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Preparation and Evaluation of Captopril Oral Floating Controlled Release Formulations

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Authors' contributions

This work was carried out in collaboration among all authors. Author RV the guarantor of this study has designed and carried out the experimental process and prepared the manuscript. Authors CSKB, VS and SD have analyzed the results and contributed in preparation and review of manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Dosing frequency is a major hurdle in geriatrics with frequent drug administration. In such cases, oral controlled release floating formulations are helpful which causes reduction in dosing frequency and fluctuation of drug levels in plasma. The main aim of the current research was to prepare Captopril floating controlled release formulations in order to achieve extended gastric retention in the upper GIT.
Methodology: Captopril tablets were prepared using different concentrations of poly ethylene oxide water soluble resin (PEO WSR) 303 (5% to 30%) by direct compression technique. Captopril formulations CSP1 and CSP6 were formulated using PEO WSR 303. Pre and post compression parameters were evaluated. Dissolution studies were performed for the prepared tablets using 0.1N hydrochloric acid as dissolution medium.
Results: The dissolution studies showed controlled drug release up to 12h. The formulation CSP5 prepared using 25% w/w of PEO WSR 303 showed maximum drug release of 97.97% at 12h. Almost similar drug release profile was also observed for CSP6 which was prepared using 30%w/w

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PEO WSR 303. These two formulations were further added with various concentrations of sodium bicarbonate (5% to 15%) and citric acid (2.5% to 10%) which enhanced floating of drug in Gastro intestinal tract (GIT). Formulation CSP8 containing 10% of sodium bicarbonate with 25% PEO WSR 303 showed less buoyancy lag time and prolonged drug release. Formulation CSP15 showed very less buoyancy lag time of 5sec. Characterization studies like Fourier Transform Infra Red spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) were also carried out.

Conclusion: The prepared Captopril floating tablets could be an alternative formulation for prolonged drug release.

Keywords: Captopril; oral floating; controlled release; PEO WSR 303.

1. INTRODUCTION

Research and development of controlled as well as floating drug delivery systems has been gaining lot of focus these days. They are advantageous in case of geriatrics as they tend to forget drug administration and it also reduces the dosing frequency. This equally reduces the expenses on health demands and gives efficacious drugs at the same time [1]. Enhanced drug retention in gastro intestinal tract enhances drug absorption. Several approaches like floating formulations, inclusion of swelling agents, polymers and other delayed gastric emptying agents have been studied. Of all these, floating drug delivery systems were taken up by most of the researchers due to their ease of preparation and prolonged drug delivery [2]. The main purpose for developing these systems is to enhance the safety of a product to extend its duration of action [3]. In current research, the drug Captopril is selected for the design of floating tablets as it is the anti-hypertensive agent that is useful for geriatrics who require frequent dosing of drugs with proper drug release in body. Captopril is used as an antihypertensive agent. It acts by competitively inhibiting the enzyme angiotensin-converting enzyme, the enzyme responsible for the conversion of angiotensin-I (AT-I) to angiotensin-II (AT-II). AT-II controls blood pressure and is a key component of the renin-angiotensin-aldosterone system [4]. Captopril in aqueous solution is reported undergo oxidative degradation under increased pH conditions i.e., above 4 and hence an attempt is made to retain Captopril in the gastric region that is bellow pH 4 by formulating it as floating drug delivery agent to avoid pH induced oxidative degradation. Captopril gets rapidly absorbed after oral administration with mean elimination half-life of 2 to 3 hours [5]. Polymers like poly ethylene oxides are hydrophilic in nature and are available in various grades. They help in prolonged drug release [6]. Effervescent agents play an important role in making the formulation to float. It induces generation of carbon dioxide that causes floating [7].

The aim of present study is to formulate and evaluate floating tablets of Captopril with poly ethylene oxide WSR 303 (PEO WSR 303) as polymer, sodium bicarbonate and citric acid as effervescence agents, which could make the tablet to float on gastric fluid and deliver the therapeutic agent over an extended period of time.

2. MATERIALS AND METHODS

2.1 Materials

Captopril (Gift sample from Wockhardt Ltd., Mumbai); Poly ethylene oxide WSR 303 (Gift sample from M/s Colorcon Asia Pvt Ltd., Goa); Sodium Bicarbonate (Loba Chemie Pvt. Ltd, Mumbai); Citric acid (Thermo Electron LLS India Pvt. Ltd., Mumbai) and Methanol (Loba Chemie Pvt. Ltd, Mumbai).

2.2 Preparation of Captopril Tablets using PEO WSR 303

Captopril tablets were prepared by direct compression technique using poly ethylene oxide WSR 303 (PEO WSR 303) as polymer. The polymer concentration was increased ranging from 5% to 30% w/w of total tablet weight.The raw materials were individually weighed and transferred to mortar. Using pestle, the components were mixed well and the prepared granules were passed through sieve no. 40. The granules were taken into a plastic bag and lubricated with talc and magnesium stearate. Then they were compressed as tablets under identical conditions. The compositions of various tablet formulations are given in Table 1.

2.3 Evaluation of Pre-Compression Parameters

The prepared granules were evaluated for pre compression parameters such as angle of repose, Carr's index and Hausner's ratio [8]. The results are given in Table 2.

2.4 Angle of Repose

The powder flow properties were determined to know the good or bad material flow. The powder was taken into a funnel and poured through it. Below this, a graph sheet was placed to form a heap like structure for which, the radius and height of the heap was measured. Based on these, the angle of repose was calculated by using the formula;

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

2.5 Carr's Index

A simple test was used to evaluate the flow ability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \text{ x } 100$$

2.6 Hausner's Ratio

It is an indication of flow properties of the powder. Hausner's ratio can be calculated by using formula;

$$\text{Hausner's Ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

2.7 Evaluation of Post Compression Parameters

The compressed tablets were further evaluated for post compression parameters such as weight uniformity, hardness and friability. The prepared tablets were also evaluated for swelling index and drug content [9]. The results are given in Table 3.

2.8 Weight Uniformity

Tablets were selected from a batch in a random manner, weighed and average weight was calculated.

2.9 Hardness

The crushing strength/hardness is the force required to break the tablet in the radial direction. It was measured using Monsanto hardness tester (Tab-machines, Mumbai). The tablet should be fixed in the moving jaw and the reading as made to zero. The force was placed on the tablet until the tablet breaks. The reading noted from the scale indicates the hardness (kg/cm^2).

2.10 Friability

From each formulation batch, 10 tablets were selected randomly, weighed and kept in friabilator. It was rotated up to 100 revolutions. The tablets fall from 6 inches and experience shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight was calculated which indicates friability. The acceptance limits of weight loss should not be more than 1%. Friability is a measurement of the tablets ability to hold the worst conditions during transportation.

$$\text{Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \text{ x } 100$$

2.11 Swelling Index

The swelling index of the polymer used in the study was measured based on their water absorption and swelling properties. It was done using USP dissolution apparatus type – II apparatus in 900ml of 0.1N hydrochloric acid buffer at 50 rpm. The medium was maintained at 37±1ºC throughout the experiment. At regular intervals, the tablets were withdrawn, blotted to remove excess of water and weighed [10]. The swelling index was calculated using the formula;

$$\text{Swelling index (\%)} = \frac{\text{Weightof swollen tablet} - \text{Initial weight of tablet}}{\text{Initial Weight of tablet}} \text{ x } 100$$

2.12 Drug Content

Captopril tablets were crushed and placed in a 100ml volumetric flask with methanol. The flask was sonicated up to 30min and then filtered. After diluting the filtrate with suitable buffer, the absorbance was measured.

2.13 *In vitro* Dissolution Studies of Captopril Tablets

Dissolution studies for Captopril tablet formulations were performed in a calibrated

dissolution test apparatus (USP apparatus II method) using 900 ml of 0.1N hydrochloric acid as dissolution medium. The paddles were operated at 50rpm and temperature was maintained at 37±1ºC throughout the experiment [11]. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 10 and 12 h and replaced with equal volume of same dissolution medium to maintain the constant conditions. The drug release was compared with the marketed formulation of Captopril. The amount of drug dissolved was estimated using U.V spectrophotometer at 240 nm. The dissolution profiles are given in Fig. 1.

2.14 *In Vitro* Buoyancy Studies

All the prepared formulations were subjected to *in vitro* buoyancy studies. The *invitro* buoyancy study was characterized by measuring the floating lag time, which is the time taken by the tablet to rise to the surface and total floating time, i.e., the time the tablet constantly remained on the surface of the medium [12]. *In vitro* buoyancy results are given in Table 4.

2.15 Preparation of Captopril Tablets using Sodium Bicarbonate and Citric acid

The formulation which showed best dissolution profile with PEO WSR 303 was selected and to it, different concentrations of sodium bicarbonate (5% to 15%) and citric acid (2.5% to 10%) were added as effervescent agents and tablets were prepared by direct compression technique. The raw materials were individually weighed and transferred to mortar. Using pestle, the components were mixed well and the prepared granules were passed through sieve no. 40. The granules were taken into a plastic bag and lubricated with talc and magnesium stearate. Then they were compressed as tablets under identical conditions [13]. The composition of various tablet formulations is given in Table 5.

The prepared tablets were evaluated for pre and post compression parameters and the results are given in Tables 6 and 7. The dissolution profiles are shown in Figs 2 and 3. The *in-vitro* buoyancy test was also performed for the tablets and the results are shown in Table 8.

2.16 Statistical Analysis

The results obtained were statistically evaluated. As the procedures performed and the results obtained were in triplicates, the mean along with their standard deviations (S.D) were calculated for weight uniformity and drug content.

2.17 Characterization Studies

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected for further investigations such as Fourier Transform Infra Red spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) analysis.

2.18 Fourier-Transform Infra Red (FTIR) Spectroscopic Analysis

Fourier-transform infrared (FTIR) spectra of moisture free powdered samples of Captopril pure drug and optimized Captopril formulation were obtained by using potassium bromide (KBr) pellet method. The results are shown in Fig. 4.

2.19 Scanning Electron Microscopy (SEM)

Scanning electron microscopy was performed on Captopril pure drug, PEO WSR 303 and optimized Captopril formulation. A thin gold layer coating was given to samples by sputter coater unit and SEM images were pictured using scanning electron microscope functioned at 15kV voltage. The SEM images are shown in Fig. 5.

3. RESULTS AND DISCUSSION

3.1 Preparation of Captopril Tablets using PEO WSR 303

Captopril tablets were prepared using various concentrations of PEO WSR 303 by direct compression technique. The composition of various Captopril tablets is given in Table 1.

3.2 Evaluation of Pre-Compression Parameters

The pre compression parameter values obtained for various prepared granules are given in the Table 2. The angle of repose, Carr's index and Hausner's ratio values for granules were within the range specified. Thus all the prepared granules were found to be stable and suitable for compression of tablets.

3.3 Evaluation of Post Compression Characteristics of Captopril Tablets

The direct compression method was found to be suitable for preparation of tablets. Captopril tablets were prepared and evaluated for post compression parameters. The results are given

in Table 3. Weight uniformity, hardness and friability loss of tablet formulations were within the specified limits and were found to be suitable for further studies. As the PEO WSR 303 concentration is increased, swelling index of tablet formulations is also increased.

Table 1. Composition of captopril tablets with different polymer concentrations

Ingredient	Formulations						
	CS	CSP1	CSP2	CSP3	CSP4	CSP5	CSP6
Captopril (mg)	50	50	50	50	50	50	50
PEO WSR 303 (mg)	-----	12.50	25.0	37.50	50.0	62.50	75
MCC (PH 102) (mg)	195.0	182.50	170.0	157.50	145.0	132.50	120.0
Talc (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight (mg)	250	250	250	250	250	250	250

Table 2. Pre-Compression parameters of captopril granules

Formulation	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio
CS	31	21	1.22
CSP1	26	18	1.19
CSP2	24	17	1.16
CSP3	24	14	1.15
CSP4	23	15	1.13
CSP5	22	13	1.12
CSP6	22	13	1.12

Table 3. Post Compression Parameters of Captopril Formulations

Formulation	Weight uniformity (mg) (Mean ± S.D)	Hardness (kg/cm^2)	Friability (% loss)	Swelling Index (%)	Drug Content (mg/tablet) (Mean ± S.D)*
CS	249±1.03	3.6±0.18	0.4	---	50.01±1.11
CSP1	250±0.82	3.3±0.35	0.3	79	49.84±0.82
CSP2	249±1.14	3.3±0.42	0.2	110	50.12±0.75
CSP3	249±1.07	3.2±0.16	0.2	135	50.07±0.69
CSP4	250±1.20	3.2±0.22	0.2	196	50.14±0.92
CSP5	250±1.32	3.3±0.47	0.3	223	49.05±1.15
CSP6	250±1.32	3.3±0.31	0.4	252	48.94±1.32

**n=3; Mean ± S.D = Mean values ± Standard Deviation of three experiments*

3.4 *In vitro* Dissolution Studies of Captopril Tablets

The dissolution studies clearly indicated that as the concentration of PEO WSR 303 is increased, the sustained release property of the prepared tablet formulations has also increased. Formulations CSP5 containing 25%w/w of PEO WSR 303 exhibited controlled and prolonged drug release without any sodium bicarbonate. Similar profile was observed with CSP6 with 30%w/w of PEO WSR 303. This study thus strongly supports the usage of PEO as controlled release agent which was also supported by various recent studies [14, 15]. The results are shown in Fig. 1.

3.5 *In Vitro* Buoyancy Studies

In vitro buoyancy studies were performed on prepared Captopril formulations. The buoyancy lag time along with total floating time are indicated in Table 4.

3.6 Preparation of Captopril Tablets using Sodium Bicarbonate and Citric acid

Addition of effervescent agents in different concentrations to the Captopril formulations was preferred in order to make the tablet to float in gastric juice. The composition of Captopril formulations is indicated in Table 5.

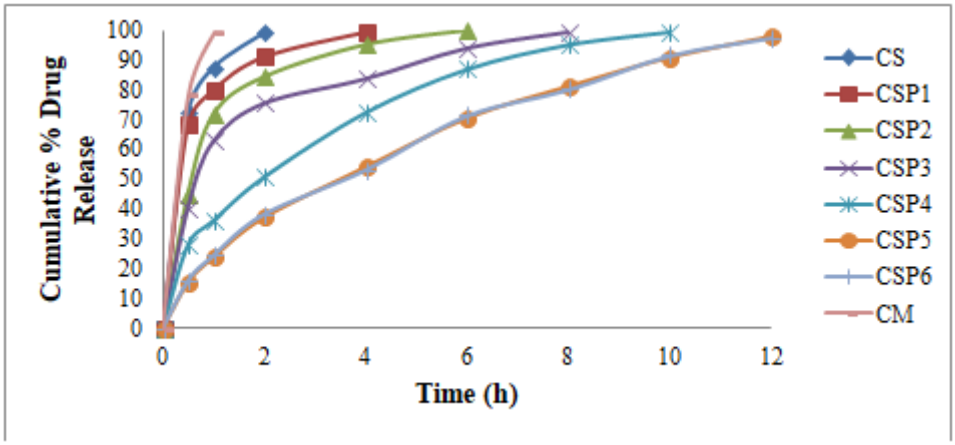

Fig. 1. Dissolution Profiles of Captopril Tablets

Table 4. Buoyancy test for various captopril formulations

Formulation Code	Buoyancy Lag Time (sec)	Total Floating Time (h)
CS	900	2
CSP1	544	4
CSP2	362	6
CSP3	304	8
CSP4	182	10
CSP5	155	12
CSP6	143	12

3.7 Evaluation of Pre-Compression Parameters

The pre compression parameter values obtained for various prepared granules were given in the Table 6. The angle of repose, Carr's index and Hausner's ratio values for granules were within the range specified. Thus all the prepared granules were found to be stable and suitable for compression of tablets.

3.8 Evaluation of Post Compression Characteristics of Captopril Tablets

The direct compression method was found to be suitable for preparation of tablets. Captopril tablets were prepared and evaluated for post compression parameters. The results are given in Table 7. Weight uniformity, hardness and friability loss of tablet formulations were within the specified limits and were found to be suitable for further studies. As the concentration of sodium bicarbonate increased, the swelling index was decreased. This decrease was even more when citric acid was added. As the effervescence agents make the drug to float faster, they reduces swelling index.

3.9 *In vitro* Dissolution Studies of Captopril Tablets Prepared using Sodium Bicarbonate and Citric Acid

The study clearly indicated that as the concentration of sodium bicarbonate has increased, due to its effervescence property, the buoyancy lag time has reduced. Almost all the formulations showed near to similar drug release at 12 hours due to the presence of PEO WSR 303. Formulation CSP8 containing 25%w/w of PEO WSR 303 with 10% w/w of sodium bicarbonate exhibited controlled and prolonged drug release with less buoyancy lag time. This study thus strongly supports the usage of effervescence agents in making the formulation floating which was also mentioned in some recent research [16-18]. The results are shown in Figs 2 and 3.

3.10 *In Vitro* Buoyancy Studies

As the concentration of sodium bicarbonate increased, the buoyancy lag time has been decreased. The tablet floats in a faster manner. When two different effervescent agents, i.e., sodium bicarbonate and citric acid have been used, the buoyancy lag time has been

extensively decreased to 5 sec. However, due to the presence of polymer PEO WSR 303 in all the formulations, the total floating time remained up to 12 hours. The buoyancy lag time along with total floating time is indicated in Table 8.

3.11 Characterization Studies

3.11.1 FT-IR spectral studies

Captopril exhibited principle FT-IR spectral peaks at wave numbers of 2980.23 cm^{-1} (O-H Stretching), 2878.56 cm^{-1} (C-H Stretching), 1473.40 cm^{-1} (C-N Stretching), 1748.01 cm^{-1} (C=O Stretching) and 2565.87 cm^{-1} (S-H Stretching). C=O stretching, O-H stretching, S-H stretching and C-H stretching of Captopril and the optimized formulation CN3 were almost in the same region of wave number. It revealed that IR spectrum of Captopril and optimized formulation were having similar fundamental peaks and pattern. This indicated that there were no drug excipient interactions in the formulation and shown in Fig. 4.

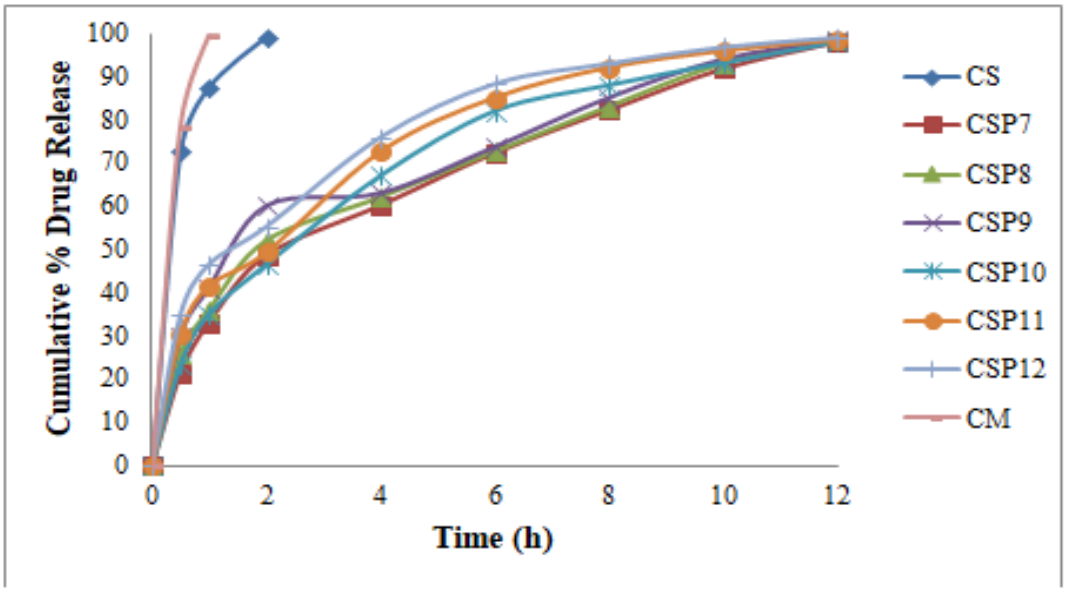

Fig. 2. Dissolution profiles of captopril tablets prepared using sodium bicarbonate

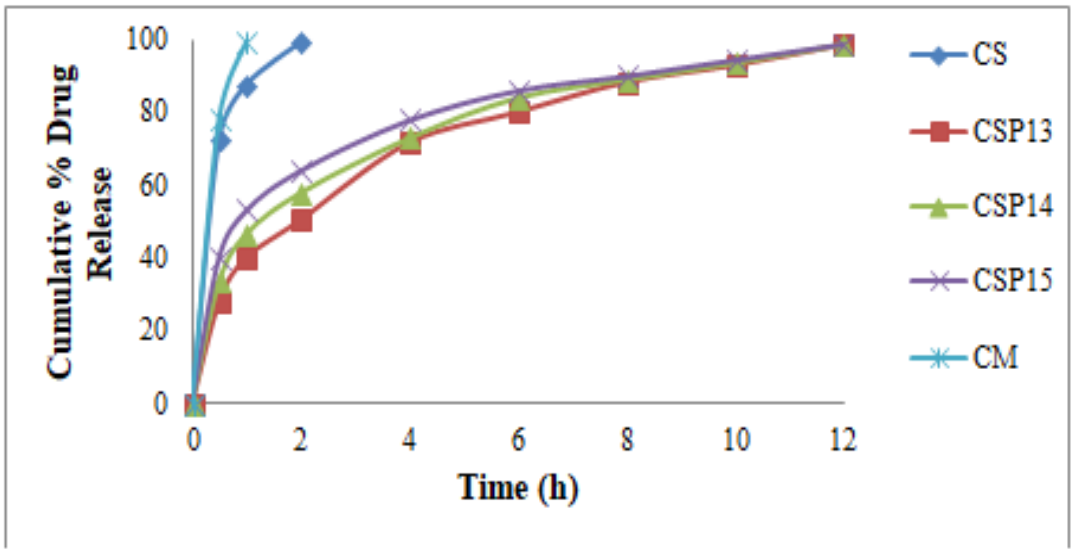

Fig. 3. Dissolution Profiles of Captopril Tablets Prepared using Sodium Bicarbonate and Citric Acid

Table 5. Composition of Captopril tablets with different polymer concentrations

Ingredient	Formulations									
	CS	CSP7	CSP8	CSP9	CSP10	CSP11	CSP12	CSP13	CSP14	CSP15
Captopril (mg)	50	50	50	50	50	50	50	50	50	50
PEO WSR 303 (mg)	-----	62.50	62.50	62.50	75.0	75.0	75.0	62.50	62.50	62.50
MCC (PH 102) (mg)	195.0	120	107.5	95	107.5	95	82.50	113.75	95.0	82.5
Sodium Bicarbonate (mg)	-----	12.5	25.0	37.50	12.5	25.0	37.50	25.0	25.0	25.0
Citric Acid (mg)	-----	-----	-----	-----	-----	-----	-----	6.25	12.50	25.0
Talc (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight (mg)	250	250	250	250	250	250	250	250	250	250

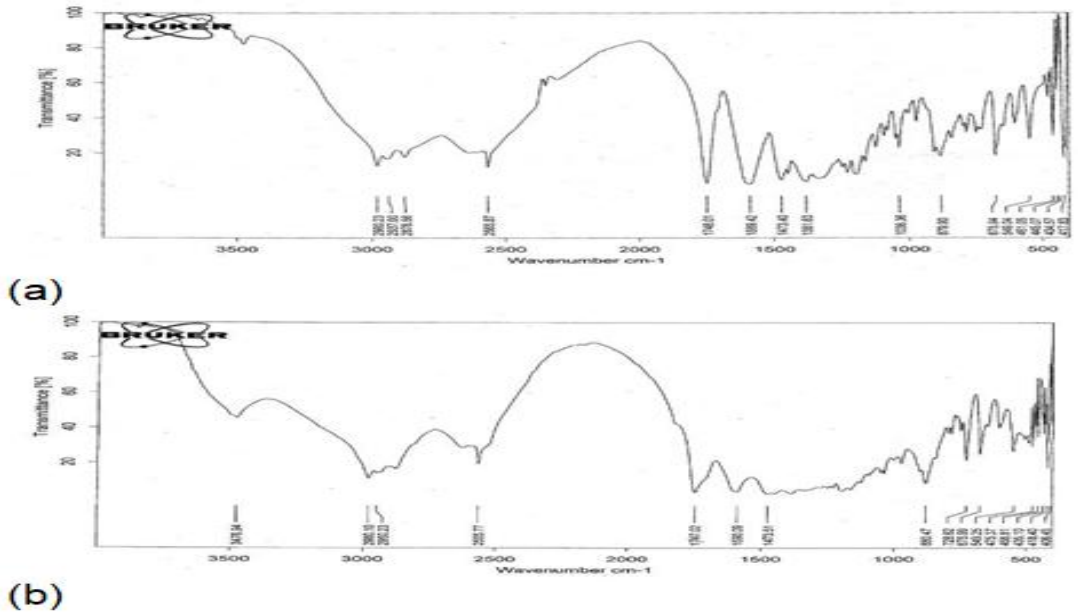

Fig. 4. FTIR Spectra of (a) Captopril Pure Drug (b) Optimized Formulation (CSP8)

Table 6. Pre-Compression Parameters of Captopril Granules

Formulation	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio
CS	31	21	1.22
CSP7	22	13	1.13
CSP8	21	13	1.11
CSP9	22	13	1.12
CSP10	23	14	1.13
CSP11	22	13	1.12
CSP12	22	13	1.11
CSP13	21	12	1.11
CSP14	22	13	1.12
CSP15	21	11	1.13

Table 7. Post compression parameters of captopril formulations

Formulation	Weight uniformity (mg) (Mean ± S.D)	Hardness (kg/cm^2)	Friability (% loss)	Swelling Index (%)	Drug Content (mg/tablet) (Mean ± S.D)*
CS	249±1.03	3.6±0.98	0.4	---	50.01±1.11
CSP7	251±1.04	3.2±0.11	0.3	202	50.48±1.00
CSP8	250±1.25	3.3±0.10	0.4	183	51.02±0.91
CSP9	249±1.31	3.2±0.22	0.2	170	50.15±0.38
CSP10	251±0.91	3.2±0.15	0.2	235	49.97±0.82
CSP11	250±0.99	3.3±0.31	0.3	210	50.05±1.11
CSP12	251±1.07	3.3±0.16	0.4	189	49.99±1.20
CSP13	249±0.82	3.2±0.08	0.3	181	50.08±0.85
CSP14	250±1.01	3.3±0.03	0.2	163	50.38±1.01
CSP15	251±1.33	3.2±0.18	0.2	145	49.69±1.17

**n=3; Mean ± S.D = Mean values ± Standard Deviation of three experiments*

Table 8. Buoyancy test for various captopril formulations

Formulation Code	Buoyancy Lag Time (sec)	Total Floating Time (h)
CS	900	2
CSP7	45	12
CSP8	35	12
CSP9	22	12
CSP10	40	12
CSP11	31	12
CSP12	18	12
CSP13	13	12
CSP14	9	12
CSP15	5	12

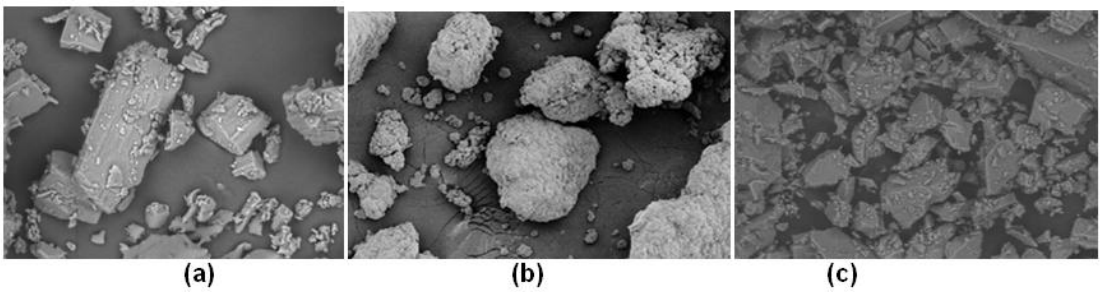

Fig. 5. SEM Photographs of (a) Captopril Pure Drug (b) PEO WSR 303 (c) Optimized formulation (CSP8)

3.11.2 SEM analysis

SEM analysis was performed for the optimized formulation along with Captopril pure drug and PEO WSR 303. The SEM photographs showed that formulation found to be crystalline in nature without any clumps. SEM image of optimized formulation showed equal distribution of Captopril crystals with polymer. SEM photographs were shown in Fig. 5.

4. CONCLUSION

The current research work focused on preparation of controlled release floating tablets of Captopril. It was concluded that incorporation of PEO WSR 303 in formulation delayed drug release. Sodium bicarbonate and citric acid have increased the buoyancy of the formulation which made them to float with in short period. Thus the formulations made using PEO WSR 303 as polymer and sodium bicarbonate and citric acid as effervescent agents brought a promising novel controlled release floating formulation which could be a boon for many hypertensive patients.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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