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Research Article

Design and Development of Captopril Gastro-Retentive Tablet Using Natural Polymers of Maize and Jowar Plant

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Abstract: Nowadays, the use of natural polymers as an alternative to synthetic gastro-retentive polymers is increasing. Such natural raw materials are highly biocompatible and biodegradable with no or significantly fewer side effects and are economical too. The main aim of this research work was to design a gastro-retentive tablet of Captopril by using Maize Stem Pith (MSP) powder and Jowar Stem Pith (JSP) as novel natural low-density polymers and also to sustain the drug release for up to 12 hours. Our objective behind this research is to prepare the gastro-retentive tablet, evaluate it for floating behavior, and to achieve the sustained release effect for at least 12 hours. The novelty of this research work is that MSP powder and JSP powder possesses low density. Thus, gastro-retentive tablets with a low-density (floating) approach can be prepared at a very lost cost compared to the currently marketed formulation. Gastro-retentive tablets of Captopril were designed by using MSP and JSP powder. Using design-expert® version 13, the formulations were prepared using a 3^2-complete factorial design. The gastro-retentive tablet showed good floating behavior and dissolution pattern, which sustains the release of the drug for up to 12 hours. The optimization study using a contour plot and response surface plot suggested that formulation R9 is an optimized batch among all batches. The current research indicated that there is an increase in floating time with a corresponding decline in the dissolution rate of the tablet as the concentration of MSP powder and JSP powder increases. The optimized formulation R9 consists of MSP powder and JSP powder at 12% and 8 %, respectively, in combination with HPMC (K-100M), and has proven excellent floating behavior and expected drug release pattern. Therefore, MSP powder and JSP powder could be used as suitable low-density novel polymers to design gastro-retentive tablets of Captopril.

Keywords: Captopril; Maize Stem Pith; Jowar Stem Pith; Floating Behavior and Sustained Release

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1. INTRODUCTION

Oral-controlled release (CR) formulations have been widely utilized for a while to regulate the delivery of medications. However, poor bioavailability is caused by the drug's release in the non-absorbing distal segment of the GIT due to the drug's short transit time with the absorption window in the stomach.[1,2] The development of gastro-retentive formulations is based on these characteristics[3,4]. In the pharmaceutical sector, the use of gastro-retentive dosage forms, which can overcome several obstacles and result in a rapid gastric emptying time, is widespread. Additionally, the method used in these dosage forms considerably enhances drug absorption and prolongs local drug action in the stomach. Due to the instability of Captopril in the intestines and the fact that it is primarily absorbed from the upper gastrointestinal tract, numerous researchers have created floating gastro-retentive tablets to promote bioavailability[5]. Stomach retentive dosage forms are categorized into the following categories: bio (muco) adhesive devices, swelling devices, expanding systems, floating systems, and inflatable systems.[6]The floating system was revealed to be the most effective gastro-retentive system for delaying stomach transit time.[7]Swellable polymers, gas-generating substances, sodium bicarbonate, and citric or tartaric acid are all used in effervescent systems.[8] In the world of pharmaceutical technology, introducing a gastro-retentive system has proven to have good scope for development[9]. Captopril is an ACE-Inhibitor used in the therapy of various heart diseases.[10,11] The water-soluble molecule captopril is highly stable in the stomach's acidic environment. Moreover, it is absorbed to a greater extent from the stomach. On the other hand, as pH rises due to the alkaline environment of the intestine, Captopril is unstable and thus not absorbable from the intestine[12,13]. Natural polymers are becoming more popular in designing novel formulations with improved unique characteristics. Naturally obtained plant materials are cost-effective, free of side effects, biocompatible, biodegradable, renewable, processable in an environmentally friendly manner, and more patient-friendly.[14] There are just a few polymers that could be included in the formulation of GRDDS as low-density excipients. We employed maize stem pith powder and jowar stem pith powder as low-density polymers in this study. Maize (Zea mays L.), a member of the Poaceae family, is the world's most frequently cultivated grain in Central America. Maize is recognized as the "*Queen of Cereals*" in the world because it is abundantly cultivated with high-yield production in the world's market. Maize crop can be cultivated in all seasons throughout the year. As a result, maize stem pith could be used as a substitute for currently available low-density excipients. Jowar is globally known as the "new quinoa" for its gluten-free and whole-grain goodness. It goes by the name of Sorghum in English. The botanical name of Jowar is Sorghum bicolor, belonging to the family Poaceae. The cultivation and harvesting of jowar is carried out similarly to that of the maize[15]. The wet granulation method is utilized in this experiment for tablet formation; a gastro-retentive captopril tablet is made with natural polymer Maize Stem Pith powder and Jowar Stem Pith powder in varied quantities. The batches were prepared by using design expert software. The study aimed to create a captopril gastro-retentive sustained-release tablet using Maize Stem Pith powder and Jowar Stem Pith powder with a dissolution profile similar to BRUTORIL 50.

2. MATERIALS AND METHODS

2.1 Materials

The fresh stems of the maize plant and jowar plant were collected from the home farm of Jamthi, Tal. Bodwad, Dist. Jalgaon (Maharashtra) in December. The maize plant and Jowar plant were authenticated before the research study. The Department of Botany, Arts, Commerce and Science College Bodwad identified these plants. The voucher specimen of Maize plant (Voucher specimen No: NHR/BOT/2022/223) and Jowar plant (Voucher specimen No: NHR/BOT/2022/224) has been deposited in the herbarium of the Department of Botany, Arts, Commerce and Science College Bodwad. Captopril was purchased from Balaji drugs Surat, (Gujarat). Vishal Agencies, Jalgaon, Maharashtra, provided HPMC (K100M), PVP (K90), Microcrystalline cellulose, Talc, Magnesium stearate, Isopropyl alcohol (99.90 %) AR grade and Hydrochloric acid (37 %) AR grade. During entire research, distilled water was utilized. BRUTORIL 50, a marketed tablet procured from Shriram Medico, Jamner, District Jalgaon (Maharashtra) was used in this study.

2.2 Methods

2.2.1 Preformulation Studies On Captopril

Preformulation studies the physicochemical characteristics of drug molecules alone or in combination with excipients.

2.2.1.1 Melting Point Determination of Captopril

Captopril melting point was determined by digital melting point apparatus.[16]

2.2.1.2 Determination of Maximum Wavelength (Λ_{max})

The wavelength of maximum absorbance was determined as per the previously established methods by using a UV-visible spectrophotometer.[17]

2.2.1.3 Linearity Curve of Captopril

Similarly, to that of the Λ_{max} determination, the captopril standard solution series were prepared with concentrations of 10, 20, 30, 40, and 50 µg/mL using 0.1N HCl. The resultant solutions were then analyzed with a UV-visible spectrophotometer by scanning between 200-400 nm at 205 nm.[17]

2.2.1.4 Compatibility Between Drugs and Excipients

- ***IR (Infra-red) study***

IR spectra of Captopril (CPT) alone, physical mixture of CPT and MSP, physical mixture of CPT and JSP, and physical mixture of CPT, MSP, and JSP were performed on Fourier Transform Infrared Spectrophotometer (MIRacle 10), as per the previously established methods.[18]

- ***DSC (Differential Scanning Calorimetry) study***

Thermogram of Captopril (CPT) alone, physical mixture of CPT and MSP, physical mixture of CPT and JSP, and physical mixture of CPT, MSP, and JSP were performed on a Mettler Toledo, as per the previously established methods.[19]

2.2.2 *Preparation of MSP and JSP Powder*

The maize plant is sowed between the last week of May to 2nd the week of June (Kharif season) and harvested in late September or October. After the harvesting of maize from the plant, the remaining stem part was allowed to dry completely. Then dried stem was used for further use. First, the outer covering of the stem was removed and the inside spongy pith portion was separated. The obtained pith portion was then separated for any other impurities. The crude pith was then subjected to size reduction using a cutter mill to obtain MSP powder. In a similar war JSP powder was prepared.

2.2.3 *Formulation of Gastro-Retentive Tablets*

Ingredients mentioned in the formula were weighed accurately. Weighed PVP-K90 was then slowly added to isopropyl alcohol and stirred until it dissolved. The resultant clear solution is used as a binder for wet granulation method of tablet preparation. Then Captopril, MSP powder, JSP powder, HPMC (K100M), sodium bicarbonate and microcrystalline cellulose were blended uniformly using mortar and pestle for 30 minutes. The previously prepared binder was added dropwise to the resultant blend. The precaution was taken to avoid the formation of a lump during granulation. The granulation yielded a cohesive mass which was then passed through 20# sieve to prepare the granules. The granules were subjected to drying in an oven maintained at a temperature of 40 °C. After drying, the granules were screened through 16# sieve. Finally, produced granules were uniformly mixed with talc and magnesium stearate for lubrication after passing through a 30# screen. Finally, a tablet compression machine was used to compress 300 mg of the granules into a tablet.[20]

2.2.4 *3^2 Full Factorial Design*

Using Design-Expert 13.0.12.0, the compositions were designed using a 3^2 full factorial design. In this study, two components were examined on three levels for each of them, and nine combinations of experimental trials were made. Table 1 lists the coded components and levels for the 3^2 full factorial designs, and Table 2 provides the formula for the gastro-retentive tablet.[21,22]

Table 1: 3^2 full factorial design with coded factors and levels

Coded factor	Actual factor	Unit	Type	Coded level			Actual level		
				Low	Medium	High	Low	Medium	High
X1	The concentration of MSP powder	%	Numerical	-1	0	+1	6	9	12
X2	The concentration of JSP powder	%	Numerical	-1	0	+1	4	6	8

Table 2: Formula for gastro-retentive tablet

Sr. No.	Ingredients	R1	R2	R3	R4	R5	R6	R7	R8	R9
1	Captopril	50	50	50	50	50	50	50	50	50
2	MSP powder	18	18	18	27	27	27	36	36	36
3	JSP powder	12	18	24	12	18	24	12	18	24
4	HPMC (K100M)	36	36	36	36	36	36	36	36	36
5	Sodium bicarbonate	30	30	30	30	30	30	30	30	30
6	PVP-K90	10	10	10	10	10	10	10	10	10
7	Microcrystalline cellulose	136.5	130.5	124.5	127.5	121.5	115.5	118.5	112.5	106.5
8	Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
9	Magnesium stearate	3	3	3	3	3	3	3	3	3
10	Isopropyl alcohol	Q. S. (Applicable to all batches)								
Total tablet weight		**300** (Applicable to all collections)								

All values in the table are in mg.

2.2.5 *Evaluation of Granules*

- Bulk density: The granules were poured into a measuring cylinder having 100 mL capacity and tapped 4-5 times to determine the bulk density. Bulk density was calculated as the granules' weight to volume ratio. It is often given in (g/cm^3).[23]
- Tap density: The granules were poured into a measuring cylinder having 100 mL capacity and tapped 100 times to determine the tap density. Tap density was calculated as the granules' weight to volume ratio. It is often given in (g/cm^3).[23]
- The angle of repose: The angle of repose determines the flow properties of the granules. A paper was placed on a horizontal plane, and a funnel was kept straight in a stand above it. 10 g of granules were added into the funnel. The powder will then be released from the tip of the funnel and create a sharp, uniform and conical heap on the paper. Using a scale, the heap height was noted. The following formula was used to compute the angle of repose. [23]

  $Ø = \tan^{-1}(h/r)$
- Compressibility index: The compressibility index also describes the flow properties of the granules. It is calculated by using the following formula. [23]

Compressibility index = 100 * (Tap density – Bulk density) / Tap density.

Where, Ø- angle of repose, h- height of heap, and r- radius of the heap

2.2.6 *Evaluation of Gastro-Retentive Tablets*

- **Physical dimension:** The tablet's thickness and diameter was measured using a vernier caliper.

[23]ardness**:** Hardness indicates the measure of the tablet to withstand mechanical shocks during handling and transportation. It was determined by using a Monsanto hardness tester. [23]

- **Weight variation test:** Random 20 tablets were selected, weighed individually, and the average weight was determined. The % deviation of each pill following the average weight was calculated. % Deviation was cross-checked as per the tablet weight variation test's IP standard. [23]
- **Friability:** The friability was tested using the Roche friabilator. The apparatus mentioned above, which rotates at a speed of 25 rpm, was loaded with twenty tablets after being precisely weighed. The tablets were considered after 4 minutes to assess the % weight loss. [23]

$$\% \, Loss = \frac{Initial\ weight\ of\ the\ tablets - Final\ weight\ of\ tablets}{Initial\ weight\ of\ tablets} \, X\ 100$$

- **Drug content:** Randomly, twenty tablets were selected and triturated to obtain the powder. The powder containing the drug equivalent to 25 mg was weighed and placed in a volumetric flask (capacity- 100 ml) containing 0.1 N HCl. It was shaken to dissolve the medication properly. The volume was made using 0.1 N HCl. The same medium was used for further dilutions to prepare the resultant solution of 10 µg/mL of Captopril. The final solution was then filtered, and the filtrate was analyzed using UV visible spectrophotometry at 222 nm to get the absorbance. The drug content was then determined. [24]
- **Floating lag time:** When tablets are placed into a dissolution medium, the time taken by the tablet to come to the surface is called floating lag time. A glass beaker of 250 mL capacity containing 0.1 N HCl was used for the test. [25]
- **Floating time:** It is the time up to which the tablet remains floating on the surface of the dissolution medium. Floating time was measured using a USP type-II dissolution test apparatus containing 900 mL of 0.1 N HCl maintained at 37±0.5 °C. [25,26]
- **Swelling index:** The swelling index is the ability of dosage form to absorb water and swell. It was performed using a USP type- I (basket) dissolution test apparatus containing 900 mL of 0.1 N HCl maintained at a temperature of 37±0.5 °C. Periodically the tablets were withdrawn, and excess water was removed using blotting paper and weighed. The swelling index was determined by using the following formula.[27]

$$\% \, Swelling\ index = \frac{Final\ weight\ of\ the\ tablet - Initial\ weight\ of\ tablet}{Initial\ weight\ of\ tablet} \, X\ 100$$

- **In-vitro dissolution studies:** In-vitro dissolution study was performed for 12 hrs. by using a USP type- II dissolution test apparatus containing 900 mL of 0.1 N HCl maintained at 37±0.5 °C with the rotational speed of paddle 50 RPM. Periodically 7 mL sample was removed and filtered and 5 mL of which was diluted to 10 mL. The resulting samples were analyzed using a visible UV spectrophotometer to measure absorbance at 222 nm[28]. Under dissolution studies, various parameters were estimated such as the estimation of t_{75} of % CDR[29], f1, and *f2*[30]*, and* drug release kinetic studies 31 and mean dissolution time (MDT).[32]

2.2.7 Optimization Study

The optimization study was conducted to find the optimal formulation that meets most specified tablet properties. The most effective formulation was found using dependent factors such as floating time, t_{75} of drug release, and swelling index. This study utilizes Design-Expert 13.0.12.0 and a 3^2 full factorial design. The rationale for choosing or identifying the optimum formulation among all nine trials of the gastro-retentive pill can be found in optimization research, which looks into the impact of all independent factors on all dependent factors.[24]

2.2.8 Stability Study

The best-selected optimized tablets (R9) were subjected to six months accelerated stability study at 40 °C and 75 % RH. As per the stability guideline protocol, tablet samples were periodically tested with various parameters. (FDA: guidelines for stability studies, www.ich.org/ stability testing-for-new-dosage-forms. HTML).[33]

2.2.9 Statistical Analysis

When n is 3, data are shown as mean standard deviation (SD). Student t-test differences were used for statistical analysis, and statistical significance was determined at $p \leq 005$.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies on Captopril

3.1.1 Melting Point Determination of Captopril

According to the melting point apparatus, Captopril has a melting point of 106-108 °C.

3.1.2 Determination of Maximum Wavelength (Λ_{max})

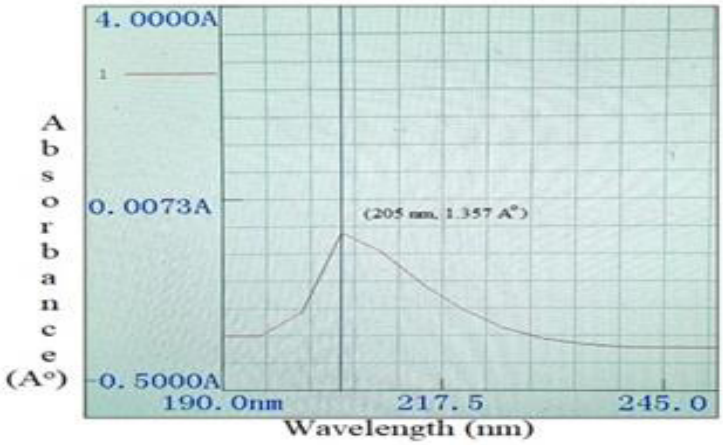

Fig 1: λ_{max} of captopril in 0.1N HCl

The Λ_{max} of captopril solution having a concentration of 30 µg/mL in 0.1 N HCl was found to be 205 nm. It helps determine drug concentration in drug release studies every time. [34]

3.1.3 Linearity Curve of Captopril

Captopril's concentration versus absorbance curve in the concentration range from 10 to 50 µg/mL showed a linear relationship with the equation of straight line y = 0.0344x + 0.1862 and R^2 value 0.993. [34]

3.1.4 Compatibility Between Drugs and Excipients

3.1.4.1. IR (Infra-red) Study

Table 3: Interpretation of Captopril by IR

Sr. No.	Observed peak (cm^{-1})	Functional group
1	1755.2	C=O (stretching)
2	1336.7	C-N (Stretching)
3	1477.5	CH_3 group
4	1612.5	C=O of Amide
5	1755.2	C=O of -COOH group
6	2585.4	SH stretching
7	2980.1, 2879.8	C-H stretching

FTIR spectra of Captopril (CPT), physical mixture of CPT and MSP, physical mixture of CPT and JSP, and physical mixture of CPT, MSP, and JSP as shown in Figure2, 3, 4, and 5respectively were taken to check the compatibility of the drug with excipient used in the tablet formulation. Various prominent peaks with their corresponding functional groups are given in table 3. The active group in the structure of polymers provides an idea about the chemical nature and its reactivity toward various drugs. [35]

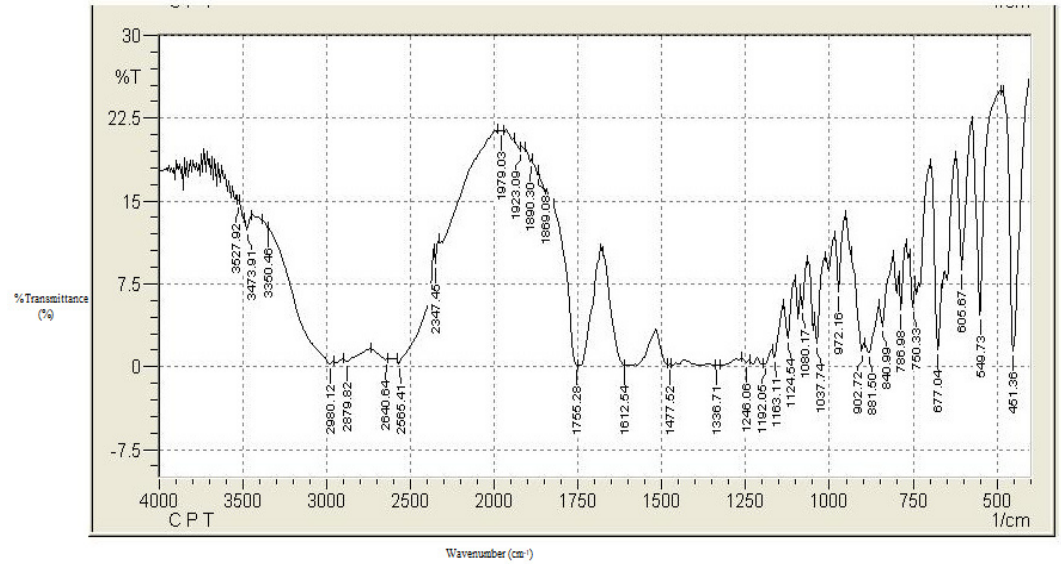

Fig2: IR spectra of CPT

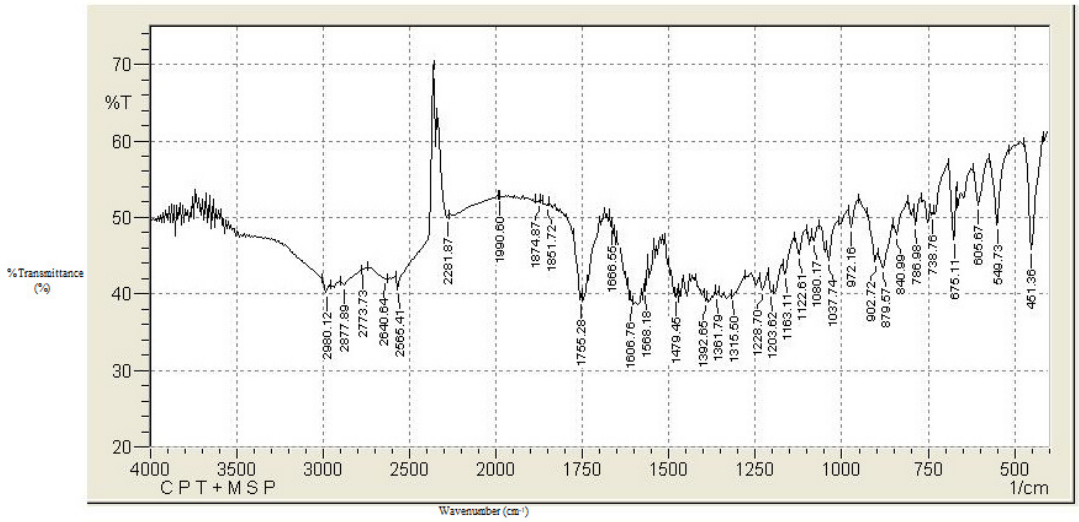

Fig 3: IR spectra of physical mixture of CPT and MSP

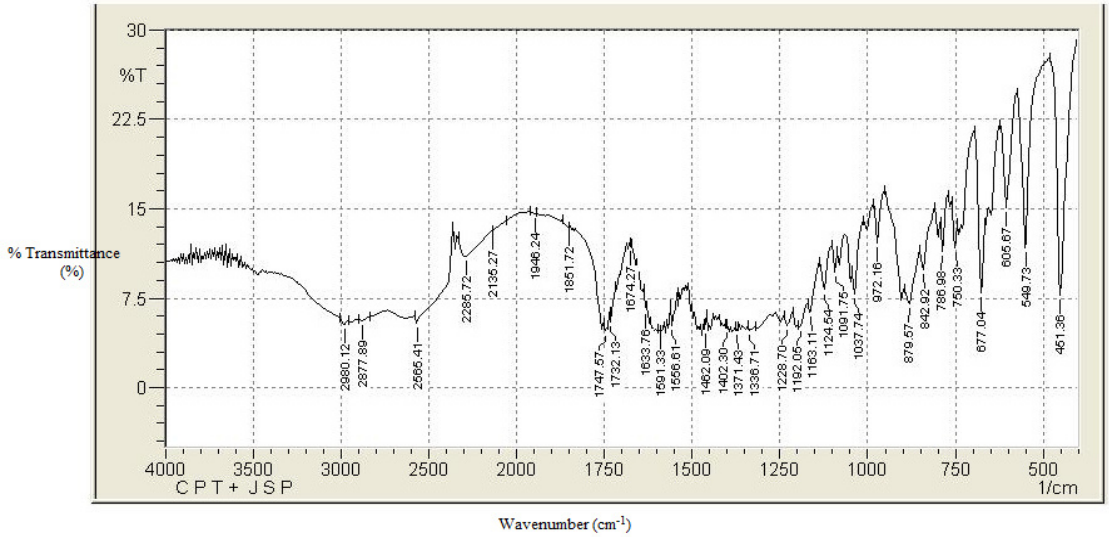

Fig 4: IR spectra of physical mixture of CPT and JSP

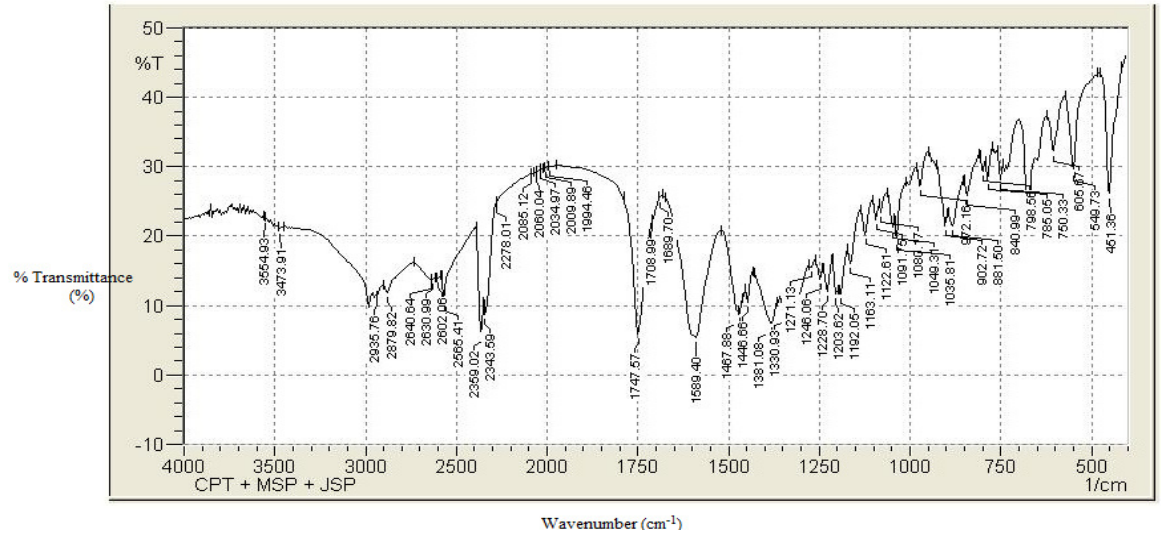

Fig 5: IR spectra of physical mixture of CPT, MSP and JSP

Cross-checking the prominent peaks of some characteristic functional groups in CPT alone with the IR spectra of physical mixtures of CPT and MSP, physical mixture of CPT and JSP, and physical mixture of CPT, MSP, and JSP, it can be revealed that there is no significant shifting of peaks observed. As a result, there appears to be no chemical interaction among the CPT, MSP, and JSP.

3.1.4.2. DSC (Differential Scanning Calorimetry) Study

The DSC thermogram of Captopril indicated a characteristic endothermic peak at 107.55 ˚C, which suggests the melting point of Captopril. However, when 2 or more chemicals are mixed, there are chances of occurring specific chemical reactions which may lead to the degradation of active molecules. So degraded drug doesn't show the sharp endothermic peak strictly at its melting point. Thus DSC technique helps check the compatibility of novel polymer/s with the drug. [19] When DSC spectrum of CPT was compared with a physical mixture of CPT and MSP, a physical mixture of CPT and JSP, and a physical mixture of CPT, MSP and JSP, no shifting of the endothermic peak of the drug was found. Thus it can be revealed that there is no interaction among the CPT, MSP and JSP.

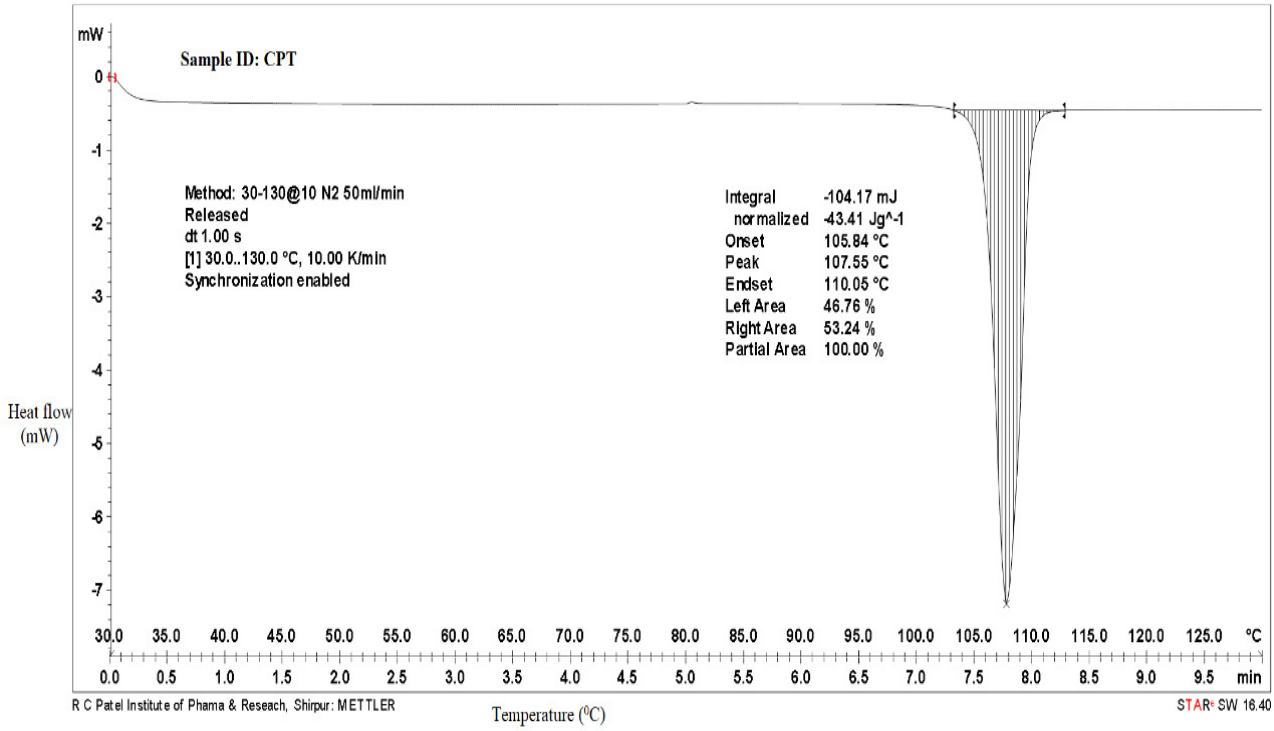

Fig 6: DSC spectrum of CPT

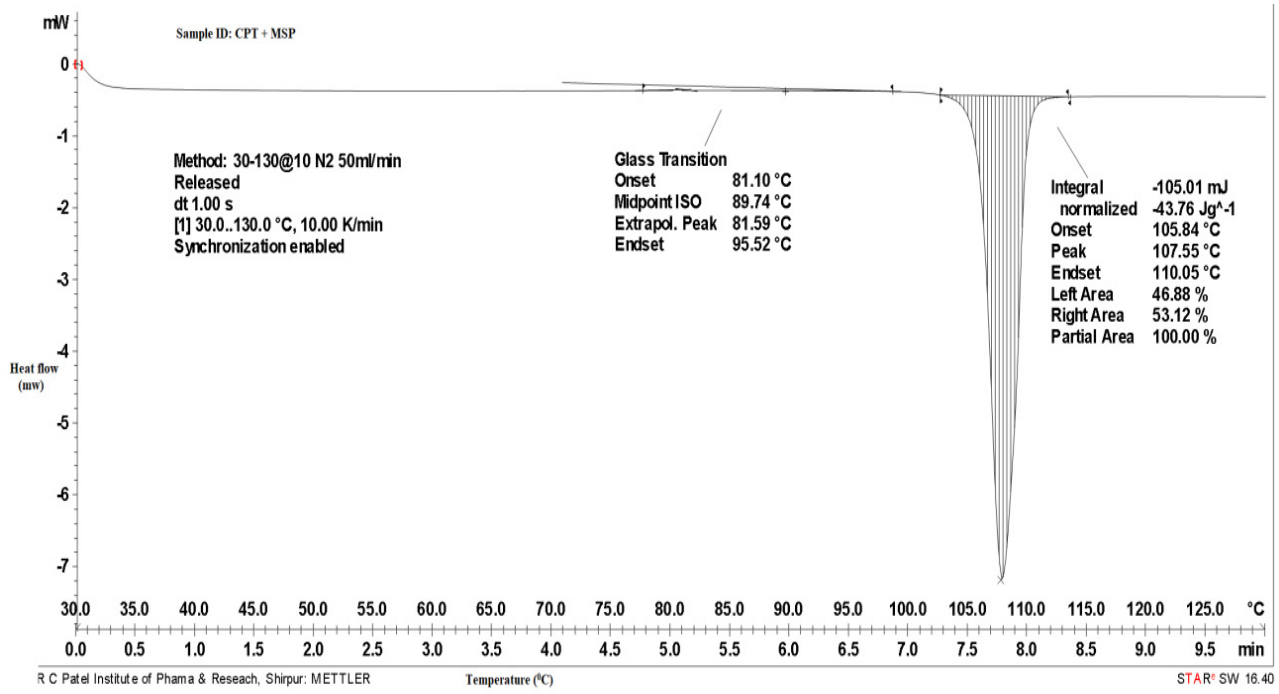

Fig 7: DSC of physical mixture of CPT and MSP

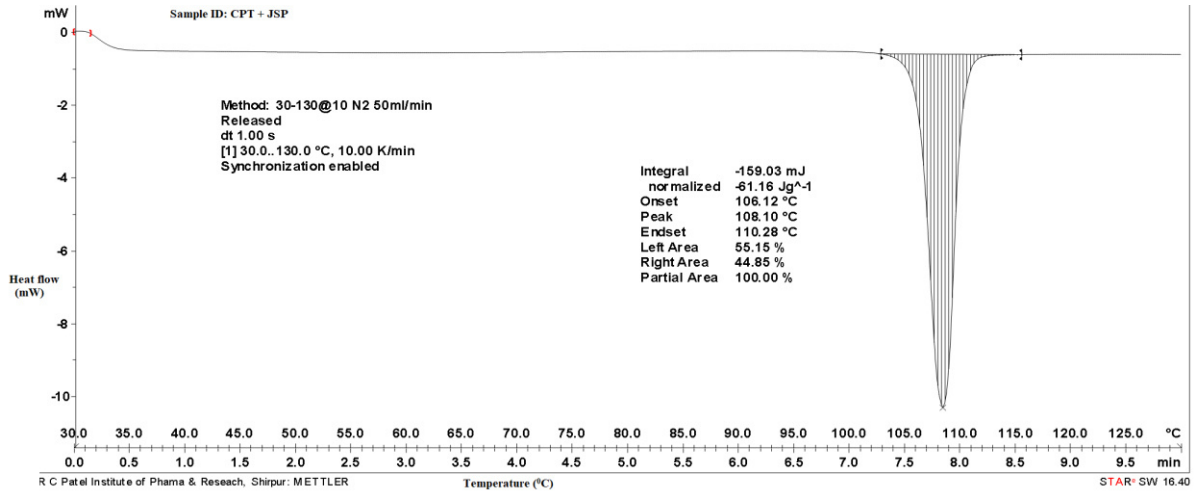

Fig 8: DSC of physical mixture of CPT and JSP

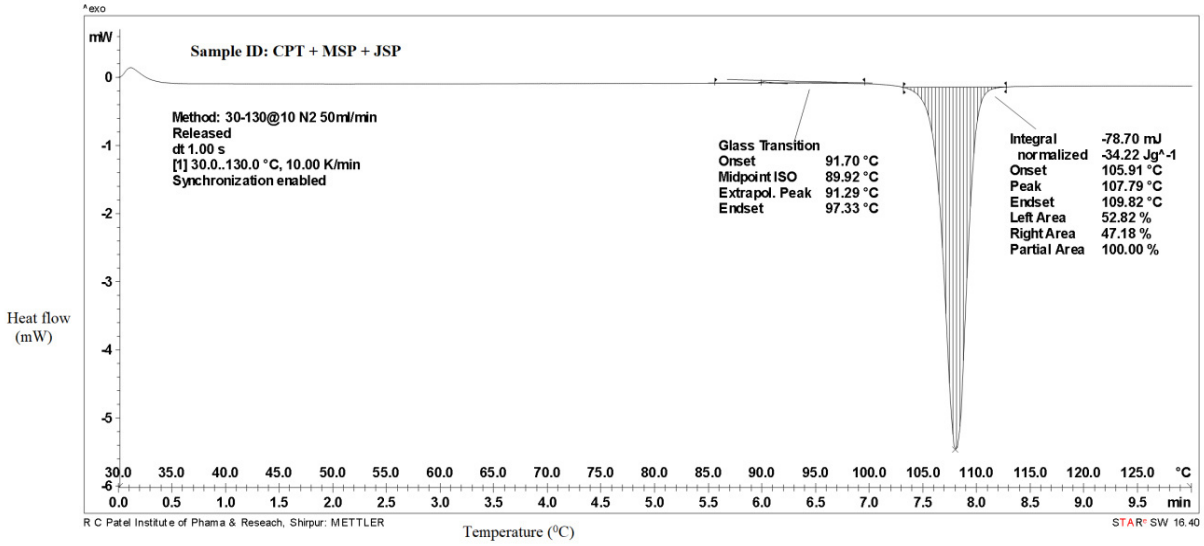

Fig 9: DSC of physical mixture of CPT, MSP, and JSP

Table 4: Interpretation of Captopril by DSC			
Sr. No.	Name of sample	Sharp endothermic peak (°C)	Inference
1	CPT	107.55	No significant shifting of the sharp endothermic peak was observed.
2	CPT + MSP	107.55	
3	CPT + JSP	108.10	
4	CPT + MSP + JSP	107.79	

3.2 Evaluation of granules

Table 5: Evaluation of granules					
Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	The angle of repose (^{0})	Compressibility index (%)	Hausner's ratio
R1	0.352±0.1	0.593±0.3	25.6±0.3	12.6±0.2	1.3±0.3
R2	0.356±0.5	0.482±0.7	24.7±0.6	14.5±0.6	1.1±0.2
R3	0.366±0.2	0.632±0.5	26.4±0.3	10.9±0.2	1.3±0.6
R4	0.482±0.4	0.549±0.8	27.2±0.5	9.4±0.3	1.2±0.7
R5	0.321±0.2	0.471±0.1	24.4±0.8	13.1±0.7	1.1±0.8
R6	0.387±0.5	0.495±0.2	28.4±0.3	13.4±0.3	1.3±0.3
R7	0.548±0.5	0.654±0.2	27.4±0.1	12.4±0.2	1.1±0.3
R8	0.458±0.7	0.589±0.4	25.1±0.2	18.6±0.3	1.2±0.5
R9	0.356±0.9	0.486±0.3	25.9±0.1	17.8±0.7	1.2±0.2

**** n=3; values are expressed as mean ± SD***

The flow characteristics of granules were assessed using a variety of measures. Table 5 shows the results of granule evaluation parameters. Table 5 suggested that the granules of all 9 batches possess good flow properties. The evaluation of granules indicates the flow characteristics which decide the compression properties of the tablet. [36]

3.3 Evaluation of Gastro-Retentive Tablets

Table 6: Physical properties of gastro-retentive tablets					
Batch	Thickness (mm)	Diameter (mm)	Hardness (Kg/Cm^2)	Weight variation (mg)	Friability (%)
R1	1.95±0.5	7.90±0.3	4.88±0.7	297±0.5	0.15±0.4
R2	1.80±0.7	8.00±0.1	5.07±0.3	301±0.9	0.12±0.3
R3	1.85±0.3	7.90±0.2	4.98±0.3	294±0.5	0.11±0.9
R4	1.91±0.9	8.10±0.1	4.98±0.8	298±0.3	0.13±0.9
R5	1.93±0.3	7.90±0.6	5.10±0.5	304±0.4	0.11±0.4
R6	1.82±0.5	7.90±0.3	5.10±0.4	298±0.8	0.13±0.5
R7	1.92±0.9	8.10±0.5	4.76±0.3	295±0.7	0.16±0.4
R8	1.91±0.4	8.10±0.4	5.13±0.9	302±0.8	0.14±0.2
R9	1.87±0.3	8.10±0.5	4.60±0.3	295±0.8	0.16±0.7

**** n=3; values are expressed as mean ± SD***

All the physical properties of gastro-retentive tablets as mentioned in table 6, lies in the acceptable range of their specifications.

3.3.1. Floating Behavior and Drug Content

The values of all batches of gastro-retentive tablets for drug content, floating lag time, and floating time are cited in table 7. By looking at the importance of flowing time, it could be said that as the concentration of MSP powder and JSP powder increases, the floating time increases. Formulation R9 containing MSP powder at 12 % while as JSP powder at 8 %, showed a maximum floating time of 12 h. The photographs of the floating behavior of the gastro-retentive tablet (R9) are shown in figure 10. The pictures clearly explained that at the initial time, when the tablet was immersed into a glass beaker containing 0.1 N HCl, the tablet settled at the bottom. Then the tablet absorbed water from the surroundings, and thus, the effervescence of CO_2 was generated, which further resulted in the floating of the tablet. Here floating lag time was observed to be 5-7 sec. The tablet floated continuously till 6 and 12 hours as shown in the photograph. This suggests that the combined use of MSP powder and JSP powder in gastro-retentive tablet formulation helps to ameliorate the floating time, which could be attributed to the low density of both novel polymers[37]. As mentioned in table 7, drug content values range from 95 to 105 %. So drug content satisfied the criteria of Captopril as per IP.

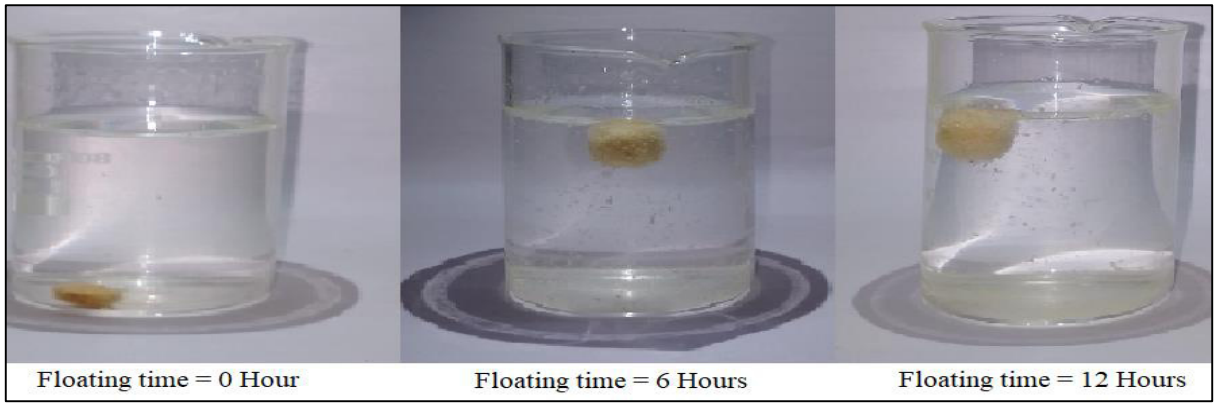

Fig 10: Floating behavior of gastro-retentive tablet (R9)

Table 7: Drug content with floating behaviour of gastro-retentive tablets

Batch	Drug Content (%)	Floating lag time (Sec.)	Floating time (Hrs.)
R1	103.22±0.3	16±0.5	5±0.3
R2	101.97±0.2	12±0.4	6±0.2
R3	102.12±0.2	20±0.2	6.5±0.9
R4	102.22±0.4	11±0.1	7±0.7
R5	100.39±0.3	15±0.2	8±0.7
R6	99.67±0.7	12±0.7	9.5±0.3
R7	102.98±0.5	10±0.8	8±0.5
R8	101.57±0.9	22±0.6	11±0.8
R9	99.45±0.7	7±0.4	12±0.9

*** n=3; values are expressed as mean ± SD**

3.3.2. Swelling Index

By observing the table 8 and Figure 12, it could be revealed that the swelling index of gastro-retentive tablet ameliorates as the combined concentration of both MSP powder and JSP powder increases. But the concentration of MSP powder affects the swelling index to a greater extent than that of the JSP powder in the given combination. The highest swelling index (145.77 % at 11 h) was obtained for the formulation batch R9. The photographs of swelling behavior of gastro-retentive tablet (R9) are shown in figure 11. The gastro-retentive tablet at initial time was found to be intact with no water absorption. But as time proceeded, the polymer MSP powder, JSP powder, and HPMC (K100M) absorbed water and led to swelling of the tablet. The tablet dimension increased after 5 hrs and 10 hrs due to swelling, as shown in photographs. This indicated that MSP powder and JSP powder both possess swelling properties, which may be useful to achieve sustained release properties from the gastro-retentive tablet. [38]

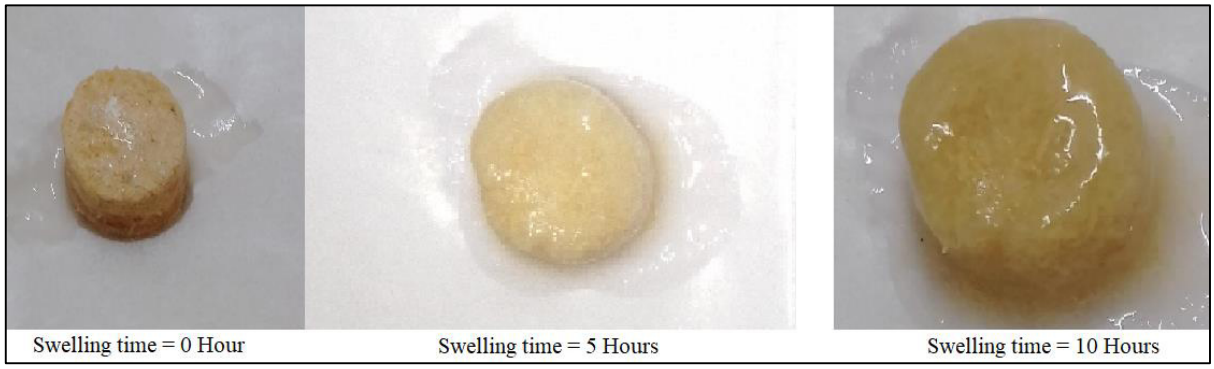

Fig 11: Swelling behavior of gastro-retentive tablet (R9)

Table 8: Swelling index of gastro-retentive tablets

Time (h)	Swelling index (%)								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
0	0	0	0	0	0	0	0	0	0
1	18.93±0.4	20.32±0.6	23.45±0.5	25.76±0.1	22.47±0.3	20.40±0.2	18.28±0.4	22.38±0.3	27.33±0.2
2	50.22±0.5	54.67±0.3	50.65±0.2	48.09±0.2	52.56±0.5	47.80±0.2	42.46±0.9	46.56±0.5	48.43±0.2
3	71.86±0.9	75.89±0.1	78.56±0.5	82.45±0.2	78.49±0.7	77.86±0.9	72.90±0.3	75.89±0.5	82.38±0.1
4	71.72±0.3	83.35±0.2	87.32±0.2	94.12±0.7	87.90±0.8	92.47±0.8	90.43±0.2	87.55±0.3	95.46±0.4

5	-	85.98±0.2	90.23±0.8	103.23±0.4	98.38±0.9	102.49±0.8	105.77±0.2	107.45±0.8	109.67±0.2
6	-	-	92.34±0.9	105.68±0.3	112.37±0.1	109.26±0.7	118.30±0.2	118.37±0.3	116.29±0.8
7	-	-	-	-	118.45±0.6	117.19±0.9	128.39±0.1	123.88±0.2	125.55±0.3
8	-	-	-	-	-	122.31±0.4	-	127.22±0.7	132.46±0.8
9	-	-	-	-	-	127.57±0.2	-	130.44±0.2	138.77±0.6
10	-	-	-	-	-	-	-	132.57±0.2	142.33±0.7
11	-	-	-	-	-	-	-	-	145.77±0.4

** n=3; values are expressed as mean ± SD*

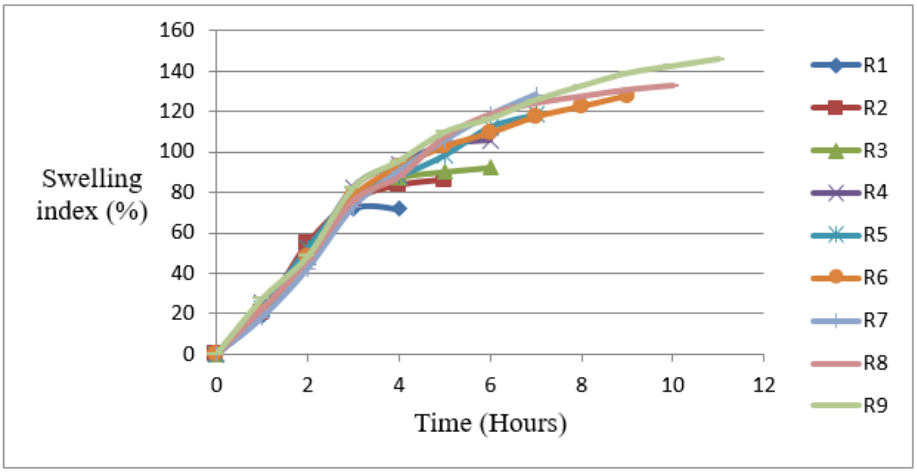

Fig 12: Comparison of swelling index of R1 to R9

3.3.3. In Vitro Dissolution Studies

Table 9: % Cumulative drug release of gastro-retentive tablets

Time (Hrs.)	% Cumulative drug release (%)									
	R1	R2	R3	R4	R5	R6	R7	R8	R9	BRUTAL 50
0	0	0	0	0	0	0	0	0	0	0
0.5	10.48±0.4	14.27±0.6	9.22±0.7	10.27±0.3	14.69±0.2	13.53±0.6	16.69±0.1	17.95±0.3	13.53±0.6	13.53±0.4
1	25.22±0.7	21.74±0.9	17.64±0.5	18.48±0.2	24.27±0.5	26.06±0.6	21.95±0.2	25.01±0.2	19.95±0.4	24.90±0.5
1.5	35.11±0.5	31.01±0.8	24.69±0.8	26.06±0.4	31.85±0.3	32.69±0.3	29.01±0.7	32.8±0.8	28.06±0.5	30.8±0.2
2	40.16±0.4	38.69±0.2	36.37±0.2	37.22±0.3	40.16±0.5	41.85±0.3	35.74±0.5	38.8±0.9	34.69±0.3	39.01±0.9
3	45.22±0.7	44.06±0.4	43.74±0.1	45.95±0.3	46.69±0.8	47.85±0.8	43.32±0.9	46.16±0.1	41.64±0.1	44.48±0.1
4	48.37±0.8	47.95±0.7	49.22±0.2	51.53±0.8	52.37±0.3	53.32±0.2	49.01±0.7	52.58±0.8	46.90±0.3	52.48±0.1
5	52.16±0.9	52.37±0.9	51.95±0.7	53.85±0.2	56.27±0.2	56.69±0.2	53.11±0.4	55.43±0.8	52.37±0.8	56.80±0.7
6	-	54.27±0.7	56.8±0.5	58.90±0.1	59.95±0.4	61.64±0.9	59.11±0.2	61.64±0.4	60.06±0.7	66.06±0.3
7	-	-	60.16±0.6	62.06±0.5	64.8±0.3	65.22±0.2	63.74±0.1	67.95±0.1	67.22±0.1	74.90±0.2
8	-	-	-	-	67.43±0.3	68.27±0.5	68.16±0.8	71.53±0.2	72.69±0.1	78.69±0.6
9	-	-	-	-	-	72.16±0.7	-	78.06±0.6	78.06±0.7	83.85±0.9
10	-	-	-	-	-	76.16±0.1	-	83.11±0.7	84.16±0.9	-
11	-	-	-	-	-	-	-	85.85±0.6	91.32±0.8	-
12	-	-	-	-	-	-	-	-	93.53±0.8	-

**n=3; values are expressed as mean ± SD*

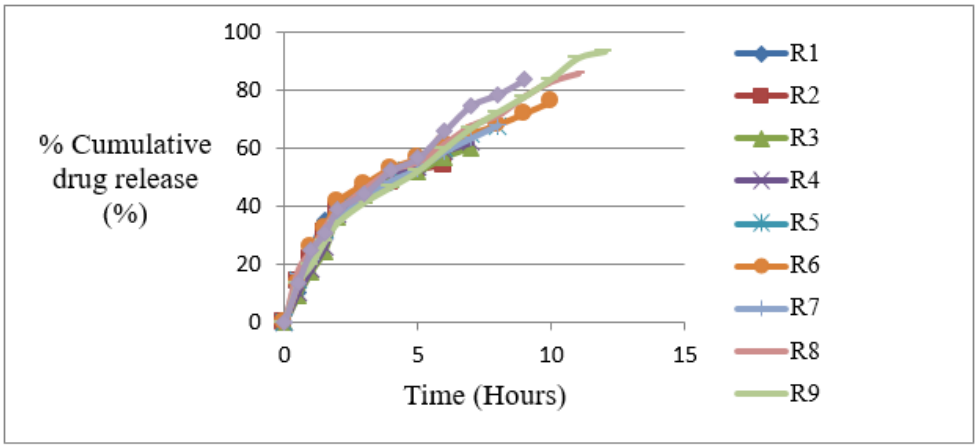

Fig 13: Comparison of % Cumulative drug release of gastro-retentive tablets

Table 9 and Figure 13 elaborate the in vitro dissolution pattern of the gastro-retentive tablet. In the current research, the drug release study is performed only up to the floating time of the corresponding tablet formulation. The predominant sustained release effect of the gastro-retentive tablet is related to HPMC (K100M). [39,40] HPMC (K100M) used provided a sustained release effect in all batches of the gastro-retentive tablet. Still, the sustained release effect is of greater importance for the period the tablet shows floating behavior. [41] The novel polymers offer the sustained release effect to a significantly lesser extent. The best-sustained release of 93.53 % at 12 h. was observed with the formulation R9, which contains the MSP powder and JSP powder at 12 % and 8 %, respectively. On the other hand, BRUTORIL 50 showed drug release 83.85 % only up to 9 h.

3.3.3.1. Estimation of t_{75} of % CDR

Table10: t_{75} of % Cumulative drug release of gastro-retentive tablets

Formulation	R1	R2	R3	R4	R5	R6	R7	R8	R9	BRUTAL 50
t_{75} (Hrs.)	6.5±0.5	7.5±0.4	7.8±0.6	7.5±0.7	7.9±0.8	8.6±0.4	8.1±0.1	8.3±0.2	8.5±0.7	6.9±0.4

**** n=3; values are expressed as mean ± SD***

t_{75} is the time required for the formulation to release 75 % of the drug. [42] It becomes very difficult to understand the effect of novel polymers on drug release by directly using drug release values. So better way, drug release can be easily understood if t_{75} values are taken for the study. [43] Table 10 showed that best formulation R9 and BRUTORIL 50 showed t_{75} value 8.5 and 6.9 h. respectively.

3.3.3.2. Estimation of f1 and f2

This research compares all prepared gastro-retentive tablets with the marketed formulation BRUTORIL 50. Table 11 shows *f1* and *f2* values. The *f1* values of all formulations are less than 15, while *f2* values are more than 50, which fulfills the similarity and dissimilarity factor criteria. The requirements for identical formulations in respect to drug release are similarity factor should be greater than 50 while as dissimilarity factor should be less than 15. [44]

Table 11: f1 and f2 values of gastro-retentive tablets

Formulation	R1	R2	R3	R4	R5	R6	R7	R8	R9
f1	6.9±0.6	7.8±0.2	13.1±0.5	10.3±0.4	8.5±0.8	8.6±0.4	11.9±0.2	7.0±0.1	11.0±0.5
f2	77.6±0.3	67.4±0.7	58.3±0.3	62.5±0.9	63.6±0.3	64.7±0.2	61.2±0.6	62.2±0.6	63.6±0.4

**** n=3; values are expressed as mean ± SD***

3.3.3.3. Drug Release Kinetic Studies

Dissolution study data was fitted to various release kinetic models to know the drug release mechanism. R^2 values are shown in table12, suggesting the best-fit model of gastro-retentive tablets among all gastro-retentive tablets. [45]

Table 12: Curve fitting of drug release of gastro-retentive tablets

Formulation	R^2				Release exponent (n)
	Zero order	First order	Higuchi	Korsmeyer Peppas	
R1	0.822±0.4	0.637±0.5	0.953±0.2	0.934±0.3	0.419±0.3
R2	0.852±0.2	0.762±0.2	0.976±0.6	0.939±0.2	0.482±0.5
R3	0.896±0.6	0.741±0.1	0.972±0.5	0.944±0.9	0.606±0.4
R4	0.893±0.7	0.750±0.2	0.973±0.9	0.945±0.7	0.600±0.9

R5	0.875±0.7	0.771±0.2	0.986±0.8	0.776±0.5	0.469±0.6
R6	0.872±0.8	0.733±0.7	0.982±0.6	0.982±0.4	0.438±0.8
R7	0.918±0.9	0.863±0.8	0.997±0.4	0.990±0.9	0.522±0.7
R8	0.930±0.	0.857±0.1	0.997±0.1	0.994±0.6	0.491±0.8
R9	0.966±0.2	0.860±0.8	0.991±0.2	0.993±0.7	0.595±0.7
BRUTAL 50	0.944±0.2	0.833±0.2	0.991±0.2	0.991±0.2	0.543±0.9

**** n=3; values are expressed as mean ± SD***

The curve-fitting results of drug release data indicated that the release of Captopril from most gastro-retentive tablets follows the Higuchi model. Some formulation also follows Korsmeyer Peppas model due to the presence of HPMC (K100M) rate-controlling polymer matrix. The release exponent (n) values indicate mostly the anomalous (non-fickian) diffusion mechanism of drug release. [46]

3.3.3.4. Mean Dissolution Time (MDT)

MDT indicates the drug release retarding efficiency of polymer. A higher MDT indicates a higher drug release retarding ability of the polymer and vice versa. [47] Values of MDT of all the formulations are mentioned in table 13. By looking towards MDT values it could be said that as the concentration of MSP powder and JSP powder ameliorates, a slight rise in MDT was observed. [48]

Table 13: MDT of gastro-retentive tablets

Formulation	R1	R2	R3	R4	R5	R6	R7	R8	R9	BRUTORIL 50
MDT (Hrs.)	1.44±0.5	1.68±0.6	2.26±0.1	2.22±0.3	2.37±0.4	3.03±0.9	2.67±0.1	3.70±0.7	4.53±0.9	3.28±0.2

**** n=3; values are expressed as mean ± SD***

3.3 Optimization study

Figures 14, 15, 16, 17, 18, and 19 illustrate how the plots from the design expert study explain the influence of independent variables on dependent variables. The concentration of MSP powder has a predominant effect on both floating time and swelling index. [49] As the concentration of MSP powder increases, floating time and swelling index increase. Similarly, the concentration of JSP powder also significantly affects the floating time and swelling index. But the effect of JSP powder is less predominant than that of MSP powder. The concentration of MSP powder and JSP powder has significantly less effect on t_{75} of % CDR. Therefore, it can be revealed that R9 is the optimized formulation among all formulated tablets. Hence, novel polymers MSP powder and JSP powder could be used as good low-density polymers in designing the gastro-retentive tablet. Polynomial equations in coded factors are given below.

$$\text{Floating time: } Y1 = 8.11 + 2.25X1 + 1.33X2 + 0.625X1X2$$

$$t_{75} \text{ of \% CDR: } Y2 = 7.86 + 0.5167X1 + 0.4667X2$$

$$\text{Swelling index: } Y3 = 112.05 + 26.12X1 + 9.98X2$$

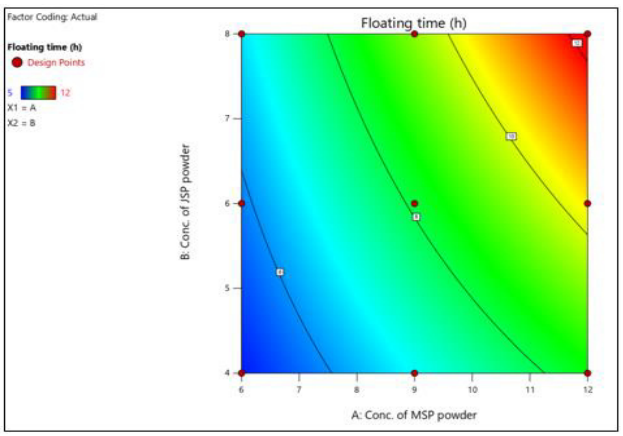

Fig 14: Contour plot of floating time

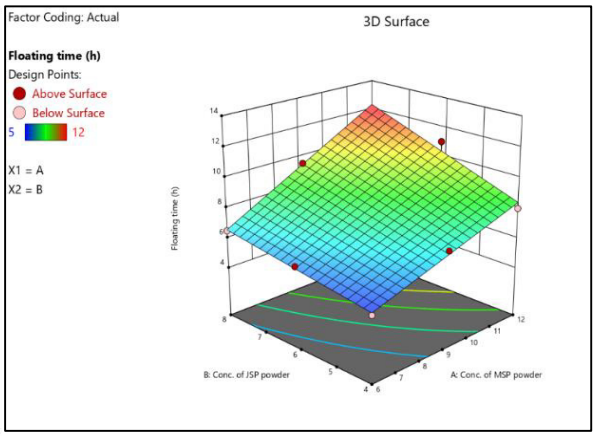

Fig 15: Response surface plot of floating time

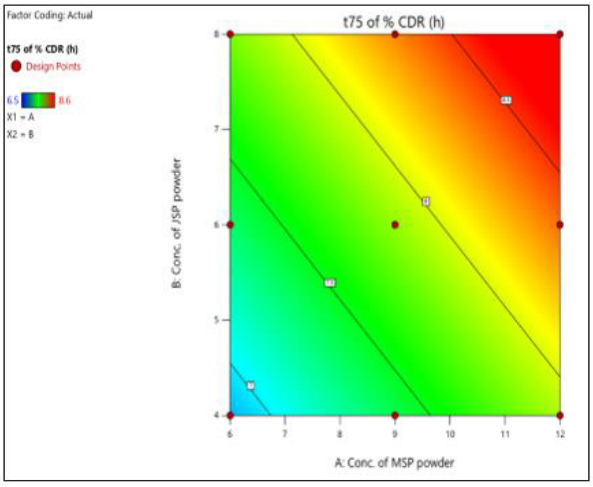

Fig 16: Contour plot of t_{75}

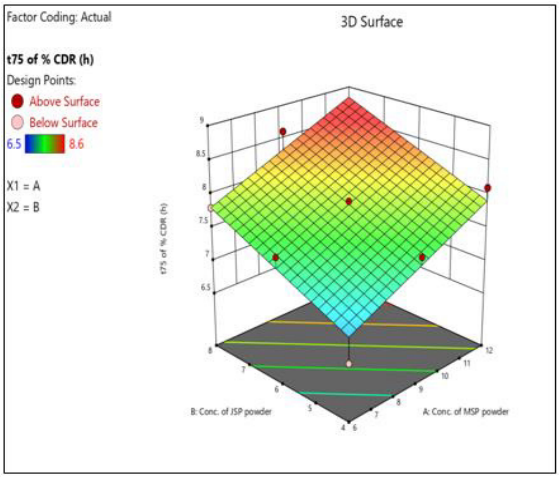

Fig 17: Response surface plot of t_{75}

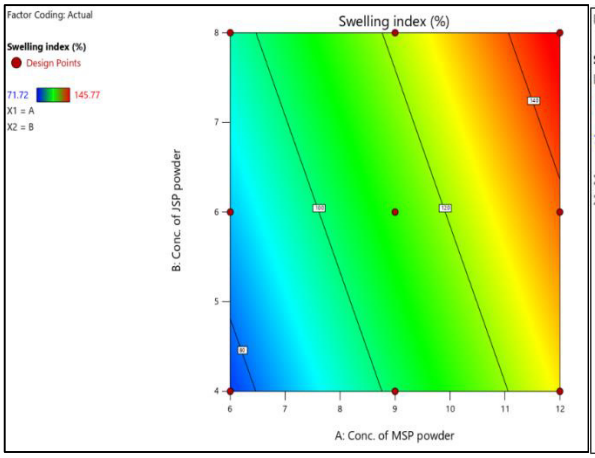

Fig 18: Contour plot of swelling index

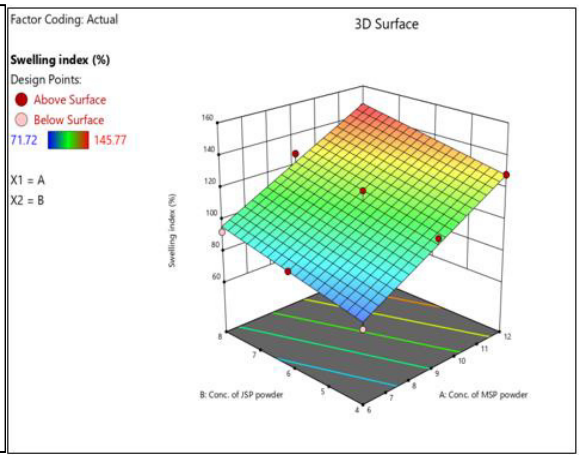

Fig 19: Response surface plot of swelling index

3.4 Stability study

The best-selected formulation R9 was then subjected to an accelerated stability study at 40˚C ±2˚C temperature, and 75% ±5% relative humidity (RH)are mentioned in table 14.

Table 14: Accelerated stability study

Duration of stability study	Description	Floating time (Hrs.)	t_{75} of % CDR (Hrs.)	Swelling index (%)	Drug content (%)
Initial	Yellowish tablet	12±0.5	9.0±0.8	149.60±0.2	99.77±0.2
After 3 months	Yellowish tablet	12.5±0.2	8.5±0.6	155.36±0.5	102.55±0.7
After 6 months	Yellowish tablet	12±0.9	8.5±0.2	142.33±0.1	100.75±0.2

**** n=3; values are expressed as mean ± SD***

The accelerated stability study was carried out for the best-selected formulation, R9. The stability study results revealed that floating time, t_{75} of % CDR, swelling index, and drug content are within acceptable limits. Furthermore, no considerable change in the results was observed after 3rd and 6th month of the stability study. Thus, formulation R9 can be said to be stable.

4. CONCLUSION

Based on the result and discussion in this research, formulation R9 of gastro-retentive captopril tablet containing MSP powder and JSP powder at 12 % and 8 % concentration showed good buoyancy (floating) up to 12 h. On the other hand, it showed an expected sustained release profile for 12 h with HPMC (K100M). The results suggested that when the gastro-retentive tablet of Captopril (R9) showed a better-sustained release profile than that of BRUTORIL 50. An optimization study indicated that the concentration of MSP powder and JSP powder has a predominant effect on both floating time and swelling index when used in combination, which is directly proportional. Based on optimization studies, it is obvious that MSP powder and JSP powder could be used as compelling low density novel natural polymers with desired floating and swelling ability to prepare gastro-retentive tablet of Captopril.

5. ACKNOWLEDGEMENT

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6. AUTHORS CONTRIBUTION STATEMENT

Bhushan P. Gayakwad designed the entire research work, including collection of natural polymers, procurement of chemicals, formulation, and evaluation of gastro-retentive tablets. Sunil R. Bavaskar performed preformulation study of drug. Sandip Fulzele carried out an evaluation study of granules. Reenu Yadav performed stability studies of gastro-retentive tablet. Vinod Gauttam conducted optimization study. Jyotiram Sawale prepared manuscript. All authors read and approved the final version of the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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