Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 1, 2014

Research Article

DESIGN FABRICATION AND *IN VITRO* EVALUATION Of NOVEL DONUT SHAPED TABLET

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Received: 01 Nov 2013, Revised and Accepted: 23 Nov 2013

ABSTRACT

Objective: To obtain controlled release of captopril in the stomach donut-shaped tablets were designed.

Materials and methods: Donut-shaped tablet were made of different ratios of diluents to polymer or combination of polymers by direct compression method. The core tablet consisted hydroxypropyl methylcellulose, dicalcium hydrogen phosphate, magnesium stearate, talc. *In vitro* study has been performed at acidic dissolution mediums. Stability studies of optimized batches have been performed.

Results: At pH 1.2, optimized batch of tablet made with hydroxypropyl methyl cellulose (HPMC) E15 as binder showed 80% w/w drug release within 6-7h. However maximum average release of 98% w/w was obtained for formulation M4 and had a plateau formation making it the optimum formulation amongst this batch for controlled release. All formulations followed zero order kinetics. Stability studies were not positive for the above mentioned combinations. Drug release kinetics was governed by the erosion process.

Conclusion: donut-shaped tablet is good design to obtain zero-order or nearly zero-order release kinetics and to obtain controlled release of drug.

Keywords: Captopril, Donut-shaped, Coating, Tablet, Erosion, Diffusion.

INTRODUCTION

Oral drug delivery is highly desirable [1]. However there have been considerable limitations associated with formulation of oral drug delivery. So the controlled release of therapeutically active agents is being investigated extensively. But high retention of drug at the site of action, lower tolerability and toxicity due to dose dumping were the point of concern with this mode of delivery. So a novel design of controlled release formulation in the form of donut tablet is being studied so as to overcome the problems associated with traditional controlled release formulation.

The effect of geometry for matrix release of donut tablet has been reported by many researchers. One such approach has been the use of porous disc matrices where by the drug is loaded into the matrices to an amount greater than the solubility limit in the dissolution medium [2]. The Hixson-Crowell cube root law Eq. (i) describing the release from systems where there is a change in surface area and diameter of particles or tablets with the progressive dissolution of matrix as a function of time (Hixon and Crowell, 1931) formed the basis for the formulation of donut tablet [3].

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t \quad (i)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The device comprises of a body having donut-like configuration with a cylindrical hole extending co-axially through the centre of the body. The core material consists of at least one active pharmaceutical agent, one hydrophilic water soluble polymeric carrier [4]. The drug release from this type of tablet follows erosion (square- root time relationship by established Higuchi) mechanism [3]. The surface area is directly proportional to the release of the drug from the tablet upon dissolution. The ratio remains constant even during the tablet dissolution. This is made possible by the fact that there is concomitant increase in the inner surface area with a decrease in outer surface area with progressing time of tablet dissolution. The drug release rate is expressed by the formula as expressed below in equation (ii) [5]:

$$\frac{dM_t}{dt} 2\pi L K_e C_0 (x + y) \text{ (ii)}$$

where Ke, C_0, x and y are the erosion rate constant, initial concentration of the drug in the tablet, the outer radius and the inner radius respectively.

Captopril, an orally angiotensin-converting enzyme (ACE) inhibitor was used as the model drug as it has an outstanding clinical effectiveness in the treatment of essential hypertension and congestive heart failure [7, 8]. However it has a short half – life which necessitated the development of controlled release formulation to maintain relatively constant blood levels for longer duration of time. Nevertheless, the development of oral controlled release formulation of captopril is somewhat difficult due to instability of the drug [9, 10].

The objective of the present study was to formulate and evaluate the most suitable molar combination of the drug and hydrophilic carrier that will maintain uniform drug levels over a sustained period of time.

MATERIALS AND METHOD

Captopril was obtained from Macleods Pharmaceuticals Ltd. Mumbai, India as a gift sample. Hydroxypropylmethyl cellulose (HPMC) and Calcium hydrogen phosphate dihydrate (CaHPO4, 2H2O) were obtained from Loba Chemie (Pvt.) Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade.

Drug - Excipient Compatiblity Studies

Seven samples of 1mg of drug and 1mg of lactose, 1mg of drug and 1 mg of HPMC, 1 mg of drug and 1 mg of magnesium stearate, 1mg of drug and 1 mg of talc, 1mg of drug and 1 mg of DCP, 1 mg of HPMC, DCP, Talc, Magnesium Stearate respectively, 1 mg of DCP, lactose, Talc, magnesium stearate , HPMC respectively were kept in open petridish at room temperature and 40°C & 75% relative humidity (RH) in humidity chamber (Thermolab, Mumbai, India) for 3 months. Colour change, change in state were evaluated at regular interval of 15 days for 3 months. [6]. This seven samples were further considered for ATR- FTIR study.

ATR- FTIR Spectroscopy

Seven samples of 1mg of drug and 1mg of lactose, 1mg of drug and 1 mg of HPMC, 1 mg of drug and 1 mg of magnesium stearate, 1mg of drug and 1 mg of talc, 1mg of drug and 1 mg of DCP, 1 mg of HPMC, DCP, Talc, Magnesium Stearate respectively, 1 mg of DCP, lactose, Talc, magnesium stearate , HPMC respectively were kept in the tray of Specac Golden Gate Type IIIA for carrying out the ATR- FTIR study.

Determination of λmax and development of calibration curve of Captopril

Maximum absorbance (**λmax**) of Captopril were measured at pH 1.2 (hydrochloric acid buffer) using UV/Vis spectrophotometer (JASCO V-

550). Captopril contains one thiol group, which is susceptible to oxidative degradation specifically in aqueous solution. This thiol group forms disulphide bond during degradation. But the degradation is lesser in acidic solution. So aqueous solution is not used for establishing the calibration curve for captopril. Calibration curves were prepared using concentration of 0, 1, 2, 2.5, 5, 10, 20 mcg/ml for pH 1.2. The maximum absorbance (**λmax**) was observed at 203 nm.

Fabrication of the tablet

The ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation. The blend was mixed with talc and magnesium stearate for 2 minutes and kept in desiccators until further used.

Optimization of tablet formulation

400 mg tablets were prepared using ten station specially designed donut punches (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat) having external diameter and internal diameter at 10 mm and 4 mm respectively and the coaxial hole consists of captopril as model drug (25mg), calcium hydrogen phosphate as diluents (170–185 mg), binders, talc as antiadherant (10mg), magnesium stearate as glidant (10 mg). The binders utilized were HPMC E15 (171–183 mg). The formulations were optimized with different binders to diluents ratios shown in Tables 1. The mixtures were then homogeneously blended and subsequently compressed in it. Hardness of the tablets was kept within 3 kg/cm^2 to 6 kg/cm^2.

Table 1: It shows pre-compression parameter of the formulations.

Composition	Weight Per Tablet (mg)			
	MI1	MI2	MI3	MI4
Drug	25	25	25	25
D.C.P	185	180	175	170
HPMC(E-15)	170	175	180	185
Talc	10	10	10	10
Mg-Stearate	10	10	10	10
Total Wt.	400	400	400	400

DCP - Dicalcium Hydrogen Phosphate HPMC - Hydroxy Propyl Methyl Cellulose Mg stearate - Magnesium Stearate MI1, MI2, MI3, MI4- 4 different formulations

Post compression evaluations

Hardness test

Automatic Tablet Hardness Tester (Copley Scientific, Monsanto Hand –Held Tablet Hardness tester) was used to determine the crushing strength. Six tablets were randomly selected from each formulation and the force at which each tablet crushed was recorded.

Friability test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w). The % friability was then calculated by,

Percentage of Friability = 100 (1-w/w_0)

Percentage friability of tablets less than 1% is considered acceptable.

Uniformity of weight

Twenty tablets from each of the formulation were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, Japan). The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Drug Content Uniformity [11]

Ten tablets were crushed into fine powder using mortar and pestle and an amount equivalent to 100 mg of captopril was accurately weighed and transferred to a 100 ml volumetric flask, then 70 ml of buffer pH 1.2 (0.01N HCL) was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper (No.41 having pore size 20 µm) and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for captopril content at 203 nm using a double beam UV/Visible spectrophotometer (Shimadzu 1800, Japan) and 0.01N HCL as blank.

***In-vitro* dissolution studies [12]**

The *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India). The tablets were placed in the 0.1N hydrochloric acid for 7h dissolution study. Then the apparatus was run at 37°C±0.5°C and a rotating speed of the stirrer at 50 rpm in a 900 ml dissolution medium. The 5 ml aliquots were withdrawn at intervals of 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 60 minutes, 120 minutes, 18 minutes 0, 240 minutes, 300 minutes, 360 minutes, 420 minutes, 480 minutes, 540 minutes, 600 minutes, 660 minutes, 720 minutes and replacement was done each time with equal amounts of corresponding fresh dissolution medium maintained at same temperature to maintain sink condition. Each 5 ml aliquot was filtered through Whatman filter paper (No.41 having pore size 20 µm). 5 ml of sample was diluted to 10 ml. The absorbance was measured at 203nm using UV/Vis spectrophotometer (JASCO V-550). Drug concentrations in the sample were determined from standard calibration curve.

RESULT AND DISCUSSION

Drug Compatibility Studies

The five samples remained unchanged when placed in the humidity chamber in open petridish at room temperature and 40°C & 75% relative humidity (RH) for three month. The results have been shown in detail in Table No. 2. An inference can be drawn from this study that the four samples did not undergo any interaction with the drug and hence selected for fabrication of the formulation.

ATR – FTIR Studies

Five samples namely drug and DCP, drug and HPMC, drug and talc, drug and magnesium stearate, talc, HPMC, DCP, magnesium stearate respectively did not show any interaction with Dicalcium hydrogen phosphate, Hydroxyl propyl methyl cellulose, Magnesium stearate and talc in the ATR- FTIR spectroscopy. The result has been described in Fig 1. It is revealed from the ATR- FTIR spectral results that there was no interaction between the drug and the polymers used in the formulation of donut tablet. IR spectra of the main drug showed the major peaks at wave number which was compared with the IR spectra of the drug mixed with polymer mixture required for the formulation of donut tablet. It was observed from the spectra of the pure drug and formulation that there was no remarkable shift in the wavenumbers of the peak not in the intensity of peaks of drug between two graphs which proved that drug and polymer were any devoid of any interaction.

Table 2: It shows change in appearance after keeping 3 months under 40^{0}C and 75% RH

Materials	Initial color	Change of color					
		10 days	20 days	1 month	2 months	4 months	6 months
D + Lactose	Off-white	change	change	change	change	change	Change
D + HPMC	White	No change	No change	No change	No change	No change	No change
D + Mg Stearate	White	No change	No change	No change	No change	No change	No change
D + Talc	White	No change	No change	No change	No change	No change	No change
D + DCP	Off-white	No change	No change	No change	No change	No change	No change
HPMC+ DCP + Talc + Mg Stearate	Off-white	No change	No change	No change	No change	No change	No change
Lactose+ DCP + Talc + Mg Stearate	White	No change	Yellowish	Yellowish	Yellowish	Brownish	Brownish

D= drug, Mg Stearate= Magnesim Stearate

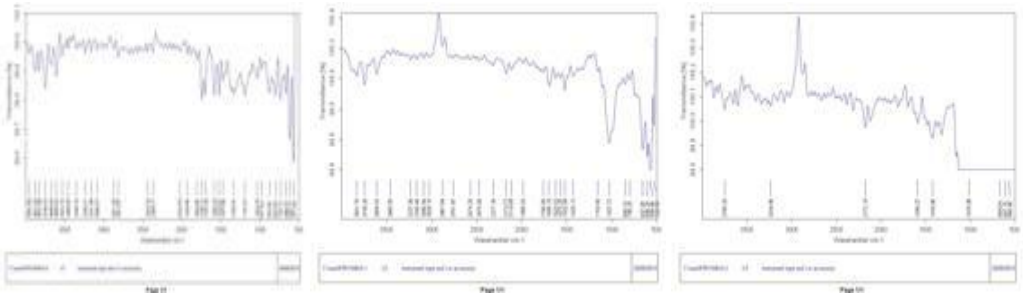

Fig. 1: It shows ATR- FTIR studies of Captopril and Excipients

Assessment of Calibration Curve

UV study of Captopril showed maximum absorbance at 203 nm which showed that the Captopril was pure. When the concentration of captopril was plotted against time, the coefficient of variance R^2= 0.984, thus producing a linear plot. The calibration plot has been shown in Fig 2.

Post Compression parameter Studies

All batches of tablet were prepared under similar condition to prevent processing variables. The average weight of the tablet was 399.7±1.41g, thickness 4.85±.026mm and hardness. The percentage friability of all formulation was 0.19±0.017. The optimum hardness and percentage of friability range indicates good handling properties of the manufactured tablet. From the crushed tablets, when 100mg was taken and assayed, the drug content percentage was in the range 100.2±0.3 and uniform mixing of the prepared tablet was achieved. This has been described in Table No. 3.

***In vitro* dissolution Studies**

In vitro dissolution has been performed using three formulations of the same batch (Fig 4) to confirm their release pattern as shown in Fig 3. In the fig average values were given with corresponding standard deviations. In this study of the four formulations (M1, M2, M3, M4) shown in Table 4 followed zero order release upto 6 h. It was then followed by a plateau phase upto 13 h.

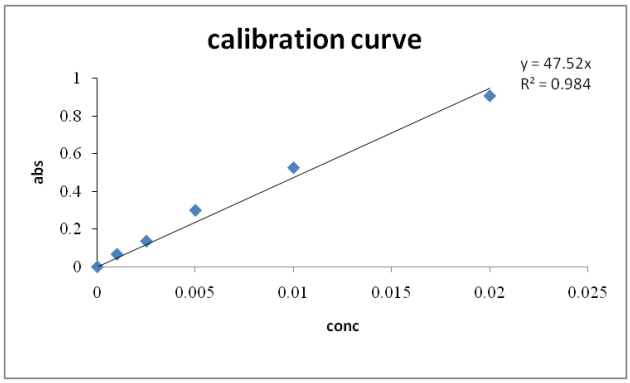

Fig. 2: It shows calibration curve for captopril

Table 3: It shows post-compression parameter of tablets

Code	Dimension		Hardness (kg/cm^2)±S.D	Friability (%)±S.D	Weight Variation(gm) ±S.D	Drug content (%w/w)±S.D
	Diameter (mm)±S.D	Thickness (mm)±S.D				
M1	9.55±0.031	4.84±0.024	5.24±0.061	0.16±0.017	399±1.40	98.3±0.3
M2	9.66±0.026	4.90±0.035	4.87±0.045	0.15±0.018	400±1.38	100.1±0.4
M3	9.51±0.023	4.87±0.022	4.45±0.034	0.20±0.021	400±1.45	100.4±0.2
M4	9.56±0.017	4.92±0.026	4.29±0.032	0.26±0.012	398±1.41	101.3±0.5

It was found that M1 followed zero order as observed from the regression coefficient. Hence this formulation did not follow diffusion mechanism for the release from the matrix. This may be due to the higher concentration of DCP leading to zero order release. Formulations M2 and M3 showed a slight decrease increase in their regression coefficient thus suggesting that the concentration for diffusion controlled release of the drug from the matrix entirely depends on the optimum concentration ration of the DCP and HPMC(45.00, 43.75 and 43.75, 45.00 respectively). The optimum release of 98% (Table 5) in 8 hours is obtained when the percentage of DCP is 42.50 and HPMC (E-15) is 46.25 (M4) and the regression coefficients for the zero order was 0.97 compared to0.94 of the first order plot which showed that the release was independent of concentration .The regression coefficient for Higuchi plot was 0.99, thereby ensuring release by fickian diffusion only which varied as with square root of time. However the plateau phase was maintained upto 10 hours and there was a visible downward movement of the curve. The plateau was due to saturation of drug within the dissolution medium and balance between drug release and degradation of drug due to short half-life.

Table 4: It shows release parameters of captopril controlled release tablet

Code	Zero order	First Order	Higuchi	Korsmeyer Peppas	Hixon Crowell
	r^2	r^2	r^2	r^2	r^2
M1	0.989	0.918	0.927	0.957	0.975
M2	0.987	0.930	0.975	0.986	0.922
M3	0.985	0.896	0.989	0.994	0.893
M4	0.976	0.945	0.991	0.990	0.882

* For zero order 0.89< r^2< .99

Table 5: It shows cumulative percentage release of the four formulations

Code	CPR
M1	86
M2	92
M3	95
M4	98

CPR – Cumulative Percentage Release

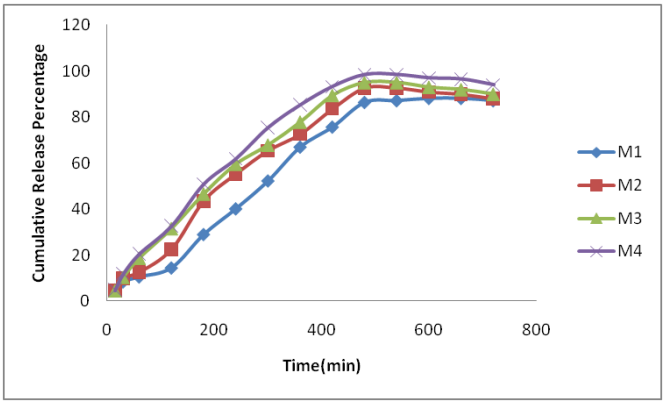

Fig. 3: It shows cumulative percentage release of the four formulations

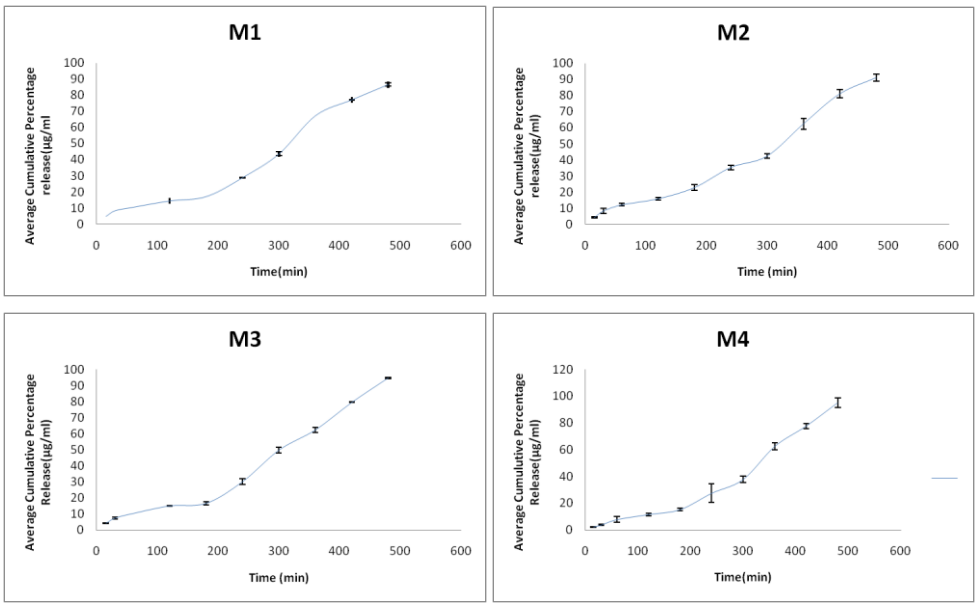

Fig. 4: It shows error bar for M1, M2, M3 and M4

CONCLUSION

From the *in vitro* study of the formulation that nearly 80% of the drug is released in 6 hours in the first three formulations but more than 80% drug is released in the last formulation in 6 hours showing that this formulation is more desirable than the remaining formulations. All the four formulations followed zero order kinetics and therefore independent of initial concentration. The plateau phase was maintained for 13 hours, thereby reducing the dose frequency as well. But the last formulation (M4), having the optimum percentage of DCP and HPMC (E -15), provided the optimum release as well as the plateau formation reduces the dose frequency. Hence it can be concluded that the donut shaped captopril tablet provides a good platform for controlled release of highly water soluble drug especially when the hydrophilic agent is used in optimum ratio thereby providing sustained release of the drug and increases the sustainability of highly water soluble drug with lower half – lives thereby reducing the dose frequency and enhancing patient compliance.

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