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A Research Paper Captopril as a prolonged release matrix tablet: Formulation, Characterization and In-vitro dissolution study

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Abstract

Background: In current situation conventional dosage forms fails in sustaining the release from dosage form lead to fluctuation in dosage and shows peak-valley drug plasma profile. To overcome these problem associated with drug release, need to design such type of dosage form which extend the release with efficacy and to achieve steady state plasma drug conentration.

Objective: Design and delivery characteristics of prolonged release matrix tablet of captopril and evaluation was subjected for Swelling Index and In-vitro release of drug from formulation.

Material & method: By using HPMC K100, Ethyl cellulose, Xanthan gum, PVP K30, as release retardant polymer, captopril drug and other ingredients were mixed thoroughly and subjected to direct compression method in order to get Sustained release matrix tablet. Total 9 formulations were prepared and subjected for all the necessary evaluation tests.

Result: In the preparation of sustained release tablet, pre-compression and post compression parameters found to be within the limit. Among all 9 formulations R-4 formulation was found to optimize in context with physicochemical parameters, swelling index, Drug content, weight variation and in-vitro drug release.

Conclusion: Captopril prolonged release matrix tablet were prepared successfully and from the result it can be concluded that unique combination of Xanthan gum and Ethyl cellulose at concentration of 20 % and 15 % respectively produces better dosage form in order to release retardation.

Keywords: Captopril, sustained release, prolonged release, tablet, ethyl cellulose, xanthan gum.

INTRODUCTION

Because sustained release technology is a relatively new topic, research in it has been quite fruitful and has led to several discoveries. A steady state blood level that is therapeutically beneficial and non-toxic for a lengthy period of time is the main objective of many medications. An essential component to achieving this goal is the formulation of an appropriate dosage form [1]. Drug delivery systems that are intended to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose are referred to by the terms sustained release, sustained action, prolonged action, controlled release, extended action, timed release, and depot dosage form. Depending on how long the formulation stays in the GIT, an effect from an oral sustained-release dose form lasts for a number of

hours. The right distribution method is just as important to a therapy's success as the medicine itself[2] Sustained release dosage forms are made to work in conjunction with the drug's pharmacological activity to increase selectivity and lengthen the duration of action [3]. Captopril is a kind of inhibitor of the enzyme angiotensin converting (ACE inhibitor). It has an impact on the rennin-Angiotensin system and prevents Angiotensin I from becoming active Angiotensin II. As a result, ACE inhibitors reduce or completely eliminate reactions to angiotensin I but not angiotensin II [4]. Therefore, inhibiting ACE might have effects unrelated to lowering angiotensin II levels. By increasing bradykinin synthesis and stimulating prostaglandin biosynthesis, ACE inhibition increases [5]. Bradykinin and prostaglandin help the ACE inhibitor work pharmacologically. All of these impacts result in pharmacological processes like vasodilation and other things that ultimately lower blood pressure [6]. Captopril has a 1.9-hour half-life and is easily soluble in water. Patients with chronic illnesses who need long-term use for therapeutic purposes are typically the ones who are prescribed it [7]. The creation of an oral formulation for captopril would have a major positive impact on patient compliance and reduce drug side effects by reducing drug blood concentration variations, especially in long-term therapy [8]. This study's objective was to create Captopril matrix tablets utilising various ratios of Xanthan gum and ethyl cellulose [9].

Angiotensin converting enzyme captopril, also known as 1-[(2S)-3-mercapto-2-methyl propionyl]- 1-proline, is frequently used to treat hypertension and congestive heart failure. Due to its efficiency and minimal toxicity, the medication is regarded as a medicine of preference in antihypertensive therapy [10]. Patients who need long-term treatment medications for chronic illnesses are the ones who are typically prescribed it. The recommended dosage is 37.5–75 mg, divided into three doses per day. The medication only has a 6- to 8-hour window of antihypertensive action after a single oral dose [11].

A major benefit for patient compliance and the decrease of drug side effects would result from the development of a once-daily captopril oral formulation, particularly for long-term therapy [12]. This is because drug blood concentration fluctuations would be reduced. It can be challenging to create captopril formulations for oral controlled release [13]. This problem arises from the drug's in vitro and in vivo instability, which results in degradation to various metabolites and pseudo-first order type degradation response with slight pH range changes in vitro. Additionally, the medicine exhibits a variable type of GIT absorption (being passively absorbed in part and through the peptide-carrier mediated in the other part) [14]. When prepared in a sustained or controlled formulation, the medication also experiences the dosage phenomenon and burst effect (because to its freedom from water solubility). However, the medication exhibits substantial food interactions and its bioavailability is reduced when food is present [15]. This study's objective was to create Captopril matrix tablets utilising various ratios of Xanthan gum and ethyl cellulose.

MATERIALS & METHODS

Drug Captopril was purchased from Yarrow Chem Product Mumbai. Polymers Xanthan Gum, Ethyl Cellulose and HPMC K100 were purchased from Chemdyes Corporation Gujrat. Other excipient PVP K30 and solvent of Analytical grads were obtained from Central Drug House New Delhi.

PREPARATION OF PROLONGED RELEASE TABLET

Captopril matrix tablets were created utilizing a direct compression process and a combination of polymers in various ratios. Table -1 lists the ingredients in matrix tablets. Except for glidant and lubricant, each item was separately filtered through a sieve with a mesh size of 60. For each formulation, the precise weights of the required amounts of Captopril and the polymer (xanthan gum and ethyl cellulose) were used to mix the

ingredients for roughly 30 to 45 minutes in a polybag. For an additional five minutes, talc and magnesium stearate were used to lubricate the resulting mixture. Utilizing an 8 station rotary tablet press with 11 mm flat faced punches from CEMACH machineries ltd in Ahmedabad, India, the correct quantity of the mixture was weighed before being squeezed to generate tablets with a hardness of 2-4 kg/cm2. For later use, all of the tablets were kept in sealed containers [16].

Table 1: Formulation code for each Batch.

Sr. no.	Excipients (%)	R1 (%)	R2 (%)	R3 (%)	R4 (%)	R5 (%)	R6 (%)	R7 (%)	R8 (%)	R9 (%)
1	Drug	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
2	HPMC K-100	15	15	15	15	15	15	15	15	15
3	Ethyl cellulose	15	20	25	15	20	25	15	20	25
4	Xanthan gum	15	15	15	20	20	20	25	25	25
5	Lactose	27	22	17	22	17	12	17	12	7
6	PVP	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
8	Talc	5	5	5	5	5	5	5	5	5

PRE-COMPRESSION STUDIES

Angle of repose (θ)

The maximum angle that can be formed between a pile of powder's surface and a horizontal plane is known as the angle of repose. The angle of repose can be used to calculate the frictional force present in loose powder or granules [17].

$$\tan\boldsymbol{\theta} = h / r$$

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

Where, **θ** is the angle of repose
h = is height of pile
r = is radius of the base of the pile

Carr's compressibility index

The Carr's compressibility index was used to calculate the granules' compressibility index [18]. (percent) This formula can be used to determine Carr's Index:

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

POST-COMPRESSION STUDIES

The physical characteristics of the prepared matrix tablets, such as hardness and friability, swelling index, and drug content, were assessed.

Hardness test

For tablets to withstand mechanical shocks of handling during manufacture, packaging, and shipping, they need to have a particular amount of strength, or hardness, and resistance to friability. Using a digital hardness tester, the tablets' hardness was assessed. Kg/cm2 is the unit of measurement. From each formulation, three tablets were chosen at random, and the mean and standard deviation values were computed [19].

Friability test

When exposed to mechanical shock or attrition, it is a condition where tablet surfaces are harmed and/or show signs of lamination or fracture.

The USP EF 2 friabilator from Electro Lab was used to assess the tablets' friability. It is stated as a percentage (percent). Ten pills were placed into the friabilator after being originally weighed (Winitial). For four minutes, the friabilator was run at 25 RPM. The tablets were once more weighed (Wfinal). Next, the % friability was determined using [20],

$$F = \frac{Wi - Wf}{Wi} \times 100$$

Where,

F= Friability Wi= initial weight, Wf= final weight

% Friability of tablets less than 1% is considered acceptable.

Swelling index

A liquid is absorbed by a tablet, causing it to swell and gain weight and volume. Liquid uptake by the particle may result via hydration of macromolecules or saturation of capillary spaces inside the particles. The hydration of macromolecules or the entry of liquid into the particles. Through pores, the liquid enters the particles and binds to the big molecules, breaking the hydrogen bond and causing the particle to inflate. The amount of swelling can be quantified by the tablet's percentage weight gain. The swelling index of tablets was assessed at room temperature in 0.1 N HCl (pH 1.2). The tablet was taken out of the beaker after each interval, the excess buffer was wiped away with filter paper, and the scale was readjusted every eight hours [21].

The following equation was used to determine the swelling index:

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

Where, Wt= Weight of tablet at time t.

W0 = Initial weight of tablet

Drug content

Take the 20 tablet powder. A amount of powder containing 0.1gm of captopril was weighed with 150ml of phosphate buffer pH6.8 for 10 minutes, followed by the addition of 200ml of phosphate buffer pH6.8 and filtering. 100 ml of water should be added to 10 ml of filtrate before measuring absorbance at 233 nm [22].

In vitro dissolution study

At 37°C (0.5°C) and 50 rpm speed in 900 mL of dissolve medium, eight-station USP XXII type II dissolution test apparatus (Electro lab TDT-08, India) was used to conduct in vitro drug release experiments on matrix tablets. The dissolution medium was composed of phosphate buffer pH 6.8 for the first three hours and 0.1N

hydrochloric acid for the first two hours. At regular intervals, five milliter (5ml) samples were obtained via filtration, and 5ml of phosphate buffer (pH 6.8) was added to the dissolving media after each sample. Spectrophotometric analysis is used to determine the amount of medication emitted [23].

RESULTS AND DISCUSSION

Pre-compression parameters:

Angle of repose, bulk density, tapped density, and compressibility index were all measured in the powder combination of all formulations, and their results are shown in table 2. With a bulk density of 0.36 to 52 g/ml and a powder blend, the angle of repose values ranged from 22.56 to 31.44, indicating good flow characteristics. All of the formulations' compressibility indices were determined to be under 22%, which shows that the powder mixture had superior flow characteristics. The Hausner's ratio, which had a range of 1.07 to 1.28, was also calculated.

Table 2: Pre-compression evaluation parameters for R-1 to R-9 formulation.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose(0)	Carr's index (%)	Hausner's ratio
R1	0.39±0.06	0.53±0.13	30.89±0.16	23.34±0.17	1.32±0.16
R2	0.37±0.10	0.43±0.83	23.68±0.19	14.23±0.19	1.09±0.38
R3	0.34±0.08	0.39±0.71	28.12±0.12	13.21±0.16	1.21±0.17
R4	0.53±0.12	0.61±0.31	29.14±0.21	12.75±0.29	1.24±0.15
R5	0.49±0.09	0.64±0.26	26.43±0.39	20.47±0.23	1.18±0.24
R6	0.36±0.15	0.46±0.23	24.76±0.21	18.45±0.16	1.23±0.17
R7	0.46±0.17	0.57±0.14	31.34±0.37	14.36±0.15	1.25±0.32
R8	0.44±0.14	0.54±0.17	23.32±0.38	18.98±0.26	1.31±0.18
R9	0.42±0.12	0.58±0.15	30.98±0.42	22.12±0.31	1.31±0.19

Evaluation of postcompression parameters

Captopril sustained release matrix tablets were created using the direct compression method. Nine formulations in total were created. Table 3 displays the variation in tablet weight, hardness, friability, and content homogeneity for each formulation. The weight variation test revealed that all pill formulations' percentage deviations fell within the pharmacopoeially permissible range. All of the pills had a hardness between 2.8 and 3.9 kg/cm. Using a double beam UV spectrophotometer, the absorbance of the sample at 233 nm was measured to quantify the drug content in each batch (LABINDIA). The drug content ranged from 82.23 to 90.75 percent, indicating uniform drug distribution in all formulations, and the content uniformity was found to be higher between various formulations.

Table 3: Post compression parameters for sustained release matrix tablets of captopril R1 to R9

Formulation code	Friability	Hardness	Weight variation	Thickness
R1	0.74±0.05	3.4±0.18	207.0±0.23	2.43±0.03
R2	0.49±0.14	3.5±0.07	198.8±1.24	2.75±0.05
R3	0.58±0.04	2.8±0.13	218.4±0.69	2.74±0.06

R4	0.68±0.24	4.1±0.32	205.6±1.46	2.78±0.17
R5	0.87±0.26	3.1±0.13	215.4±0.92	2.68±0.06
R6	0.75±0.08	3.6±0.17	197.4±0.32	2.59±0.14
R7	0.49±0.43	3.3±0.26	218.4±0.58	2.76±0.24
R8	0.63±0.16	2.5±0.19	200.6±0.79	2.63±0.04
R9	0.54±0.46	3.7±0.38	209.8±0.62	2.81±0.25

Swelling Index

By observing a dose unit's weight growth, the swelling behaviour of that unit was determined. The swelling index of tablets was calculated by dissolving the tablets in 0.1N HCL (pH 1.2) and pH 7.4 phosphate buffer in a petridish. 1, 2, 4, 6, and 8 hours have passed. For each time period, each tablet was carefully removed and blotted with tissue paper.

Table 4. Swelling index of formulations (R1-R9)

Time (h)	Standard	R1	R2	R3	R4	R5	R6	R7	R8	R9
1	0	0	0	0	0	0	0	0	0	0
2	46.38	53.23	36.37	36.86	46.32	43.67	28.57	46.37	54.36	46.38
3	52.48	59.67	39.56	58.58	52.56	52.47	39.87	58.47	63.47	56.39
4	65.43	68.98	43.26	78.26	58.48	63.58	62.15	63.86	71.43	64.98
5	76.54	79.96	57.87	87.59	63.26	74.47	72.15	83.57	86.38	73.08
6	87.47	88.58	62.48	103.38	72.58	87.39	75.68	95.67	94.67	89.70
7	106.49	105.86	71.48	109.79	95.38	97.48	83.27	104.37	106.38	106.48
8	114.38	117.49	83.27	121.43	109.38	108.43	92.17	114.78	118.37	117.27
9	123.54	127.69	94.39	132.34	115.58	117.47	104.38	123.47	138.47	127.48

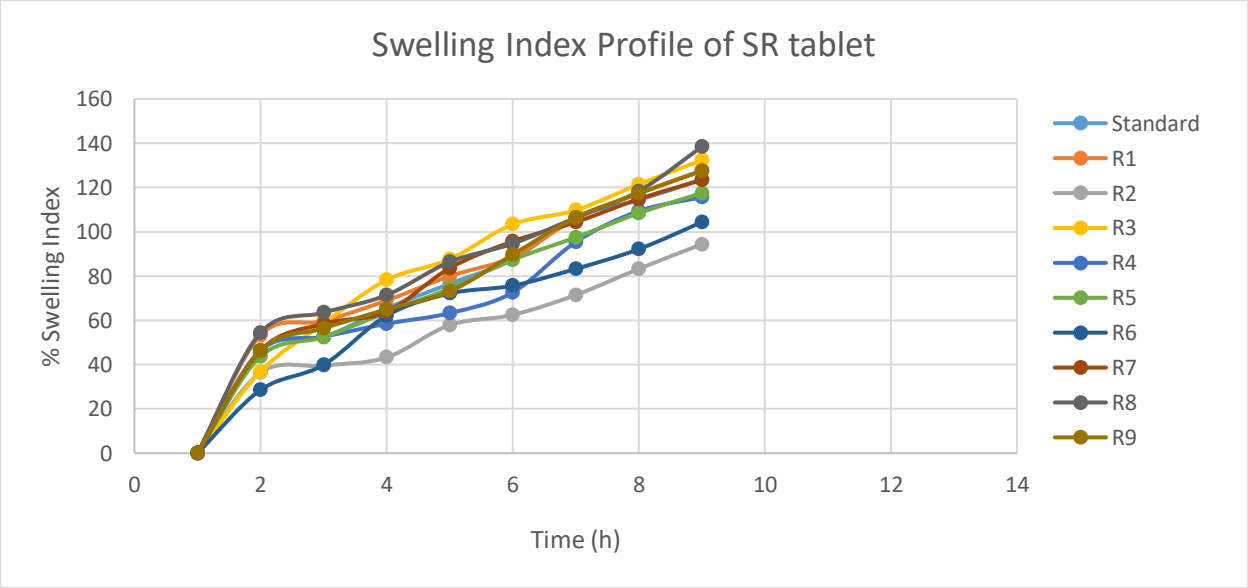

Figure 2: Release profile of drug captopril from sustained release matrix tablet.

In vitro dissolution study

The first two hours of captopril release from the matrix tablets were examined in 0.1 n HCL, and the following six hours were in phosphate buffer at pH 6.8. A total of nine formulations using Xanthan gum and ethyl cellulose in various ratios were created. Xanthan gum and ethyl cellulose were utilised as sustained release polymers in batch R1, R2, andR3. Results of the preformulation research and physical chemical analysis of matrix tablets are displayed in tables 18 and 19. Results of the R1 in vitro dissolution investigation indicated a 98.69 percent drug release within 8 hours. The cumulative drug release in 8 hours was 94.39 percent on R2 and 95.67 percent on R3. As a result, a sustained release profile was not attained. Therefore, it was decided to add more xanthan gum to the subsequent batch, R4. As compared to batches R1, R2, and R3, more xanthan gum was employed in batch R4. The results of the dissolution research revealed a cumulative drug release of 90.75 percent within 8 hours, which is in accordance with the desired drug release profile. It occurred as a result of an increase in xanthan gum. The usage of xanthan gum results in the production of directly compressed matrices with a high degree of swelling brought on by water uptake.
Different ratios of xanthan gum and ethyl cellulose were utilized in batches R5, R6, R7, R8, and R9. 106.67 percent, 104.38 percent, 76.76 percent, 97.89 percent, and 98.49 percent cumulative drug release were shown in an in vitro dissolution assay to occur in 8 hours. These findings suggested that when coupled with ethyl cellulose, Xanthan gum could regulate the release of captopril for up to 8 hours.

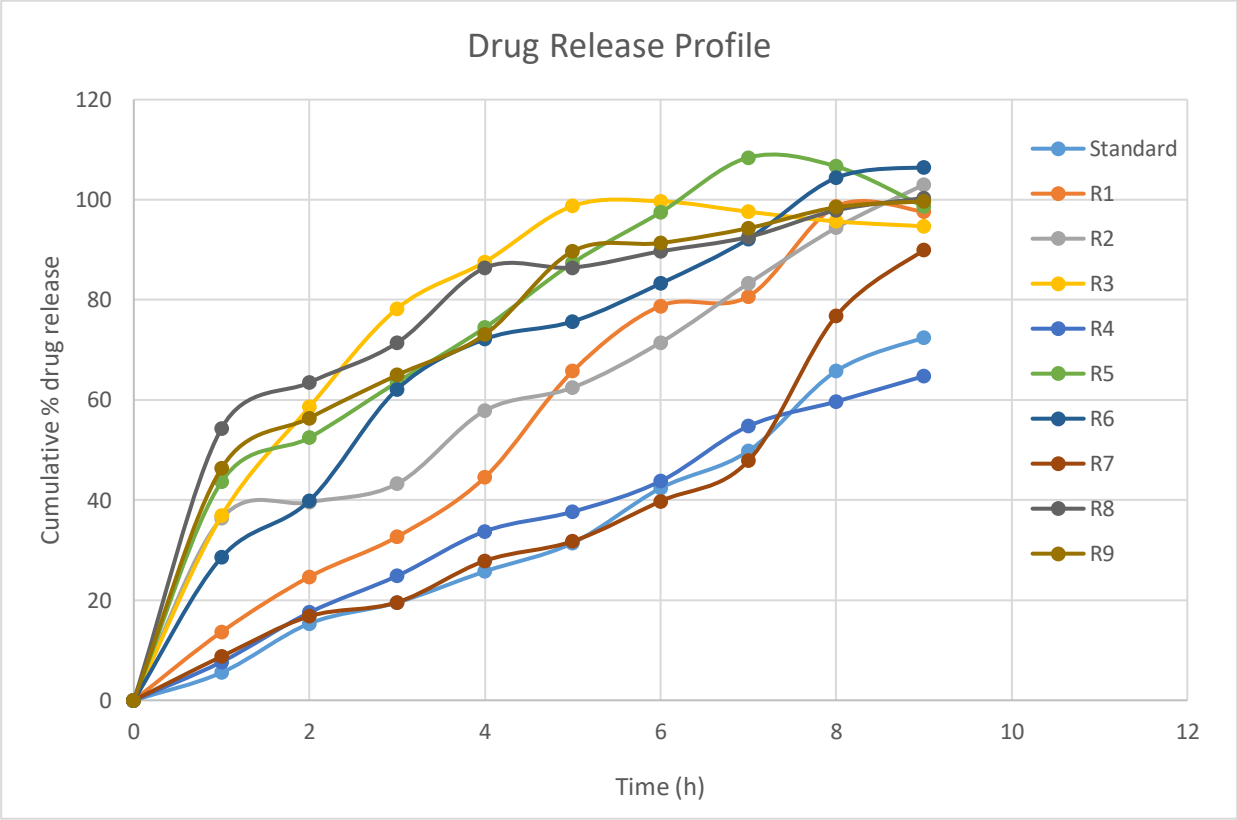

Figure 2: In-Vitro release profile of Captopril formulations along with standard.

CONCLUSION

Utilizing various ratios of xanthan gum and ethyl cellulose, sustained release matrix tablets of captopril were created using the direct compression method. The findings of the current investigation show that xanthan gum and ethyl cellulose successfully restrict the release of captopril for 8 hours. Conclusion: Formulation (F-4) with a high concentration of Xanthan gum and ethyl cellulose enabled sustained release of captopril over an 8-hour period. The frequency of administration and the dose-dependent side effects connected to repeated administration of conventional Captopril tablets are projected to diminish with the use of sustained release matrix tablets of captopril.

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CONFLICT OF INTERESTS

Declared None.

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