DEVELOPMENT AND EVALUATION OF CAPTOPRIL CONTROLLED RELEASE FLOATING MICROBALLOONS

Sasidhar R. Lankapalli[a]*, Vidyadhara Suryadevara[a] , Sowjanya L. Battula[a] and Ramu Anne[a]

(Received 21 July 2017) (Accepted 19 March 2022)

ABSTRACT

The objective of the present study was to develop floating microballoons of captopril in order to achieve an extended gastric retention in the upper GIT which may enhance the absorption and improve bioavailability. The floating microballoons were formulated with calcium silicate as porous carrier, Eudragit L100 and ethyl cellulose 7 cps as coating polymers and captopril as model drug. The prepared microballoons were evaluated for particle size, angle of repose, Carr's index, buoyancy studies, drug content and for *in vitro* drug release. Based upon the dissolution data obtained and various physical parameters evaluated, formulation containing drug to polymer ratio at 1:9 was optimised and further trials were carried out by changing the parameters like temperature, rpm and surfactant concentration to obtain more uniform and stable microballoons. In the optimized formulation, the drug release form was at a steady state manner when compared to the other formulations. The floating drug delivery system of captopril is a promising alternative way of achieving prolonged release with potential for achieving enhanced absorption and bioavailability.

Keywords: Floating microballoons, calcium silicate, dichloromethane, methanol, PVA

INTRODUCTION

Research, development and sales of drug-delivery systems are increasing at a rapid pace throughout the world. This worldwide trend will intensify in the next decade as cuts in public health expenses demand lower costs and higher efficacy[1].

Many attempts have been made in recent years to provide dosage forms with a longer retention time and therefore a more efficient absorption. These approaches include floating drug delivery systems, swelling and expanding systems, polymeric bio-adhesive systems, modified-shape systems, high density systems and other delayed gastric emptying devices. Compared to these approaches, the gastric floating drug delivery systems (FDDS) developed has provided several advantages as shown by the encouraging results reported till now.

Floating delivery systems have also been coupled with sustained delivery approaches for further optimization of therapy. Sustained delivery describes a drug delivery system with delayed and/or prolonged release of drug. The main purpose for developing these systems is to enhance the safety of a product to extend its duration of action[3].These systems are usually more expensive than the conventional systems[4].

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (microballoons) are, in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 μm[2].

Furthermore, the buoyancy action provided by the FDDS seems to offer a greater safety for clinical uses than some of the above mentioned approaches. In fact, no adverse effects due to floating devices have been reported till date, but the sudden gastric emptying often affects their therapeutic efficacy. For the present study, a low dense adsorbent like calcium silicate was selected as carrier, which was then micro encapsulated with suitable compositions of ethyl cellulose and Eudragit L100[5].

In the present investigation, the drug captopril was selected for the design of FDDS. Captopril is

[a] Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chandramoulipuram, Chowdavaram, Guntur - 522 019, Andhra Pradesh, India

*For Correspondence: E-mail: rlcsasidhar@gmail.com

https://doi.org/10.53879/id.59.08.11130

an antihypertensive agent. It is a potent, competitive inhibitor of angiotensin-converting enzyme, the enzyme responsible for the conversion of angiotensin-I (AT-I) to angiotensin-II (AT-II). AT-II regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system[6]. Captopril in aqueous solution is reported to undergo oxidative degradation under increased pH conditions i.e., above 4 and hence an attempt is made to retain the captopril in the gastric region that is below pH 4 by formulating floating drug delivery to avoid the pH induced oxidative degradation of captopril[6].

The dosage of conventional oral formulations of captopril is 100 mg per day (i.e. 25 to 50 mg twice daily and doses should not normally exceed 50 mg three times daily). Captopril gets rapidly absorbed after oral administration and has a mean elimination half-life (t½) of 2 to 3 h. There are no reports on the use of floating concept in the formulation of gastric retention systems of captopril[7-8]. Hence, it is aimed to design and evaluate FDDS of captopril, by emulsion solvent evaporation method.

The aim of the present investigation was to formulate and evaluate floating microballoons consisting of calcium silicate as porous carrier and captopril an antihypertensive drug with EudragitL 100 (EL) and ethyl cellulose 7cps as coating polymers, which are capable of floating on gastric fluid and deliver the therapeutic agent over an extended period of time.

EXPERIMENTAL

Materials

Materials employed in the study included captopril (gift sample from Apotex Labs, Bengaluru); calcium silicate, Eudragit L 100 and polyvinyl alcohol (gift sample from M/s Colorcon Asia Pvt. Ltd., Mumbai); ethyl cellulose 7 cps (S.D. Fine Chem. Ltd., Mumbai); dichloromethane and methanol (Loba Chemie Pvt. Ltd., Mumbai).

PREPARATION OF CAPTOPRIL CONTROLLED RELEASE FLOATING MICROBALLOONS

Preparation of drug adsorbed porous carrier

Calcium silicate (1.0 g) was dispersed in 10 mL aqueous solution of captopril (1.0 g) to prepare a slurry. The slurry was ultra-sonicated for 10 minutes to absorb the drug solution into the pores of the porous carrier. The excess aqueous solution was removed by filtration and then the drug loaded carrier was dried under vacuum to produce the drug adsorbed porous carrier.

Preparation of floating microballoons

The micro balloons were prepared by using emulsion solvent evaporation method. The drug adsorbed porous carrier was added into the polymer solution of Eudragit L 100 and ethyl cellulose 7 cps dissolved in methanol and dichloromethane (2:1V/V) and sonicated for 5 minutes. The resulting suspension was injected drop wise into an aqueous solution of polyvinyl alcohol at 40 °C. The suspension was stirred at 500 rpm for 2 h. During stirring process, the solvent evaporated to yield micro particles. Microballoons were separated by filtration and dried at room temperature in a desiccator for 24 h. The microballoons were further evaluated for their physical parameters such as weight uniformity[9].

Formulations F1 to F10 were initially prepared under similar processing conditions by changing the polymer concentration. Based upon the dissolution data obtained and various physical parameters evaluated, F9 formulation containing drug to polymer ratio at 1:9 was selected and further trials were carried out by changing parameters like temperature, rpm and surfactant concentration to obtain more uniform and stable microballoons. The composition of various captopril floating microballoons is shown in Table I and II.

Table I: Drug: Polymer ratio in various preliminary trials for preparation of microballons

S. No	Composition	Ratios *Drug: Polymers
1	F1	1:1
2	F2	1:2
3	F3	1:3
4	F4	1:4
5	F5	1:5
6	F6	1:6
7	F7	1:7
8	F8	1:8
9	F9	1:9
10	F10	1:10

Evaluation of floating microballoons

The microballoons were evaluated for particle size, angle of repose, Carr's index, buoyancy studies and drug content[10].

Table II: Processing variables for optimization of captopril microballoons

Formulation	F9A	F9B	F9C	F9D
Surfactant concentration	0.75	1	0.75	1
Temperature	30 °C		40 °C	
RPM	500 RPM	500 RPM	500 RPM	500 RPM
Formulation	**F9E**	**F9F**	**F9J**	**F9K**
Surfactant concentration	0.75	1	0.75	1
Temperature	30 °C		40 °C	
RPM	1000 RPM	1000 RPM	1000 RPM	1000 RPM
Formulation	**F9L**	**F9M**	**F9N**	**F9O**
Surfactant concentration	0.75	1	0.75	1
Temperature	30 °C		40 °C	
RPM	1500 RPM	1500 RPM	1500 RPM	1500 RPM

Drug content

The drug content of the prepared microballoons was determined by dispersing accurately weighed microballoons equivalent to 100 mg captopril in 10 mL of ethanol followed by agitation with a magnetic stirrer up to 12 h to dissolve the polymer and extract the drug. The solution was filtered through 5 µm membrane filter and drug concentration was determined spectrophotometrically at 240 nm using double beam UV spectrophotometer.

The percentage drug entrapment was calculated by using the formula

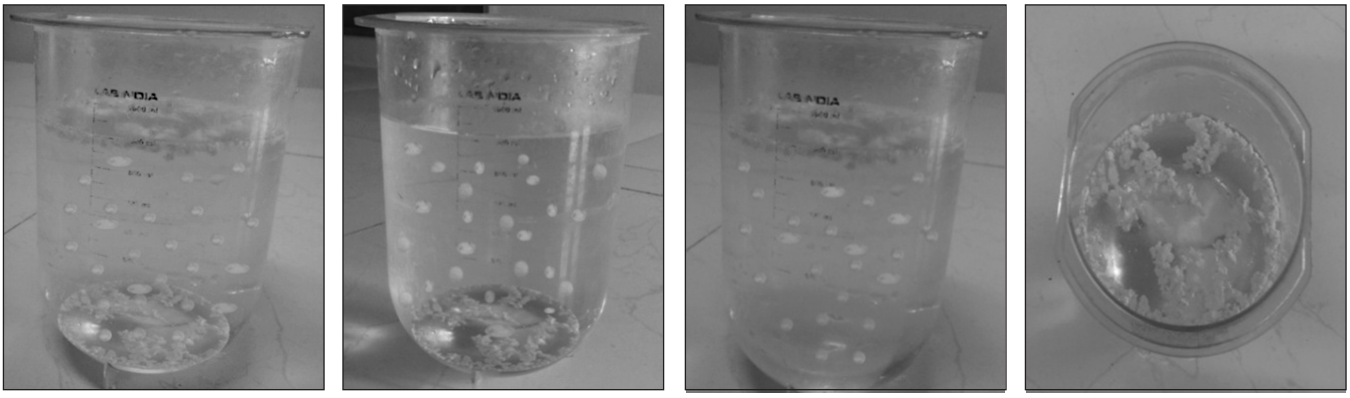
$$\% \text{ Drug entrapment} = \frac{\text{calculated drug concentration}}{\text{theoretical drug concentration}} \times 100$$

In vitro dissolution studies

The dissolution tests for the prepared micro particles were carried out in USP Apparatus Type II (paddle) [USPNF, 2007] employing 900 mL of 0.1 N HCl as the dissolution medium. 5 mL of samples was withdrawn regular time intervals at 1, 2, 4, 6, 8, 10, 12 h. The

Table III: Results of the buoyancy test for various captopril floating microballoons

Formulation code	Buoyancy lag time (Min)	Total floating time (h)
F1	10 min	>4 h
F2	8.1 min	>4 h
F3	6.2 min	>4 h
F4	5.5 min	>4 h
F5	4.8 min	>6 h
F6	3 min	>6 h
F7	1.5 min	>6 h
F8	1 min	>6 h
F9	43 sec	>12 h
F10	45 sec	>12 h
F9N	15 sec	>12 h
F9O	20 sec	>12 h



(a) (b) (c) (d)

Fig. 1: Photographs of buoyancy test showing captopril microballoons a) at zero time b) at 10 seconds c) at 30 seconds d) after 1 h

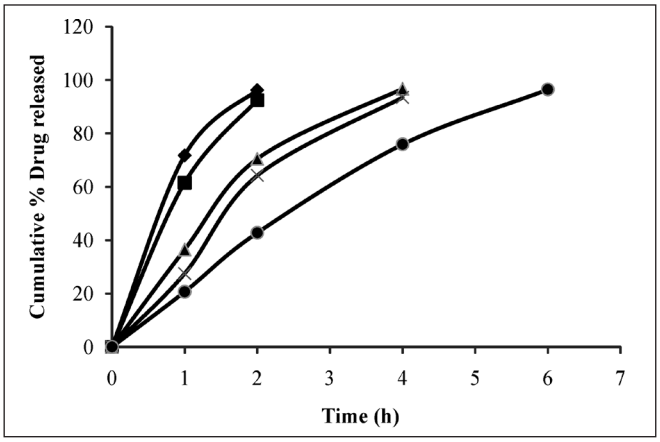


Fig. 2 (a) : Dissolution profile captopril floating microballoons *-♦- F1, -■-F2, -▲-F3, -X- F4, -●- F5*

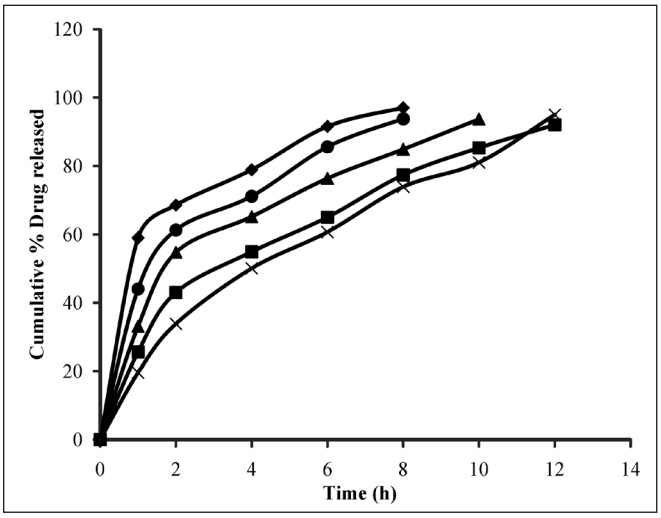


Fig. 2 (b): Dissolution profile captopril floating microballoons *-♦- F6, -●-F7, -▲-F8, -■- F9, - X - F10*

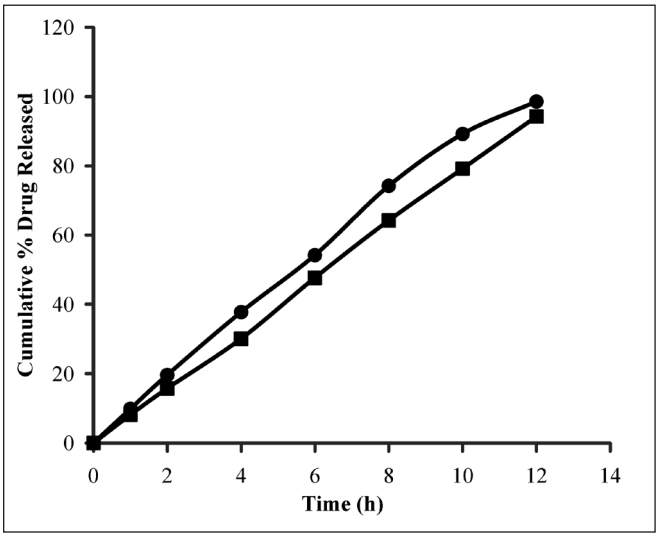
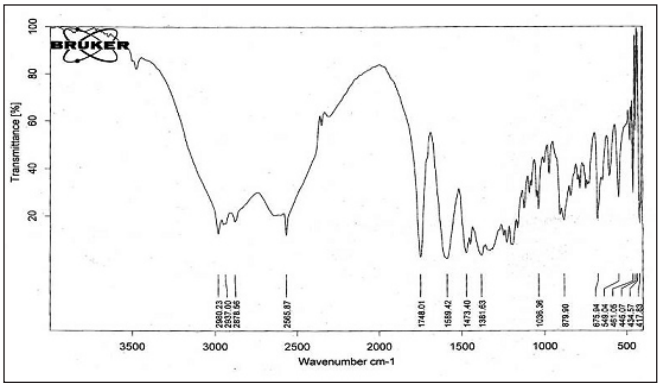
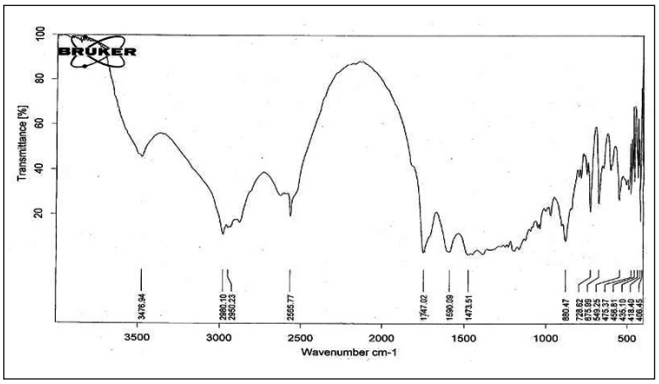


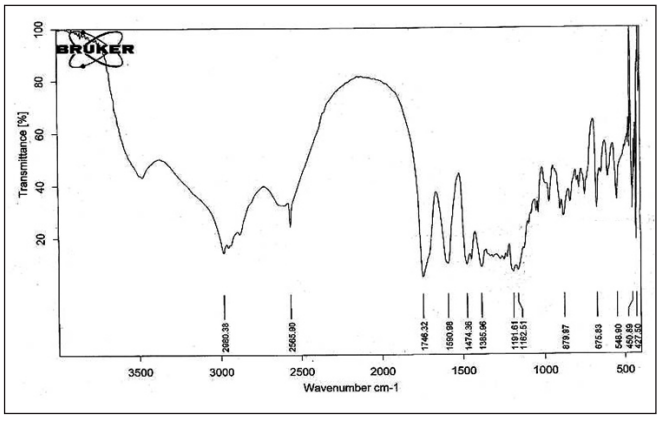
Fig. 2 (C): Dissolution profile captopril floating microballoons *-■- F9N, -F9O*



(a)



(b)



(c)

Fig. 3: FTIR Spectra of (a) pure drug (b) formulation F9N, (c) formulation F9O

withdrawn volume was replaced with fresh volume of the medium to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by ELICO SL-210 double beam spectrophotometer at 220 nm and subsequently analyzed for the cumulative percentage of drug released.

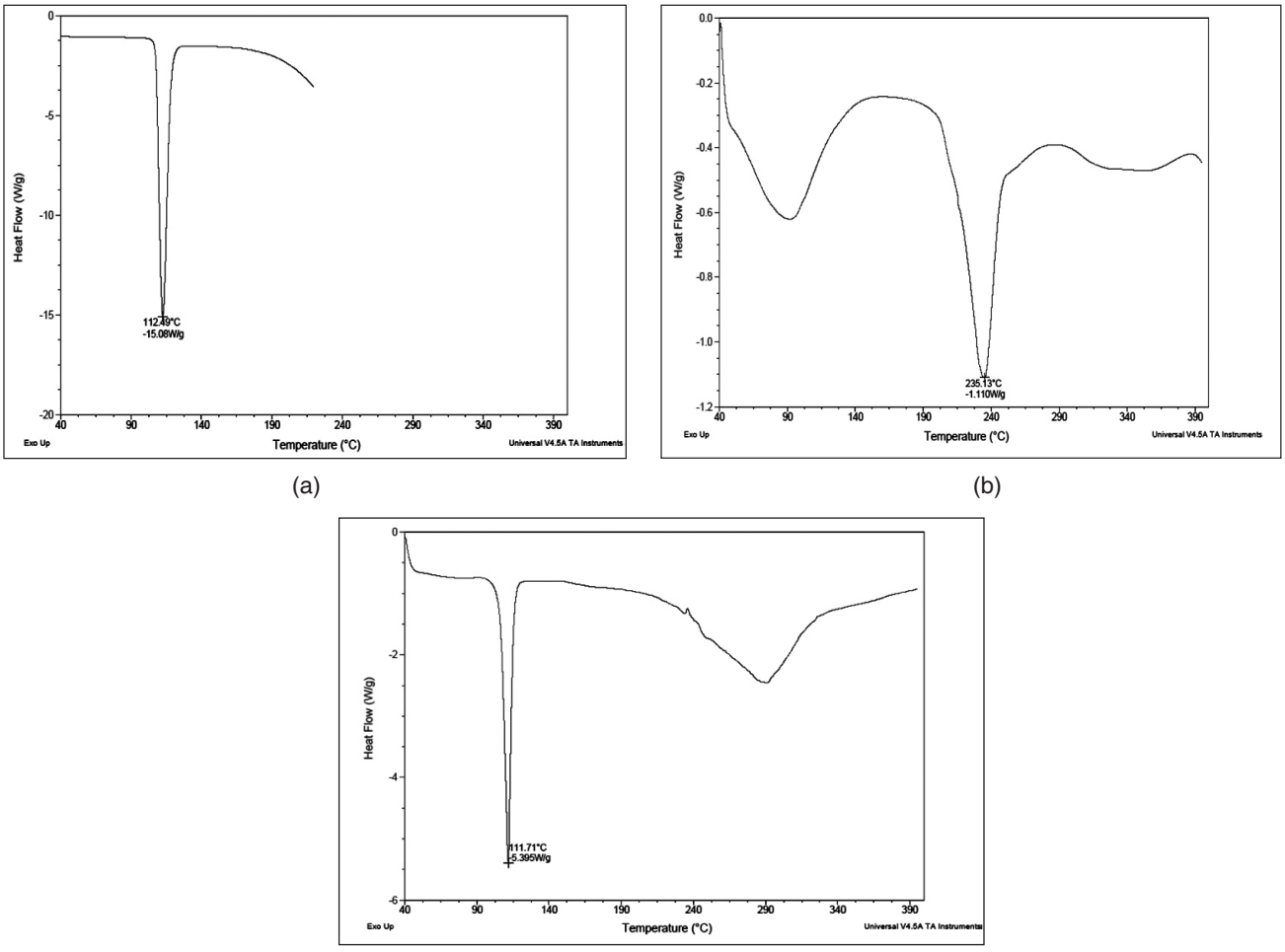
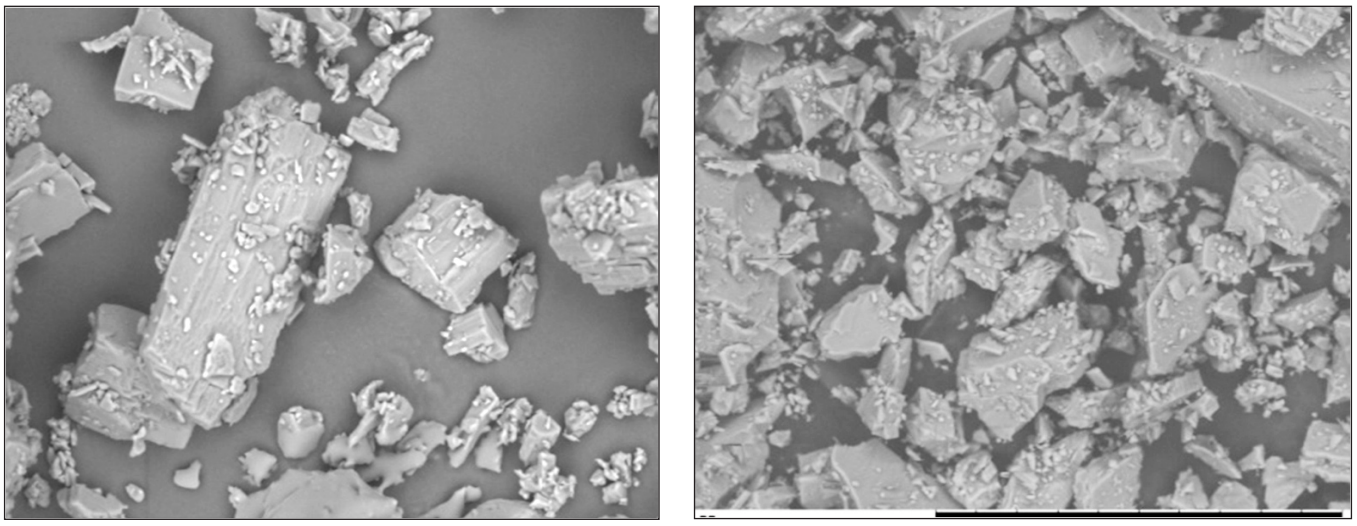


Fig. 4: DSC Thermograms (a) pure drug (b) formulation (F9N) (c) Formulation (F9O)

Table IV: Dissolution parameters of captopril floating microballoons

Formulation	Zero order constant		First order constant		Higuchi's constant		Peppas's constant	
	K(mg)	R^2	K(h^{-1})	R^2	K($mg^{1/2}$)	R^2	n (value)	R^2
F1	24.51	0.925	2.01	0.979	57.75	0.953	0.513	0.953
F2	30.97	0.970	1.637	0.973	75.53	0.980	0.530	0.990
F3	34.02	0.935	0.991	0.978	60.28	0.970	0.675	0.958
F4	33.02	0.959	0.727	0.976	66.04	0.973	0.543	0.953
F5	27.64	0.981	0.438	0.992	52.65	0.998	0.616	0.990
F6	6.52	0.702	0.298	0.969	22.63	0.974	0.531	0.99
F7	8.31	0.804	0.384	0.967	23.62	0.983	0.501	0.984
F8	8.65	0.842	0.224	0.971	21.39	0.974	0.703	0.965
F9	6.22	0.913	0.231	0.982	23.26	0.993	0.640	0.987
F10	6.66	0.946	0.280	0.982	35.00	0.997	0.573	0.993
F9N	6.02	0.996	0.280	0.882	17.00	0.997	0.956	0.993
F9O	6.66	0.993	0.280	0.816	15.00	0.991	0.901	0.993



(a) (b)

(c) (d)

Fig. 5: SEM photographs of a) captopril pure drug b) calcium silicate c) formulation F9N (d) formulation F9O

In vitro buoyancy studies

All the prepared floating microballoon formulations were subjected to *in vitro* floating studies. The *in vitro* buoyancy study was characterized by floating lag time and total floating time[11].

Characterization

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected for further investigations, namely FTIR, DSC, and SEM analysis.

RESULTS AND DISCUSSION

The floating microballoons were prepared by emulsion solvent evaporation technique. A suspension of Eudragit L100, ethylcelluose 7cps with ethanol and dichloromethane was poured into an agitated aqueous solution of PVA. The ethanol rapidly partitioned into the external aqueous phase and the polymer precipitated around dichloromethane droplets. The subsequent evaporation of the entrapped dichloromethane led to the formation of internal cavities within the microballoons.

Initially, 10 formulations of microballoons were prepared by absorbing captopril into the porous inert calcium silicate in different ratios. After evaluation, the ratio resulting in microballons with desirable characteristics was selected and further optimized.

All the formulations were evaluated for physical parameters such as particle size, angle of repose, compressibility index, Hausner's ratio, % yield, % buoyancy, % entrapment efficiency and dissolution studies.

The particle size obtained for various formulations was in the range of 110 µm to 350±0.3 µm. The angle of repose obtained for various formulations was in the range of 19 ° to 20 °, indicating excellent flow properties. This was also reflected in the compressibility index obtained for various formulations, in the range of 11.38 % to 18.94 %, and the Hausner's ratios obtained in the range of 1.011 to 1.333. The % yield obtained for various formulations was in the range of 71.26 % to 86.34 %. The % buoyancy obtained for various formulations was in the range of 55.71 % to 88.34 %. The % entrapment efficiency obtained for various formulations was in the range of 51.28 % to 88.96 %. The tiny particle size for F9N and F9O formulations (140 µm and 142 µm) was achieved due to increased rpm, which led to dispersion of polymeric phase as very fine droplets into the aqueous phase during the emulsification. The % entrapment efficiency in F9N and F9O formulations was greatly increased up to 88.92 % than in the other formulations due to rapid emulsification in presence of high proportion of surfactant concentration of PVA i.e. 0.75 %w/V aqueous dispersion medium.

The particle shape thus obtained for F9N and F9O formulations was highly uniform and highly spherical in shape, thus leading to increased flow properties and which were indicated by angle of repose, compressibility index and Hausner's ratio values.

In vitro buoyancy studies were performed on all the floating microballoon formulations, and the optimized formulation F9 floated with a minimum floating lag time of 45 sec and continued to float throughout duration up to 12 h (Table III, Fig. 1). The % buoyancy of F9N and F9O formulations was superior to all other formulations due to its very small size and shape and thus increased surface area for greater buoyancy with floating lag time of 15 and 23 seconds, respectively. The temperature maintained at 40 °C for the F9N formulations greatly assisted in diffusing the polymeric coat across the core material to form embryonic micro capsules having uniform and continuous coating formation. Thus, the embryonic micro capsules tend to undergo slow rigidization at 40 °C, leading to the formation of very thin continuous and highly flexible film formation across the core material.

The drug release from the microballoon formulations (F1-F10) was extended up to 12 h by varying polymeric coating concentrations in different formulations (1:1 to 1:10) (Fig. 2a and 2b).

The drug release from the microballoons formulations was extend up to 12 h in the formulation F9 containing coated polymers (Eudragit L100 and ethyl cellulose) at drug to polymer ratio of 1:9. The drug release from F9 formulation was extended up to 12 h with a very low drug release when compared to other formulations. It was observed that as the amount of polymers in the microballoon formulations increases, the drug release rate decreases. Hence, in the formulations containing drug and high concentrations of Eudragit L100 and ethyl cellulose 7cps, the drug release was retarded to a greater extent.

The drug release from the microballoons formulations was extended up to 12 h in the formulations prepared by varying different input variables in the preparation method: F9A to F9D were prepared keeping 500 rpm as constant while PVA concentration and temperature were varied; formulations F9E to F9P were prepared by keeping 1000 rpm as constant while PVA concentration and temperature were varied; whereas formulations F9L to F9O were prepared by keeping 1500 rpm as constant while PVA concentration and temperature were varied.

The drug released from F9N and F9O was in a steady state manner up to 12 h due to changes in the processing parameters (Fig. 2c). These two formulations were prepared by using PVA concentration 0.75 % and 1 % w/V, while maintaining the temperature at 40 °C, by stirring the components at 1500 rpm so as to achieve stable uniformly coated flexible and spherical micro balloons.

All the designed formulations of captopril displayed first order release kinetics. Log % drug unreleased vs time plots for all the microballoons formulations was found to be linear with r^2 values in the range of 0.903-0.992 (Table IV). Amount of drug released vs square root of time plots for all the microballoons formulations was found to be linear with r^2 values in the range of 0.997-1.000. The release exponent (n) values for all the microballoons formulations was in the range of 0.507 – 0.956, which indicated the non-Fickian mechanism of drug release from the dosage form. The log amount drug released vs log time plots were found to be linear with r^2 values in the range of 0.776-1.000. All the dissolution parameters are given in Table III. These two formulations were prepared by using PVA concentration 0.75 % and 1 % w/V, while maintaining the temperature at 40 °C by stirring the components at 1500 rpm so as to achieve stable uniformly coated flexible and spherical micro balloons.

The spectrum of captopril exhibited principle 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, OH stretching, S-H stretching and CH stretching of pure captopril and the optimized formulations F9N and F9O were almost in the same region of wave number. It showed 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 (Fig. 3).

DSC endothermic peak for captopril was observed at temperature 112.49 °C. It was also observed that similar endothermic peak was observed at 111.78 °C for the optimized formulations F9N and F9O. The results revealed that there were no major interactions between the drug and the polymers during the coating process. The DSC endothermic peaks for drug and polymers are given in Fig. 4.

SEM analysis was performed for the optimized microballoons (F9N and F9O) along with pure drug inert carrier. The SEM photographs showed that microballoons were found to be discrete, free flowing and spherical in shape with rough surface and it exhibited a range of sizes. The photographs of floating microballoons showing pores on the surface confirmed that the pores were responsible for drug release and floating. The microballoons floated for prolonged time over the dissolution medium without any apparent gelation. The SEM photographs are shown in Fig. 5.

REFERENCES

1. Benita. Microencapsulation: methods and industrial applications. Marcel Dekker Inc., Newyork, 1996.
2. Joshi V. K. and Jaimini M.: Review article microballoons for drug delivery: a review. **Asian J. Pharm. Res. Dev**., 2013, 01, 07 –17.
3. Prasad G.: Advances in gastroretentive drug delivery system: a review. **Int. J. Pharm. Biomed. Res.,** 2015, 05, 1-5.
4. Ritschel W.A. and Kearns G. L.: Absorption/Transport Mechanisms, in handbook of Basic Pharmacokinetics including Clinical Applications, Ritschel W.A, and Kearns, G.L. Eds. (American Pharmaceutical Association, Washington, DC,) 1999.
5. Rao V.M., Kevin E. and Yihong Q.: Design of pH-independent controlled release matrix tablets for acidic drugs. **Int. J. Pharm.,** 2003, 252, 81–86.
6. Abhijeet A. D., Archana R. D., Shrinivas K. M. and Chandrakant S. M.: Formulation and Evaluation of Floating Microsphere of Captopril using Different Gas Forming Agents. **Am. J. Pharm. Tech. Res.,** 2012, 02, 565-575.
7. Cushman D. W., Cheung H.S. and Sabo E.F.: Design of new antihypertensive drugs: potent and specific inhibitors of angiotensin-converting enzyme. **Prog. Cardiovasc. Dis.,** 1978, 21, 176-182.
8. The United State Pharmacopeial Convention, **Inc Drug Information**; 1993, P85- 86, 159 – 170.
9. Arora S., Ali J., Ahuja A., Khar K. R., Roop K. K. and Baboota S.: Floating drug delivery systems: A Review. **AAPS Pharm. Sci. Tech.,** 2005, 6(3), E372–E390.
10. Lachman L and Liberman H.A.: Theory and practice of industrial pharmacy., Varghese Publishing House. 293, 1990.
11. Nayak K. A., Maji R. and Das B.: Gastroretentive drug delivery systems: a review article. **Asian J. Pharm. Clinical Res**., 2010, 03, 2-10.