 14.89 ± 0.00, which indicates excellent flow of the granules for all formulation. Hausner's ratio was found to be in the range of 1.13 ± 0.00 to 1.19 ± 0.00, these values indicate that the prepared granules exhibited good flow properties.

The formulated matrix tablets met the pharmacopoeial requirement of uniformity of weight. All the tablets conformed to the requirement of assay, as per USP. Hardness, percentage friability and thickness was all within acceptable limits as in Table 4.

### *In-vitro* dissolution studies

Drug release studies were carried out in pH 1.2 (0.1N HCl) for 2 hrs and the pH of the media was raised to pH 6.8 for remaining 6 hrs. The percentage drug release of all formulations after 8 hours using xanthan gum and chitosan as polymer in different proportion was found to be 96.14% (M1), 93.80% (M2), 81.10% (M3), 85.45% (M4), 76.71% (M5), 74.78% (M6), 73.51% (M7), 76.33% (M8) and 72.71% (M9). It was found that the cumulative percentage drug release of the formulation M1 was more than other formulation upto M8 and M9. The cumulative percentage of drug release in the formulation M9 showed controlled release than other formulation. The polymer

concentration played a major role in drug release. At higher concentration of the polymer, the drug release was prolonged than the lower concentration of the polymer. The controlled drug release is due to increased proportion of polymers. The graphical representation data of the captopril matrix tablet formulations with polymer is shown in Figure 1.

**Drug release kinetics**

The dissolution mechanism was characterised by using different release models. The mean correlation co-efficient ($R^2$) was used as an indicator of the best fitting for each of the models considered. The mean correlation co-efficient for zero order kinetics, first order kinetics and Higuchi model was shown in Table 5. The mean correlation co-efficient with all matrix formulations for first order release kinetics were found slightly higher ($R^2$ = 0.8805 – 0.9851) when compared to those of zero order release kinetics ($R^2$ = 0.8103 – 0.9274) indicating that the drug release from all the formulations followed first order kinetics followed by higuchi's model ($R^2$ = 0.9093 – 0.9310). The regression coefficient obtained for formulation M1 to M9 korsmeyer-peppas kinetics were found to be higher ($R^2$ = 0.9171 – 0.9945) when compared with others kinetic model (first order, zero order, higuchi).

By using korsmeyer model, if n = less than 0.45 it is Fickian diffusion, if n = 0.45-0.89 it is non-Fickian transport [23]. The result of all the formulations showed 'n' values between 0.4909-0.7612. It showed that all the formulations follow non- Fickian transport mechanism and also follow the mechanism of both diffusion and erosion (Table 5).

**FT-IR Studies**

FT-IR Spectroscopy was used as a means of studying drug excipients interaction. The FT-IR spectra of captopril exhibits principle absorption peak at 1747.39 $cm^{-1}$ due to C=O (carboxylic), 1589.23 $cm^{-1}$ due to C=O (amide) stretching, 1380.94 $cm^{-1}$ due to $CH_3$ bending, 1245.93 $cm^{-1}$ due to C-N stretching and 2565.15 $cm^{-1}$ due to S-H stretching of pure drug.The spectra of pure drug and powdered sample of matrix tablets shown in the Figure 2. No change in peak shows that there was no interaction between drug and polymers.

**Stability studies**

The stability studies indicated that matrix tablets, after storing at 40±2ºC/75±5% RH for 3 months showed no significant changes either in physical appearance, drug content and *in vitro* dissolution studies.

**Table 1. Composition of sustained release matrix tablet of captopril***

| Ingredient | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 |
|---|---|---|---|---|---|---|---|---|---|
| **Captopril** | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| **Xanthan gum** | 30 | 30 | 30 | 40 | 40 | 40 | 50 | 50 | 50 |
| **Chitosan** | 30 | 40 | 50 | 30 | 40 | 50 | 30 | 40 | 50 |
| **PVP** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **MCC** | 64 | 54 | 44 | 54 | 44 | 34 | 44 | 34 | 24 |
| **Talc** | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Mg. sterate** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Total** | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

* all weights in mg.

**Table 2. Mathematical models used to describe drug release kinetics**

| | |
|---|---|
| Zero order | $Q = K_o t$ |
| First order | $\ln Q_1 = \ln Q_o - K_1 t$ |
| Higuchi | $Q = K_H^{½}$ |
| Korsenmeyer-Peppas | $Q = K_p t^n$ |

**Table 3. Flow properties of matrix granules***

| Formulation | Angle of repose (θ) | Bulk density (g/ml) | Tapped density (g/ml) | Compressibilty index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| M1 | 26.74±1.41 | 0.30 ± 0.00 | 0.35 ± 0.00 | 14.28 ± 0.00 | 1.16 ± 0.00 |
| M2 | 30.01±0.85 | 0.29 ± 0.00 | 0.33 ± 0.00 | 12.12 ± 0.00 | 1.13 ± 0.00 |
| M3 | 29.83±0.87 | 0.33 ± 0.00 | 0.38 ± 0.00 | 13.15 ± 0.00 | 1.15 ± 0.00 |
| M4 | 30.53±0.61 | 0.41 ± 0.00 | 0.48 ± 0.00 | 14.58 ± 0.00 | 1.17 ± 0.00 |
| M5 | 27.54±2.05 | 0.40 ± 0.00 | 0.46 ± 0.00 | 13.04 ± 0.00 | 1.15 ± 0.00 |
| M6 | 28.15±1.76 | 0.31 ± 0.00 | 0.36 ± 0.00 | 13.88 ± 0.00 | 1.16 ± 0.00 |
| M7 | 26.49±3.15 | 0.40 ± 0.00 | 0.47 ± 0.00 | 14.89 ± 0.00 | 1.17 ± 0.00 |
| M8 | 27.57±1.53 | 0.36 ± 0.00 | 0.43 ± 0.00 | 16.27 ± 0.00 | 1.19 ± 0.00 |
| M9 | 27.76±2.42 | 0.36 ± 0.00 | 0.42 ± 0.00 | 14.28 ± 0.00 | 1.16 ± 0.00 |

*All values are expressed as mean± SD, n=3.

**Table 4. Physico-chemical characterization of Captopril matrix tablets (Mean ± SD)**

| Formulation | Weight variation (mg) | Thickness (mm) | Hardness (Kg/cm$^2$) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| M1 | 200.00 ± 0.50 | 4.19 ± 0.01 | 5.13 ± 0.15 | 0.402 ± 0.10 | 99.81 ± 0.31 |
| M2 | 200.83 ± 1.04 | 4.20 ± 0.01 | 5.00 ± 0.17 | 0.567 ± 0.23 | 99.69 ± 0.28 |
| M3 | 201.50 ± 1.50 | 4.19 ± 0.01 | 5.23 ± 0.20 | 0.555 ± 0.07 | 99.39 ± 0.44 |
| M4 | 201.00 ± 1.50 | 4.18 ± 0.01 | 5.33 ± 0.23 | 0.539 ± 0.17 | 98.67 ± 0.52 |
| M5 | 201.66 ± 2.02 | 4.19 ± 0.00 | 5.20 ± 0.1 | 0.645 ± 0.05 | 99.11 ± 0.19 |
| M6 | 200.33 ± 0.57 | 4.21± 0.02 | 5.36 ± 0.30 | 0.566 ± 0.09 | 100.43 ± 2.37 |
| M7 | 200.50 ± 0.86 | 4.2 ± 0.01 | 5.63 ± 0.37 | 0.518 ± 0.15 | 98.96 ± 0.05 |
| M8 | 202.50 ± 1.32 | 4.18± 0.00 | 5.46 ± 0.37 | 0.572 ± 0.12 | 98.9 ± 0.66 |
| M9 | 201.50 ± 0.5 | 4.20 ± 0.01 | 5.66 ± 0.61 | 0.526 ± 0.12 | 99.16 ± 0.29 |

**Table 5. Drug release kinetics from different matrix tablets**

| Formulation | Zero order | | First order | | Higuchi | | Korsmeyer-Peppas | | |
|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | k | $R^2$ | k | $R^2$ | K | $R^2$ | n | k |
| **M1** | 0.9006 | 0.1733 | 0.9566 | -0.0059 | 0.9094 | 10.1619 | 0.9873 | 0.4909 | 1.9677 |
| **M2** | 0.9274 | 0.1765 | 0.9756 | -0.0054 | 0.9093 | 10.1798 | 0.9895 | 0.5481 | 1.6806 |
| **M3** | 0.9094 | 0.1541 | 0.9851 | -0.0035 | 0.9100 | 9.5653 | 0.9945 | 0.5210 | 1.7140 |
| **M4** | 0.9188 | 0.1582 | 0.9808 | -0.0036 | 0.9127 | 9.6515 | 0.9875 | 0.5686 | 1.5176 |
| **M5** | 0.8609 | 0.1334 | 0.9546 | -0.0026 | 0.9173 | 8.9677 | 0.9506 | 0.5113 | 1.6978 |
| **M6** | 0.8163 | 0.1442 | 0.9169 | -0.0030 | 0.9264 | 9.3868 | 0.9171 | 0.5713 | 1.5276 |
| **M7** | 0.9247 | 0.1493 | 0.9731 | -0.0028 | 0.9152 | 9.3592 | 0.9875 | 0.6312 | 1.2363 |
| **M8** | 0.8760 | 0.1406 | 0.9711 | -0.0028 | 0.9196 | 9.1375 | 0.9413 | 0.5619 | 1.5154 |
| **M9** | 0.8103 | 0.1759 | 0.8805 | -0.0034 | 0.9310 | 9.4473 | 0.9192 | 0.7612 | 0.9839 |

**Figure 1. Cumulative percentage drug release of Captopril matrix tablet formulations**

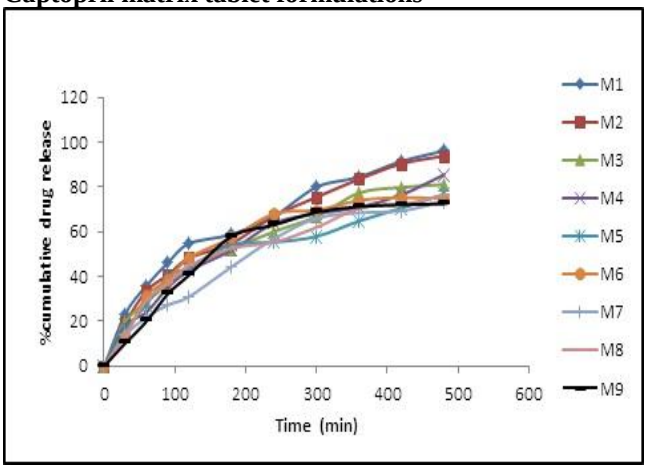
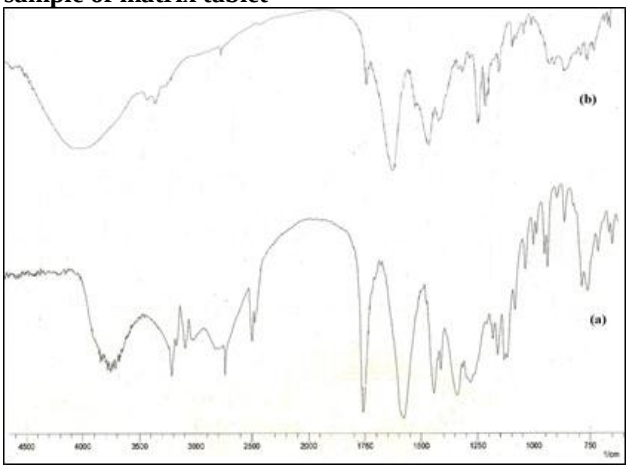



**Figure 2. FT-IR spectra of pure drug (a) and powdered sample of matrix tablet**




## CONCLUSION

The present study carried out to develop oral sustained release formulation of Captopril using the combination of xanthan gum and chitosan. Preparation of matrix tablet by wet granulation technique was found to be more effective in sustaining the release of drug. The weight variation, hardness, friability and drug content of all formulation was found to be acceptable limit with pharmacopoeial standard. Formulation M9 showed sustained drug release in compare to other formulation. The controlled drug release is due to increased proportion of polymers. The kinetics of drug release of optimized formulation was explained by first order equation followed by Higuchi's model. From the Korsmeyer-peppas study, the n value of the formulations show that the release profile obeys non-fickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism. There was no chemical interaction between drug and polymer as been confirmed by FT-IR studies. Thus, it was concluded that the potential controlled and sustained release matrix tablets could be prepared using optimized amount of hydrophilic polymers such as xanthan gum and chitosan.

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