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Formulation and Evaluation of Sustained Release Matrix Tablets of Captopril

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Abstract

The present investigation of this study was to develop Captopril SR matrix tablets that provide complete drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain its effect. Drug-polymer compatibility studies by FTIR gave confirmation about their purity and showed no interaction between drug and selected polymers. Various formulations were developed by using release rate controlling and gel-forming polymers like HPMC K100, ethyl cellulose and sodium CMC by direct compression method. Cellulose derivatives have been widely used in the formulation of hydrophilic matrix tablet for sustained drug delivery. From among all the developed formulations, F7 formulation sustained the drug release for longer period of time as compared to other formulations. So, F7 was selected as the best formulation. The best formulation was found to be stable during stability studies for two months. Thus, best formulation satisfied physicochemical parameters and *in vitro* drug release profile requirements for a sustained drug delivery system.

Keywords: Captopril, Sustained release tablet, disintegration, dissolution, HPMC

Introduction

Over recent years, as the expense and complication involved in marketing new entities have increased with accompanying recognition of the therapeutic use of controlled drug delivery, greater attention has been focused on the development of sustained or controlled drug delivery system. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form is a term used to identify drug delivery system that is designed to achieve the prolonged therapeutic effect by continuously releasing medication over an elongated period after administration of a single dose. In the case of the oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Not all the medicaments are suitable candidates for the sustained release dosage form. The goal of any drug delivery system is to provide a therapeutic amount of drug at the target site in the body. It aims to achieve and maintain the desired drug concentration within body for required time period.[1,2] Captopril is an angiotensin converting enzyme inhibitor, used in the treatment of hypertension and fulfills all the criterias, required to be formulated as a matrix tablet. Although researchers have formulated captopril as microspheres, elementary osmotic pump tablets and bilayer floating tablets, if ease of scale up and its feasibility issues are considered, matrix tablet is the most suitable formulation.[3-5]

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Material and Methods

Captopril was obtained as a gift sample from modi mundi Pharma pvt ltd. Hydroxypropylmethylcellulose (HPMC) and Ethyl Cellulose (EC) were purchased from colorcon Pvt ltd, Sodium CMC and Lactose were from Qualigens Fine Chemicals, Magnesium stearate from SD fine Chem ltd and Talc from Nice Chemicals pvt ltd.

Formulation of Captopril matrix tablet[6-7]

Matrix tablets of Captopril were prepared by direct compression technique using varying proportions of polymers in combination. The composition of matrix tablets is given in table -1. All the ingredients were individually passed through a 60 mesh sieve, except glidant and lubricant. For each formulation required quantities of Captopril, polymer, were accurately weighed according to the composition and mixed in a polybag for about 30 to 45 minutes. The obtained blend was lubricated with talc and magnesium stearate for another 5 minutes. The appropriate amount of the mixture was weighed and then compressed using 8 station rotary tablet press equipped with 11 mm flat faced punches at a constant compression force required to produce hardness of tablets about 2-4 kg/ cm^2. All the tablets were stored in airtight containers for further use.

Total weight of the tablet= 200mg

Each tablet contains= 25mg of the captopril

Table 1: Formulation Design for Each Batch

S. No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Captopril	25	25	25	25	25	25	25	25	25	25
2	HPMC K-100	30	60	-	-	-	-	30	-	30	20
3	Ethyl cellulose	-	-	30	60	-	-	30	30	-	20
4	Sodium carboxymethylcellulose	-	-	-	-	30	60	-	30	30	20
5	Lactose	129	99	129	99	129	99	99	99	99	99
6	Magnesium Stearate	6	6	6	6	6	6	6	6	6	6
7	Talc	10	10	10	10	10	10	10	10	10	10

Evaluation of preformulation parameter[8]

Angle of repose

It was measured by fixed funnel method. The fixed funnel method employs a funnel that was secured with its tip at a given height 'H,' above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with 'R' being the radius of the base of the conical pile.

$\tan \theta = h / r$

$\theta = \tan^{-1}(h/r)$

Where, θ is the angle of repose

h is height of pile

r is radius of the base of the pile

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured. Then the graduated cylinder was closed with a lid, set into the density determination apparatus. The density apparatus was set for 100 taps, and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were found to be the difference of not more than 2.0%.

The bulk density, and tapped density were calculated using the following formulas

Bulk density = W / V_o

Tapped density = W / V_f

Where, W = weight of the powder V_o = initial volume

V_f = final volume

Compressibility index (Carr's index)

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free- flowing material.

It can be calculated as per given formula

$$\text{Carr's Index (\%)} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 100$$

Hausner Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner Ratio =Tapped density / Bulk Density

Evaluation of tablets[9-11]

Tablet dimensions

Thickness and diameter were measured using a calibrated dial caliper. Ten tablets of each formulation were evaluated.

Hardness

Monsanto hardness tester was used to evaluate hardness of tablet. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bold until the tablet fractures. As the spring is compressed, a pointer rises along a gauge in the barrel to indicate the force. The force of fracture was recorded, and the zero force reading was deducted from it. Ten tablets of each formulation were evaluated. The results are shown in Table 3.

Friability

Weigh accurately 20 tablets and place them in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus at 25 ±1 RPM and observe the tablets while rotating. No tablet should stick to the walls of the apparatus. Take the tablets out and observe. No capping/breaking should be observed for the test to be valid. Weigh the tablets, after de-dusting excess powder from their surface.

Calculation**:** Calculate the Friability in %, using the formula: -

$$\text{Friability} = \frac{(W_1 - W_2) \times 100}{W_1}$$

Where W_1 = Initial weight of the tablets taken,

W_2= Final weight of the tablets after testing.

Weight Variation

Twenty tablets were sampled randomly. Tablets were weighed individually, and average weight was calculated. Then deviation of each tablet from average weight was calculated, and percent deviation was computed. The deviation was compared with the Pharmacopoeial limits.

Uniformity of Content

Five randomly selected tablets were weighed and powdered. The powdered tablet equivalent to 20 mg drug in one tablet was taken and transferred in a 250ml flask containing 100ml of 0.1N HCl (pH 1.2) and phosphate buffer pH 6.8 The flask was on a shaken on a flask shaker for 24 hours and was kept for 12 hours for the sedimentation of undissolved materials. The solution is filtered through Whatmann filter paper(0.45µm). 10ml of this filtrate was taken, and appropriate dilution was made. The samples were analyzed at 203nm using UV visible spectrophotometer. The drug content was determined from the standard curve prepared at max 203 nm. The results are shown in Table 4.

***In-Vitro* Dissolution Studies[12]**

In Vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of 0.1N HCl (pH 1.2), phosphate buffer pH 6.8 for 12 hours. The temperature of the dissolution medium was kept at 37± 0.5^{o}C, and the basket was set at 50 rpm. 1 ml of sample solution was at nm using withdrawn at a specified interval of time. The absorbance of the withdrawn samples was measured standard curve of captopril prepared in distilled water at max 203 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Swelling Index

Swelling of tablet involves the absorption of liquid increasing weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles or hydration of macromolecules. The liquid enters the particles through pores and binds to large molecule; breaking the hydrogen bond and resulting in the swelling of the particle. The extent of swelling can be measured regarding %weight gain by the tablet.

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. After each interval, the tablet was removed from the beaker, removes the excess buffer by using filter paper and weighed again up to 7 hrs. The swelling index was calculated by the following equation:

$$\text{Swelling index (SI)} = \frac{(Wt - W0)}{W_0} \times 100$$

Where W_t = Weight of tablet at time t.

W_0 = Initial weight of the tablet

Modeling of Dissolution Profiles

In vitro dissolution has been recognized as an important element in drug development under certain assessment of Bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of 't' (time) related to the amount of drug dissolved form the pharmaceutical dosage system (Costa and Lobo, 2001). Whenever a new solid dosage form is developed or produced, the drug release/dissolution from the solid pharmaceutical dosage form is necessary to ensure that the drug dissolution occurs appropriately. Several theories/ kinetic models describe drug dissolution form immediate and modified release dosage. These represent the drug dissolution profiles where f_t is a function of' (time) related to the amount of drug dissolved from the pharmaceutical dosage forms. The quantitative interpretation of the value obtained from the dissolution assay is facilitated by a mathematical equation which translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms.

Stability Studies of formulation

The success of a most effective formulation was assess only through the stability studies. The purpose of stability testing was to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage condition and peak profile.

The prepared matrix tablet ($\mathbf{F_7}$) of captopril were placed on plastic tubes containing desiccant and stored at ambient conditions like room temperature (RT), 30ºC & 60 % RH, 40 ºC & 75% RH for 30 days.

Results and Discussion

Standard Curve of Captopril

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Standard Curve of Captopril

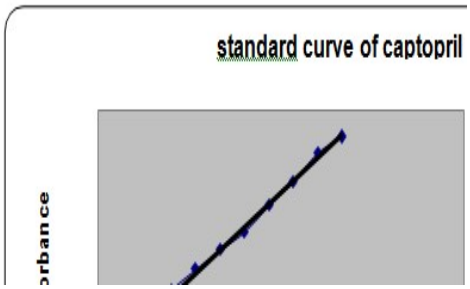

Fig. 1: Calibration curve of Captopril in 0.1N HCl Compatibility Studies

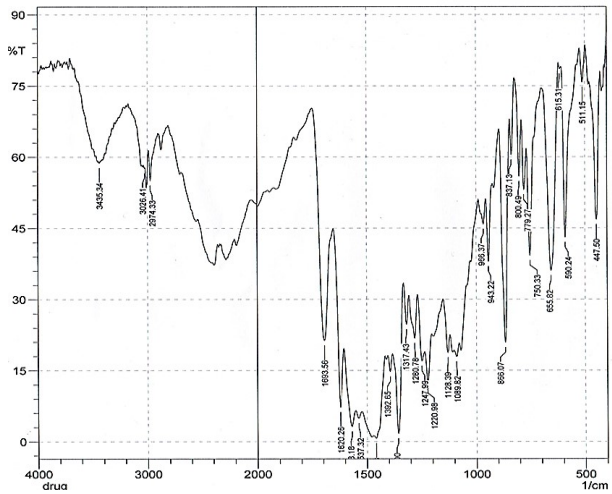

Fig. 2: IR Curve of Pure Drug (Captopril)

Preformulation study of Powders

Table 2: Preformulation Studies of Powders

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Bulk density	0.312	0.303	0.294	0.322	0.333	0.303	0.380	0.40	0.322	0.333
Tapped density	0.357	0.358	0.344	0.370	0.384	0.370	0.470	0.55	0.384	0.40
Carr' index (%)	12.60	15.3	14.53	12.97	13.28	18.10	19.1	27.2	16.14	16.75
Hausner ratio	1.14	1.18	1.17	1.14	1.15	1.22	1.23	1.37	1.17	1.20
Angle of repose(θ)	39º6'	38º6'	40º	37º5'	39º7'	31º	27º	39º8'	30º	35º

Physico-Chemical Evaluation

The results of the thickness, weight variation, drug content, Hardness, friability, the disintegration time of tablet are shown in **Table (8).**

Table 3: Results of Thickness, weight variation, Hardness, and Friability

Parameter Batch	Weight Variation (mg)	Hardness (Kg/cm^2)*	ability (%)	hickness (mm)*
F 1	Pass	6.7	0.74	3.08
F 2	Pass	6.4	0.34	3.09
F 3	Pass	6.9	0.48	3.10
F 4	Pass	6.6	0.59	3.11
F 5	Pass	6.9	0.54	3.09
F 6	Pass	6.3	0.50	3.10
F 7	Pass	7.2	0.69	3.08
F 8	Pass	7.1	0.49	3.07
F 9	Pass	6.8	0.44	3.10
F 10	Pass	7.4	0.39	3.07

Drug Content Uniformity

The results of drug content of tablets are shown in Table (8). The drug content of tablets was found to vary between 95.40% to 98.1%.

Table 4: Result of Drug content uniformity

Parameter Batch	Drug Content (%)
F 1	97.22
F 2	95.40
F 3	97.08
F 4	96.3
F 5	95.55
F 6	98.1
F 7	96.6
F 8	98.2
F 9	97.5
F 10	96.8

***In Vitro* Release Study**

As follows the dissolution profiles shows the comparative release profile of Captopril with different concentration of different polymer from batches F1, F2, F3, F4, F5, F6, F7, F8, F9 & F10 of matrix tablet.

Table 5: Result of *In vitro* Release Study

S.NO.	TIME	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
1	1	18.4	16.3	20.1	31.9	15.8	14.3	21.3	19.3	18.7	10.28
2	2	31.62	27.61	33.2	45.3	26.31	24.11	31.52	21.62	23.42	11.89
3	3	48.62	44.51	49.2	57.9	39.19	36.01	42.52	35.62	32.42	23.23

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4	4	56.13	56.12	58.3	63.24	46.9	42.42	55.53	42.33	38.75	36.38
5	5	64.76	62.16	64.6	71.66	54.44	50.64	68.05	53.14	44.14	51.02
6	6	76.70	74.99	77.9	80.99	65.87	62.87	73.29	57.89	50.54	58.27
7	7	88.55	80.75	82.4	85.33	71.62	68.31	77.95	62.33	58.89	63.72
8	8	91.51	83.20	85.0	89.67	82.17	77.16	85.81	69.87	66.13	71.48
9	9	94.98	89.01	88.5	92.02	87.63	85.72	88.55	74.63	71.48	76.94
10	10	-	-	-	-	-	-	90.01	78.28	77.82	82.51
11	11	-	-	-	-	-	-	94.38	84.65	86.49	88.09
12	12	-	-	-	-	-	-	96.65	88.11	92.06	94.87

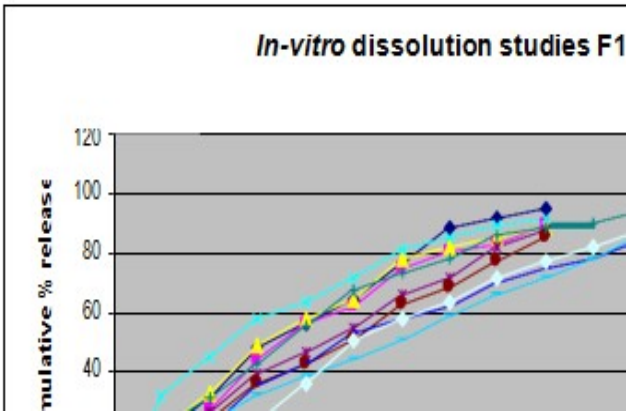

Fig. 3: Cumulative Percentage Release v/s Time for Formulation (F1 to F10) of Captopril Matrix Tablet

Table 6: Swelling Index of Tablets of Batch F1 toF10

Batch	TIME (HRS)							
	0	1	2	3	4	5	6	7
F1	0	57.5	67.4	75.5	92.2	104.5	111.3	119.2
F2	0	63.5	74.5	86.1	98.2	107.5	118.2	124.5
F3	0	34.65	45.54	56.1	64.3	72.3	85.5	96.2
F4	0	42.01	50.5	62.5	68.0	74.5	91.59	99.01

F5	0	49.0	53.50	65.5	79.0	90.50	103.5	107.5
F6	0	51.0	61.5	74.1	84.5	92.5	110.1	115.5
F7	0	69.0	76.50	94.50	102.0	114.0	125.5	131.7
F8	0	52.2	65.1	80.5	92.5	101.2	118.5	125.5
F9	0	66.5	74.1	88.2	98.5	103.2	114.3	127.0
F10	0	57.1	70.1	82.5	90.5	99.5	106.1	112.5

Table 7: Stability studies of formulation F7

Time (hr)	Cumulative % Drug Release	
	Initial	After 30Days
0	0	0
1	21.3	22.45
2	31.52	31.89
3	42.52	44.33
4	55.53	54.61
5	68.05	67.11
6	73.29	72.16
7	77.95	77.01
8	85.81	86.99
9	88.55	88.70
10	90.01	91.11
11	94.38	93.54
12	96.65	96.45
Hardness	7.2	6.9
Friability	0.69	0.74
Drug content	96.6	95.92

Conclusion

Captopril is an oral inhibitor of an Angiotensin-converting enzyme, demonstrates excellent clinical effectiveness in the treatment of essential hypertension. However, the efficacy of captopril as the first choice of the drug with antihypertensive action after oral dosing is limited to only 6-8 hrs. Therefore, clinical use requires captopril to be taken three times daily.

The present study was undertaken with an aim to formulate develop and evaluate Captopril sustained release tablets using different polymers by direct compression method. The successful application of the direct compression method in preparing the matrix type of sustained release dosage form depends on the selection of suitable matrix material.

The preformulation study was done initially and results directed for the further course of the formulation. Based on Preformulation studies different batches of Captopril were prepared using selected excipients. Granules were evaluated for tests Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. IR spectra studies revealed that the drug and polymers used were compatible.

Various formulations of sustained release tablets of Captopril were developed using various polymers viz, hydroxy propyl methyl cellulose, Ethyl cellulose, and

Sodium CMC in different proportions and combinations by Direct compression technique. The tablets were evaluated for physical characterization, *in vitro* swelling behavior, *in vitro* release study and stability studies.

Observations of all formulations for physical characterization had shown that all of them comply with the specifications of official pharmacopeias and standard references.

Results of *in vitro* release profile indicated that formulation (**F7**) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. Results of the in-vitro swelling study indicate that the formulation **F7** had a considerable swelling index.

Stability study was conducted on tablets of Batch **F7** stored at room temperature, 40^0C, and 2-8^0C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. After one month no significant changes were observed in any of the studied parameters during the study period. Thus it could be concluded that formulation was stable. It was concluded that the tablets of batch **F7** had considerable swelling behaviors and *in vitro* drug release.

From the above results and discussion, it is concluded that formulation of sustained release tablet of Captopril containing HPMC K100M and ethyl cellulose (1:1) batch F7 can be taken as an ideal or optimized formulation of sustained-release tablets for 12-hour release as it fulfills all the requirements for sustained release tablet.

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