ORIGINAL ARTICLE

Formulation Development and *in vitro* Characterizations of Captopril Triple Layer Matrix Tablets

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Abstract

Background: Captopril, an antihypertensive agent, has a relatively short elimination half-life (2 h). Thus, there is a strong clinical need and market potential for a dosage form that will deliver Captopril in a sustained manner. **Objective:** The objective of the present work was to formulation development and *in vitro* characterizations of Captopril triple layer matrix tablets using Sodium alginate for optimum drug release of Captopril to achieve sustain drug release to reach proper serum concentration in a specific period of time for sustained therapeutic action. **Results:** 200 mg of Sodium alginate granules containing 70% (S1), 80% (S2) of Sodium alginate on either sides of Captopril matrix granules (200 mg) containing either 30% (C1), 40% (C2) of Sodium alginate. The values of percent friability of multi-layered tablets were in the range of 0.24 ± 0.04–30.32 ± 0.07%. The hardness and friability test prove good binding of granules as wet granulation method was used. The drug content was well within the range of contained 98.32 ± 0.05–99.55 ± 0.06, indicating uniform mixing of Sodium alginate, drug, and other formulation excipient. The percentage *in vitro* drug release of formulations was ranges from 91.75 ± 0.16 to 99.76 ± 0.36. **Conclusion:** Formulation development and *in vitro* characterizations of Captopril triple-layer matrix tablets using Sodium alginate for optimum drug release of Captopril is done.

Key words: Captopril, Antihypertensive, Matrix tablet, Triple layered tablet

INTRODUCTION

The most popular method for the administration of medication is the oral route. The traditional delivery system of medicines only appreciates and retains the concentration of medicines within the therapeutically active range when taken many times a day, depending on the dosage regimen. The outcome indicates a major fluctuation in the amount of medication. Tactics to solve these traditional fluctuations contributed to the advancement of several Novel Drug Delivery Systems (NDDS). The aim of all NDDS systems is to provide the satisfying concentrations in the body with a therapeutic amount of medication at particular locations.[1]

Captopril, an antihypertensive agent, is one of the most commonly prescribed drugs for the treatment of patients with hypertension and congestive heart failure. It has been reported, however, that the duration action after a single oral dose of captopril is short; therefore, clinical use requires multiple dosing. Captopril has a relatively short elimination half-life (2 h). Thus, there is a strong clinical need and market potential for a dosage form that will deliver captopril in a sustained manner to a patient needing this therapy, for better patient compliance and therapeutic efficacy, to reduce the various side effects, and to reduce the cost of treatment.[2-4]

The extensive literature survey showed that till date no research article was observed on the proposed dosage form

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development Captopril using this natural polymer – Sodium alginate. Therefore, the aim of this study was be the formulation development and characterizations of triple-layer matrix tablets of Captopril using sodium alginate in various ratios to overcome all the problems of associated with Captopril.

MATERIALS AND METHODS

Captopril was purchased from Torrent Pharmaceutical Ahmedabad, Sodium alginate was purchased from Research Lab Fine Chem Industries, Mumbai. Magnesium stearate, starch, talc, Sodium hydroxide, and Phenolphthalein were purchased from SD Fine Chem, Mumbai.

Spectrophotometric characterization of captopril

λ_{max} determination of captopril in 0.1 N HCL buffer pH 1.2

The stock solution of Captopril was prepared by dissolving it in 0.1 N HCL buffer pH 1.2. A dilution of 10 µg/mL was kept in cuvette of path length 10 mm. The ultraviolet (UV) spectrum was recorded using a double beam UV-visible spectrophotometer (Labindia UV 3000+) in wavelength range 400 nm 200 nm using blank.

Infrared spectroscopy

The infrared spectrum of Captopril was recorded by Potassium bromide (KBr) dispersion technique using Fourier transform infrared spectroscopy (FT-IR) with diffuse reflectance attachment on IR Affinity-1 (FTIR-8001, Shimadzu, Japan). Drug sample was mixed along with IR-grade KBr in equal proportion and IR spectrum was recorded.

Drug polymer compatibility study

Drug polymer compatibility testing was performed by mixing Captopril with Sodium alginate in equal proportion then, mixture was kept under accelerated stability condition (i.e. 40 ± 2°C and 75 ± 5% RH) for a period of 21 days in a glass vials using Remi Programmable Enviornmental Test Chamber CHM 06, Vasai, India. It was hermetically sealed with a rubber stopper using molten carnauba wax. IR spectroscopy was carried out for the mixture at the starting of the study and after 21 days. The IR spectra of samples were recorded by KBr dispersion technique 2–3 mg of the sample was mixed with previously dried IR-grade KBr and kept in the sample cell. The cell was then fitted on a sample holder, spectra were recorded with FT-IR instrument (FTIR-8001, Shimadzu, Japan), and the spectral analysis was done.[5]

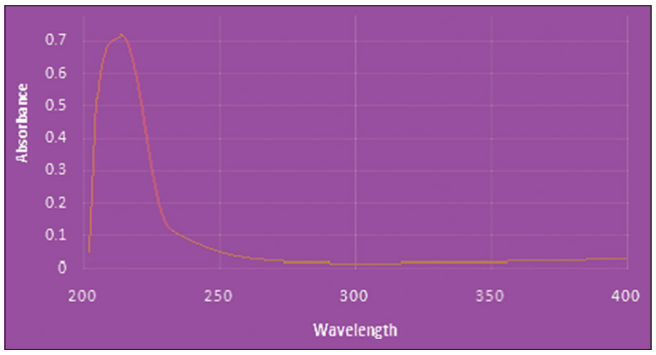

Figure 1: λ_{max} of Captopril in phosphate buffer pH 7.4

Preparation of triple layer captopril tablets by using sodium alginate

Preparation of captopril matrix granules

Captopril matrix granule formulations were prepared with 30% (D1), 40% (D2) of Sodium alginate by the wet granulation technique. The Sodium alginate was used as a matrix-forming agent. Hypromellose was used as a diluent, and Sodium alginate was included in the formulation in various proportions. The compositions of Sodium alginate matrix granules formulations used in the study containing 50 mg of Captopril in each case are shown in Table 1.

Preparation of triple-layer matrix tablets

Captopril triple-layer matrix tablets were prepared by compressing 200 mg of Sodium alginate granules containing either 70% (S1), 80% (S2) of Sodium alginate on either sides of Captopril matrix granules containing either 30% (C1), 40% (C2) of Sodium alginate. The respective batches were coded as C1S1, C1S2, C2S1, and C2S2. For the preparation of tablets, first, Captopril-matrix granules were prepared by the wet granulation method for the matrix formulation. Then Sodium alginate granules for layering over the Captopril matrix granules were prepared. The volume of the die cavity was adjusted to 600 mg. Bottom layer was prepared by slight compression of Sodium alginate granules, 200 mg, in the die cavity, which provided uniform spreading. The upper punch was lifted up, and Captopril matrix granules (for middle layer), 200 mg, were placed over the prepared bottom layer in the die cavity and slightly compressed once again. Finally, 200 mg of Sodium alginate granules (for top layer) were placed over the middle layer and compressed (08 Station Tablet Compression Machine, JMD-4-8, A Jaguar Ahmedabad, India) with a maximum compression force.

Evaluation of captopril triple-layered matrix tablets

All the different formulations of Captopril triple-layer matrix tablets prepared Sodium alginate in various concentrations were subjected for evaluation for various parameters like Diameter/Thickness, Hardness, Weight variation, Friability,[6] percent drug content,[7] *In vitro* release study, and Kinetic modeling as per standard reference procedures.

In vitro drug release studies

The in vitro release of Captopril from triple-layer tablets study was carried out using USP dissolution test apparatus

Type-II Paddle type (Electro Lab TDT 08L) using 900 mL of 0.1 N HCl pH 1.2 solution, for 2 h, and later in phosphate buffer pH 7.4 for further hours as a dissolution medium. The paddles are rotated at 75 rpm. The medium was set at 37 ± 0.50 C. Aliquot (05 mL) of the solution was collected from the dissolution apparatus at a specific time interval and was replaced with fresh dissolution medium. The withdrawn samples were analyzed by an UV spectrophotometer (Lab India 3000+) at 212 nm using blank. Aliquots were withdrawn at 1 h intervals from a zone midway between the surface of dissolution medium and the top of rotating paddle not <1 cm apart from the vessel wall. Drug content in dissolution sample was determined by software (PCP disso v2.08) version.[8]

Kinetics of drug release

The *in vitro* drug release data were analyzed by fitting them to different kinetic models to study the release kinetics and mechanism of drug from triple-layer matrix tablets.[9,10]

Selection of optimized formulation of triple-layer matrix tablets

On the basis of data obtained from the evaluation of Captopril triple layer tablets prepared using Sodium alginate gum for various official as well as non-official parameters like Diameter/Thickness, Hardness, Weight variation, Friability, percent drug content, *in vitro* release study as per standard reference procedures, etc. The formulation C2S1 had showed the best results, hence, it was selected as optimized formulation and further subjected to the accelerated stability studies according to ICH guidelines.

Table 1: Compositions of captopril triple-layer matrix tablet granules

Ingredients	Quantities (mg)	
Formulations	**C1**	**C2**
Captopril	50	50
Sodium alginate	60	80
Starch	20	20
Hypromellose	64	44
Talc	04	04
Magnesium stearate	02	02
Total weight (mg)	200	200

Table 2: Micromeritic properties of sodium alginate

S. No.	Micromeritic properties	Sodium alginate
1	Angle of repose	27.68±0.18
2	Bulk density (g/mL)	0.451±0.017
3	Tapped density (g/mL)	0.516±0.010
4	Compressibility index	12.60±0.11
5	Hausners index	1.14±0.22

Scanning electron microscopy (SEM) studies of optimized formulation of three layered matrix tablet

The three-layered matrix tablet of optimized formulation was cut into two halves by use of a sharp razor and coated with gold palladium under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The gold palladium-coated tablet was then observed with a SEM.

Accelerated stability testing of optimized formulation (C2S1) of triple layer tablets

Stability testing of optimized formulation C2S1 was carried out to determine the stability of drug and carrier, and also to determine the physical stability of formulations under accelerated storage condition at various temperatures using Remi Programmable Enviornmental Test Chamber CHM 06, Vasai, India. The prepared tablets were placed in borosilicate screw-capped glass containers. The samples were kept for 90 days at condition of 40 ± 2°C and 75± 5% RH and were analyzed at 0, 30, 60, and 90 days for their physical changes, thickness, hardness, friability, and in drug content.[11]

RESULTS AND DISCUSSION

Physiochemical characterization of sogium alginate

The Sodium alginate was selected and successfully used as a matrix-forming agent on the basis of a literature survey. The procured sample of Sodium alginate was subjected for evaluation of various physiochemical parameter:

Color and appearance

The Sodium alginate sample was examined visually and found that the Sodium alginate was light creamy-brown colored powder in color. Melting point of Sodium alginate gum was determined by open capillary method. The melting point of Sodium alginate was found 97–101°C, which was found comparable with the literature value. The swelling index of Sodium alginate was computed using the equation, and it was found as 3.95 ± 0.010. The Loss on drying value of Sodium alginate was determined as per the method A given in I.P. The Loss on drying values of Sodium alginate gum was found 4.66% w/w. which was acceptable. The pH of the 1% w/v dispersion of the Sodium alginate gum was founds 7.1 and which was comparable with the literature value. The viscosity of a 1% w/v aqueous solution, at 20°C, was found as of 190 cP. The ash value of Sodium alginate was founds 18.25% w/w. The acid value of Sodium alginate was found to be 68 due to the presence of 30–62% of alginic acid, 1,4-β-d-mannuronic (M) and α-l-guluronic (G) acids, which was found to be appropriate.

Spectrophotometric characterization of captopril

The λ_{max} value of Captopril phosphate buffer pH 7.4 was found as 212 nm [Figure 1].

Preparation of standard calibration curve of captopril in phosphate buffer pH 7.4

From a standard stock solution of Captopril in phosphate buffer pH 7.4 (1000 µg/mL), the standard working solution was prepared (100 µg/mL). Finally, from it aliquots of 0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1 mL, 1.2 mL, 1.4 mL, 1.6 mL, 1.8 mL, 2 mL were pipette into 10 mL volumetric flasks. The volume was made up with phosphate buffer pH 7.4 to get the final concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/mL, respectively. The UV absorbances of these solutions were determined spectrophotometrically using Labindia UV 3000+ at λ_{max} 212 nm. The obtained results were summarized in Figure 2.

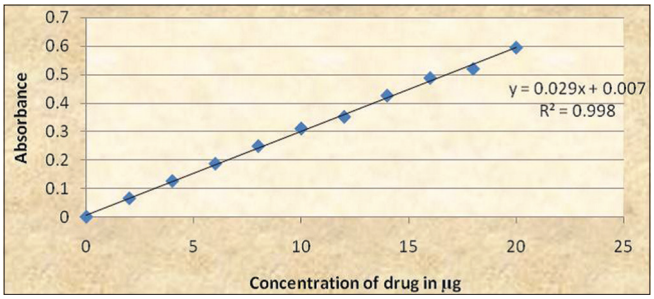

Figure 2: Calibration curve of captopril in phosphate buffer pH 7.4

Calibration curve of Captopril in phosphate buffer pH 7.4 was determined at 212 nm for 2, 4, 6., 20 µg/mL concentration of solution. The calibration curve of Captopril in phosphate buffer pH 7.4 that obeys Beer's Lambert's law [Figure 2].

Infrared spectroscopy

The infrared spectrum of Captopril was recorded by KBr dispersion technique using FT-IR with diffuse reflectance attachment on IR Affinity-1 (FTIR-8001, Shimadzu, Japan). Drug sample was mixed along with IR-grade KBr in equal proportion and IR spectrum was recorded. The obtained spectrum is shown in Figure 3.

From the obtained Captopril's FTIR spectrums it was concluded that, the various characteristics functional groups at the particular wave numbers matched with the standard FTIR spectrums of Captopril in various official books, and it was also confirms the identity and purity of the Captopril.

Drug polymer compatibility study

Drug polymer compatibility testing was performed by mixing Captopril with Sodium alginate in equal proportion, then the mixture was kept under accelerated stability condition (i.e. 40 ± 20°C and 75 ± 5% RH) for a period of 21 days in a glass vials using Remi Programmable Enviornmental Test Chamber CHM 06, Vasai, India. It was hermetically sealed with rubber stopper using molten carnauba wax. IR spectroscopy was carried out for the mixture at the starting of the study and after 21 days. The IR spectra of samples were recorded by KBr dispersion technique with FT-IR instrument (FTIR-8001, Shimadzu, Japan), and the obtained spectrums were showed in Figures 3 and 4.

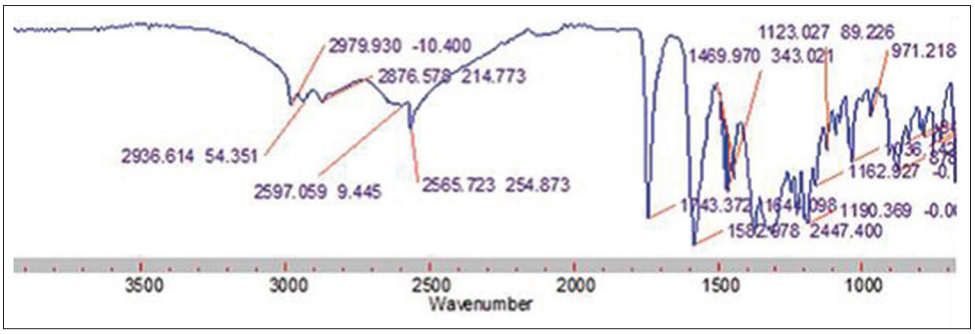

Figure 3: Fourier transform infrared spectrum of captopril

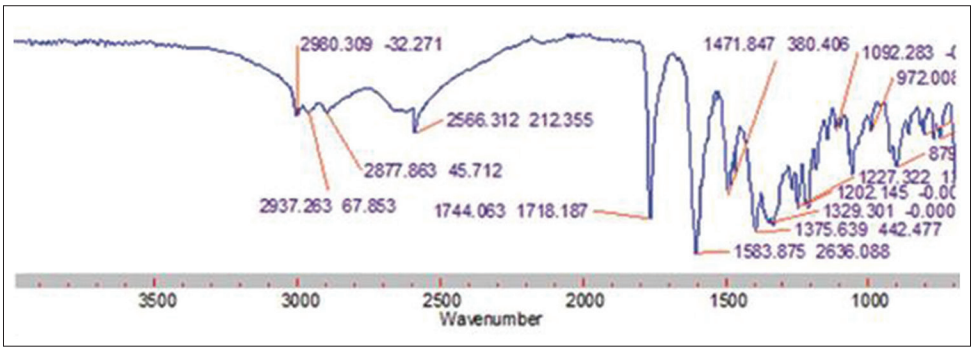

Figure 4: Fourier transform infrared spectrum of mixture of captopril with sodium alginate

When compared the individual IR spectrum of Captopril with mixture of Captopril with Sodium alginate we had found that the various characteristic peaks were obtained in the FTIR spectrum of Captopril were nearly remains unchanged, and there was no additional peaks observed in the mixtures. It did not showed any signs of incompatibility in between Captopril with Sodium alginate.

Evaluation of captopril triple-layered matrix tablets

The captopril triple layer tablets are evaluated for thickness, hardness, weight variation, friability and drug contents [Table 3].

In vitro drug release studies

The *in vitro* release of Captopril from triple-layer tablets study was carried out using the USP dissolution test apparatus Type-II Paddle type (Electro Lab TDT 08L). Drug content in dissolution sample was determined by software (PCP disso v2.08) version. The obtained results of the same were tabulated in Table 4 and summarized in Figure 5.

Images of layered matrix tablets

The photographs of Captopril triple-layer tablets and their cross-section were taken before and after swelling for 3 h in distilled water by digital camera. The photographs are shown in Figure 7. It is clearly visible that the tablet is undergoing surface swelling of release retardant layers containing a high percentage of Sodium alginate. The cross-section of tablet clearly indicates separate layers of release retardant and a middle layer present in formulation. This clearly indicates that the drug diffusion from the middle matrix drug layer is retarded due to surface swelling of the release retardant layer and hence meets the theoretical concept of controlled release formulation.

Selection of optimized formulation of triple layer matrix tablets

On the basis of data obtained from the evaluation of Captoril triple-layer tablets prepared using Sodium alginate gum for various official as well as non-official parameters like Diameter/Thickness, Hardness, Weight variation, Friability, percent drug content, *in vitro* release study as per standard reference procedures, etc. The formulation C2S1 had showed the overall best results, hence, it was selected as optimized formulation and further subjected to the accelerated stability studies according to International Council for Harmonisation (ICH) guidelines.

SEM studies of optimized formulation of three layered matrix tablet

SEM study of the Captopril three-layer tablet had clearly showed the formation of three different layers within the

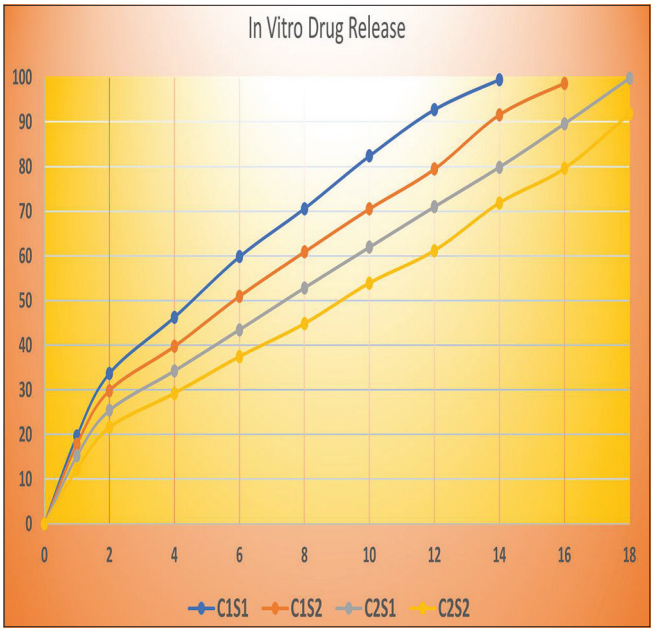

Figure 5: Graphical representation of *in vitro* release profiles of captopril triple-layer tablets

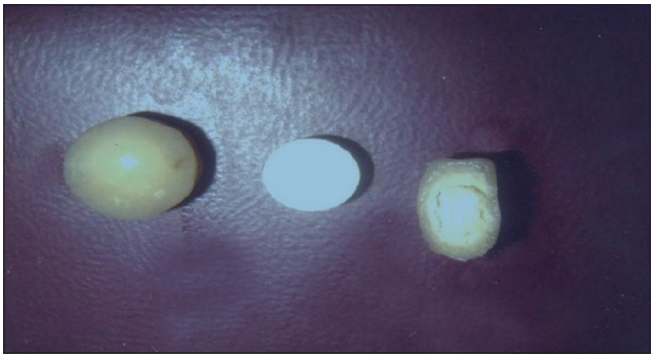

Figure 6: Images of captopril triple-layered matrix tablets before and after swelling for 3 h

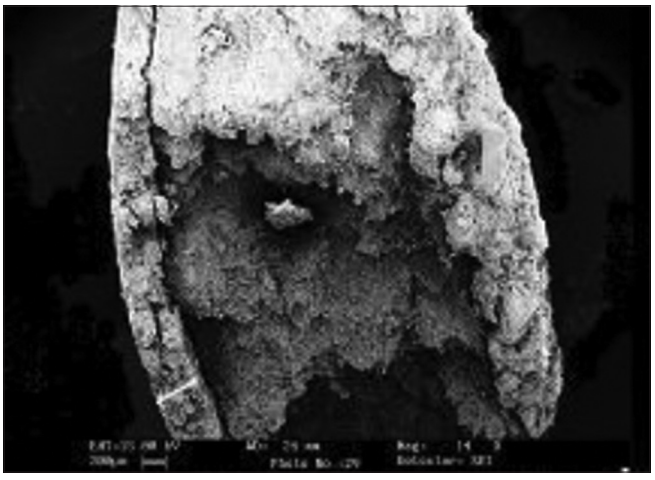

Figure 7: Scanning electron microscopy photographs of captopril three-layered tablet of optimized formulation at magnification: ×14

Table 3: Evaluation of captopril's triple-layer tablets

S. No.	Formulations	Thickness (mm)	Hardness (kg/cm²)	Deviation in weight variation test (%)	Friability (%)	Drug content (%)
1	C1S1	3.53±0.01	6.5±0.33	3.25±0.05	0.32±0.07	98.32±0.05
2	C1S2	3.55±0.03	6.7±0.25	3.23±0.08	0.30±0.02	98.67±0.02
3	C2S1	3.56±0.02	6.8±0.16	3.26±0.03	0.25±0.08	99.55±0.06
4	C2S2	3.56±0.04	6.8±0.21	3.27±0.07	0.24±0.04	99.48±0.08

Table 4: *In vitro* drug release profiles of captopril triple-layer tablets

S. No.	Formulation / Time (hours)	C1S1	C1S2	C2S1	C2S2
1	0	0	0	0	0
2	1	19.66±0.80	17.8±0.12	15.2±0.42	13.2±0.16
3	2	33.7±0.33	29.85±0.33	25.4±0.35	21.6±0.76
4	4	44.28±0.56	39.75±0.05	34.25±0.80	29.25±0.38
5	6	57.81±0.44	50.95±0.25	43.45±0.13	37.45±0.08
6	8	68.6±0.16	60.88±0.66	52.83±0.95	44.83±0.23
7	10	82.39±0.20	70.52±0.83	61.92±0.67	53.92±0.80
8	12	92.75±0.78	79.44±0.11	70.98±0.19	61.18±0.45
9	14	99.48±0.98	91.6±0.26	79.85±0.28	70.85±0.64
10	16		98.64±0.34	89.55±0.45	79.55±0.55
11	18			99.76±0.36	91.75±0.16

matrix tablet of Captopril. The SEM photograph images clearly showed the three distinct layers with the middle matrix layer [Figure 7].

Accelerated stability testing of optimized formulation (C2S1) of triple layer tablets

For the accelerated stability study optimized formulation of Captopril triple-layer tablets, C2S1 was selected and subjected to the accelerated stability studies as per the ICH guidelines. The accelerated stability study was carried out for 90 days at 40 ± 20C and 75 ± 5% RH. Form the accelerated stability study studies as per the ICH guidelines for the optimize formulation C2S1 does not founds any significant change in the various evaluation parameters of the optimized formulation and all the obtained results were within the acceptable limits and this indicates the overall stability of optimized formulation C2S1.

CONCLUSION

The objective of the present work was to formulation development and *in vitro* characterizations of Captopril triple layer matrix tablets using Sodium alginate for optimum drug release of Captopril to achieve sustain drug release to reach proper serum concentration in a specific period of time for sustained therapeutic action and so as to maintain the drug at therapeutically effective concentrations, thereby enhancing patient compliance and therapeutic efficacy, thereby reducing both cost of treatment and side effects was successfully achieved.

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