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Formulation and evaluation of captopril microencapsules: a sustained release approach

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ABSTRACT

The aim of the present study is to formulate and evaluate Captopril micro-encapsules. Microspheres and micropellets of captopril prepared with different polymers through the techniques of microencapsulation were found to have a good spherical shape, and were non-aggregated exhibiting good flow properties. In addition, all the formulations prepared, showed a good drug incorporation efficiency and an extended release of the drug, thereby enhancing the duration of action. The different techniques used in the preparation such as, emulsion-phase separation, solvent-evaporation and ionotropic- gelation techniques were found to be simple and reproducible. All the polymers used viz, chitosan, ethyl cellulose, sodium alginate and HPMC were economic, easily available and biocompatible. And hence, the industrial applicability of the methods would be simple and rapid, provided the work being extended to *in-vivo* studies. It is obvious from the above work that, the study has engineered a drug delivery profile in which the drug release is controlled to a great extend and that the formulations in therapy can minimize untoward side effects, thus improving patient compliance.

Introduction

The advance Drug Delivery Techniques Aim to Improve Overall Drug Performance and Efficacy There is now a growing realization that innovative delivery of drugs would not only increase safety and efficacy levels, but also increase the overall performance of the drug. The Advances in drug delivery systems are also expected to offer a host of additional advantages such as ease of administration, increased patient compliance, decreased side effects and cost reduction. Moreover, novel drug delivery techniques are value added features for which companies can charge a premium due to the increased convenience they provide to patients. In the study, the method adopted for sustaining the drug release was microencapsulation. The different techniques of Microencapsulation and the polymers used in the study were Emulsification-Phase separation using chitosan, Solvent evaporation using ethyl cellulose, Ionotropic gelation using sodium alginate and its combination with hydroxy propyl methyl cellulose. The process of microencapsulation enables us to achieve the Taste-masking, Selective sorption and Sustained release, Reduced gastric irritation and Conversion of liquid to solid form for stabilization, Reduction of volatility, Stabilization to oxidation. The drug used in the study was Captopril, a widely used antihypertensive drug, having a shorter half life of 2 hrs and with a bioavailability of 75%. And the daily dose being 75 to 150 mg in divided doses, the drug satisfies all the criteria needed for a drug to be formulated into a sustained release system.

Materials and methods

Material

Captopril obtained as a gift sample from Wockhardt Laboratories Ltd. Chitosan from Cochin Fisheries, Ethyl cellulose(EC) and Sodium alginate(SA) from Loba Chemie and Hydroxy Propyl Methyl Cellulose from Kemphasol. Acetone ,chloroform , Petroleum ether and Whatmann filter paper no.1 was obtained as gift sample from Qualigens, Calcium chloride – Ranbaxy, Glacial acetic acid- S.D Fine Chem Ltd, Liquid paraffin (light) - Fisher Ltd., Glutaraldehyde - Kemphasol Ltd., Hydrochloric acid - Chemspure Inorganics & Aromatics.

Pre Formulation Studies

Drug- excipients compatibility studies

Before formulation of drug substances into a dosage form, it is essential that it should be chemically and physically characterized. Pre-formulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form. In this Compatibility studies One of the requirements for the selection of suitable polymers or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work, a compatibility study was carried out by using an infrared spectrophotometer to find out if there is any possible chemical interaction between Captopril and the polymers (Chitosan, Ethyl Cellulose, Sodium Alginate and HPMC). Weighed amount of the drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-50°C), which was then compressed under 10-tonn pressure in a hydraulic press to form a transparent pellet. Similarly, was prepared the pellets of individual polymers and that in combination with the drugs which was then scanned from 4000-400cm^{-1} in IR spectrophotometer.

R Spectral Analysis

Using FTIR 410 PC spectrometer carried out the compatibility studies between the drugs and the polymers. There was no appearance or disappearance of any characteristic peaks, which confirmed the absence of any chemical interactions between the drug and polymer. the results are showed in (figure

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Captopril pure drug analysis

The absorbance of the prepared solutions was checked using a UV spectrophotometer at 226.6nm. 0.1N acetic acid was used as the blank. The procedure was repeated with P^h 1.2 buffer. The results was tabulated table no.1 and no.2 showed in (fig 2).

Method of Preparation

Chitosan microspheres

Chitosan microspheres containing Captopril was prepared by phase separation emulsion technique. Light liquid paraffin and petroleum ether was used as the external phase and a solution of chitosan in acetic acid as the dispersed phase. In this Procedure a weighed quantity of chitosan was added to 6% acetic acid and the resulting solution was stirred for one hour to form a gel. Captopril was added and stirred for fifteen minutes to get a gelled mixture. The gelled chitosan mixture was added dropwise into a dispersion medium containing liquid paraffin and petroleum ether. The resulting dispersion was stirred using a stainless steel remi-stirrer at 1000rpm for 10minutes.1ml of glutaraldehyde saturated with toluene was then added and stirring was continued for 1hr.The microspheres formed were filtered and washed several times with petroleum ether and dried overnight.

Ethyl cellulose microspheres

Ethyl cellulose microspheres were prepared by emulsification solvent evaporation method. In this Procedure a Weighed amounts of the drug and the polymer was dissolved in chloroform and added drop wise to 200ml liquid paraffin containing 2% w/v of span 80 and stirred at 1000 rpm for 3 hrs. The formed microspheres were filtered by vacuum filtration and washed several times with petroleum ether, and water and then air dried.

Sodium alginate microcapsules

Sodium alginate microcapsules were prepared by Ionotropic gelation technique. In this Procedure a Weighed quantity of the drug was added to sodium alginate solution and mixed at 500rpm. Resultant solution was extruded drop wise with the help of a syringe and needle into 2%calcium chloride solution and stirred at 100rpm. Stir for 10 minutes; the formed microcapsules were separated, washed with water and dried at 70^0C for 6hrs. in an oven. Another set of microspheres was prepared with a combination of sodium alginate and HPMC.

Evaluation Studies of Formulated Microspheres and Microcapsules

Drug content analysis

UV spectrophotometeric method was used to analyze the drug content in the prepared microspheres and micropellets of varying drug-polymer ratios. Drug was extracted from the microspheres and micropellets with phosphate buffer pH 7.2 and absorbance was measured using UV spectrophotometer at 226.6nm. The amount of drug in the prepared microspheres and microcapsules was estimated using the standard graph.

Entrapment efficiency

The entrapment efficiency of Captopril in the prepared microspheres and micropellets was determined from the ratio of weight of Captopril incorporated to the weight of Captopril initially taken.

$$\text{Entrapment efficiency (\%)} = \frac{\text{Wt. of drug incorporated}}{\text{Wt. of drug initially taken}} \times 10$$

Micromeritic studies

In this Size and Shape, Bulk density, True density and Porosity (€), Angle of repose and Hausner's ratio were studied. the results was tabulated table no.4 and no.5

Results And Discussion

The microspheres and micropellets were evaluated for drug content, and incorporation efficiency, Scanning Electron Microscopy, and particle size analysis, Micromeritic properties and in-vitro dissolution profiles. Chitosan microspheres had a good drug incorporation efficiency that ranged from 60.0% to 68.0% while that of ethyl cellulose microspheres was found to be between 68.0 to 72.0%. The entrapment efficiency of sodium alginate micropellets was between 69% to 79% where as that prepared with a combination of sodium alginate and HPMC showed an efficiency ranging between 71.0% to 79.2 SS%. The result was tabulated table no.3.

Scanning Electron Microscopy

The surface morphology of the prepared microspheres and microcapsules was shown to be spherical by the SEM photographs.

Particle size analysis

The particle size analysis was carried out using an optical microscope. The arithmetic mean particle size of various microspheres and micropellets prepared are shown in tables 5 to 20. The particle size distribution of chitosan microspheres ranged between 223.4 μm to 286.2 μm, whereas that of ethyl cellulose microspheres was between 226.8 μm to 289.5 μm. The sodium alginate microcapsules showed a particle size distribution between 281.4 μm to 369.9 μm whereas that of microcapsules prepared with a combination of sodium alginate and HPMC showed a particle size distribution that ranged between 280.1 μm to 362..4 μm. the results was tabulated table no.4 and show in figure.3.

Micromeritic properties

The various Micromeritic properties of the prepared microspheres and microcapsules were studied. Acceptable range of angle of repose is between 20^o-40^o and all the formulation showed an angle of repose within the range. Formulations C1, C2, E1, E2, S3 and SH1 showed an angle of repose less than 25^o and hence exhibit excellent flow properties. Acceptable range of Hausner's ratio is upto 1.25 and all the formulations had a value less than 1.25, thereby exhibiting good flow properties. Formulations of porosity between 9.5 to 8.4 indicate excellent compressibility. The results are shown in table no. 5

In-vitro release studies

Captopril release form the formulations were studied in acid buffer (pH 1.2) for 2 hours and in phosphate buffer (pH 7.4) for the next 6 hours. The release pattern was slow and spread over extended periods of time. The results are shown in tables 6 to 21. In the case of chitosan microspheres, C3 had the highest drug incorporation (68%) and showed a drug release of 11.70% in acid buffer and 54.36% in phosphate buffer after 8 hours. Among the ethyl cellulose microspheres prepared, E3 showed the highest drug incorporation (77.6%) and exhibited a drug release of 7.92% in acid buffer and 52.02% in phosphate buffer. Formulation S4 of the sodium alginate microcapsules showed the highest drug content (78.7%) which exhibited a drug release of 7.22% in acid buffer and 57.41% in phosphate buffer. For the micropellets prepared with a combination of sodium alginate and HPMC, formulation SH4 showed maximum drug content (79.4%) with a drug release of 4.81% in acid buffer and 46.98% in phosphate buffer.

Conclusion

The microspheres and micropellets of captopril prepared with different polymers through the techniques of microencapsulation were found to have a good spherical shape,

and were non-aggregated exhibiting good flow properties. In addition, all the formulations prepared, showed a good drug incorporation efficiency and an extended release of the drug, thereby enhancing the duration of action. The different techniques used in the preparation such as, emulsion-phase separation, solvent-evaporation and ionotropic- gelation techniques were found to be simple and reproducible. All the polymers used viz, chitosan, ethyl cellulose, sodium alginate and HPMC were economic, easily available and biocompatible. And hence, the industrial applicability of the methods would be simple and rapid, provided the work being extended to in-vivo studies. It is obvious from the above work that, the study has engineered a drug delivery profile in which the drug release is controlled to a great extend and that the formulations in therapy can minimize untoward side effects, thus improving patient compliance.

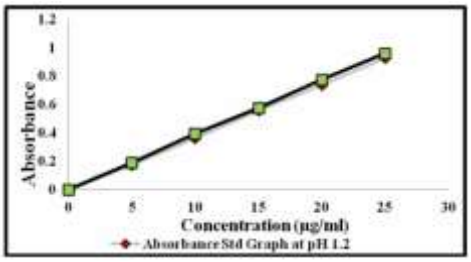


Figure 1 Standard calibration graph of CAPTOPRIL at pH 1.2 and pH 7.4

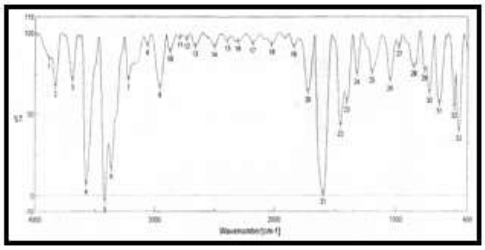


Figure 2(a) FTIR studies of pure drug Captopril

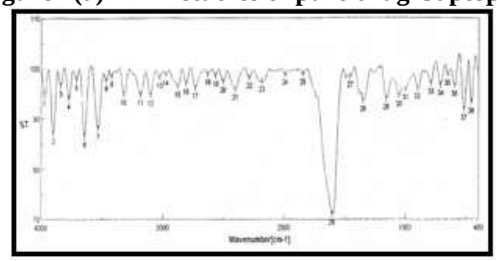


Figure 2(b) FTIR studies of Chitosan

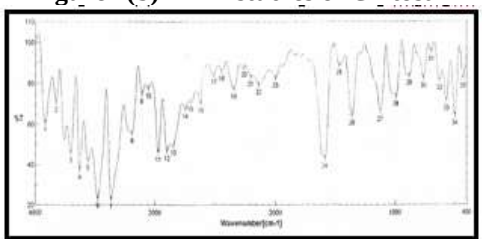


Figure 2(c) FTIR studies of Ethyl cellulose

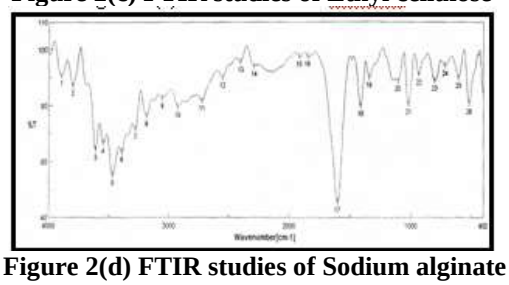


Figure 2(d) FTIR studies of Sodium alginate

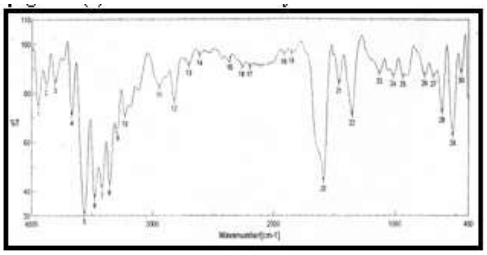
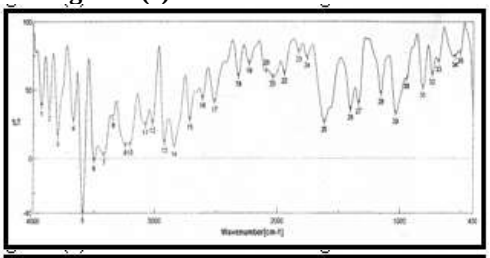


Figure 2(e) FTIR studies of HPMC



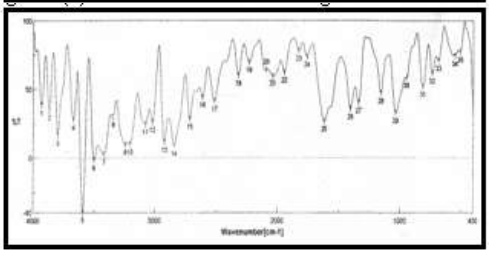


Figure 2(f) FTIR studies of HPMC+ Sod.Alginate

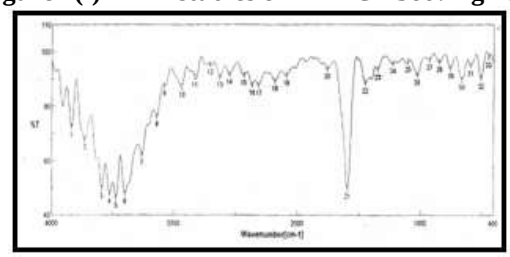


Figure 2(g) FTIR studies of Captopril + chitosan

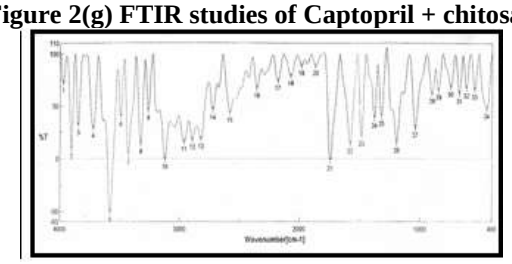


Figure 2(h) FTIR studies of Captopril + Ethyl cellulose

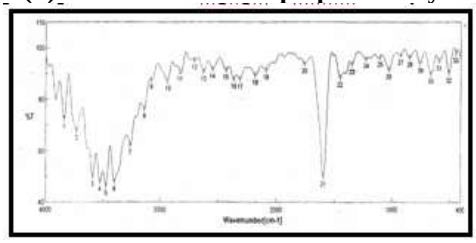


Figure 2(i) FTIR studies of Captopril + Sod.alginate

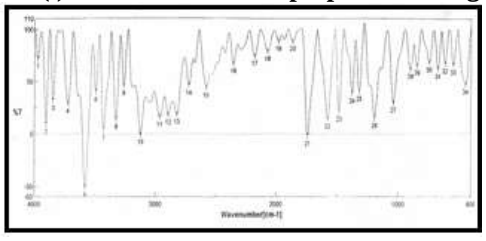


Figure 2(j) FTIR studies of Captopril + Sod.alginate+ HPMC

Table 1 Standard Graph of Captopril at 226.0nm

Concentration (µg/ml)	Absorbance	
	Std Graph at pH 1.2	Std Graph at pH 7.4
5	0.1720	0.1910
10	0.3641	0.3954
15	0.5601	0.5764
20	0.7421	0.7752
25	0.9310	0.9612

Table 2 Evaluation of formulation and Micromeritic properties

S. No	Formulation code	Formulation characters		Micromeritic Properties				
		Entrapment efficiency (%)	Arithmetic mean particle size	Bulk density (g/ml)	True density (g/ml)	Porosity (%)	Angle of repose (θ)	Hausner's ratio
1.	C_1	60	223.425 µm	2.176	2.968	27	23.97	1.3
2.	C_2	64	261.99 µm	1.947	2.4	20.8	21.96	1.26
3.	C_3	68	270.12 µm	1.714	2.007	22.7	29.28	1.176
4.	C_4	66	286.2 µm	1.626	1.828	11.11	30.96	1.125
5.	E_1	68	226.8 µm	1.19	1.31	15.38	22.9	1.18
6.	E_2	72.8	250.425 µm	1.123	1.25	12	23.4	1.93
7.	E_3	77.6	262.275 µm	0.909	1.162	18	29.7	1.22
8.	E_4	72	289.575 µm	1.9433	1.063	11.3	28.9	1.12
9.	S_1	69.2	281.475 µm	0.9433	1.010	6	28.2	1.06
10.	S_2	73.6	294.49 µm	0.8928	0.9615	7.29	26.2	1.07
11.	S_3	77.6	332.5 µm	0.8982	0.9433	5.3	28.8	1.05
12.	S_4	78.7	369.9 µm	0.8620	0.8928	5.6	30.2	1.23
13.	SH_1	72	280.15 µm	1.2081	1.4310	14.2	25.2	1.16
14.	SH_2	77.6	300.375 µm	1.2341	1.3891	7.3	27.9	1.08
15.	SH_3	77.9	326.17 µm	1.18	1.21	8.3	26.5	1.09
16.	SH_4	79.4	362.473 µm	1.06	1.18	10	29.9	1.11

Table 3 In-vitro Dissolution Studies

S. No	Formulation code	Percentage cumulative amount of drug release							
		pH 1.2		pH7.4					
		1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr
1	C1	10	15.3	23.04	35.32	42.6	48.2	55.64	59.04
2	C2	7.74	12.24	18.18	23.74	37.58	45.6	53.64	57.60
3	C3	4.15	11.7	20.88	27.36	35.22	43.01	49.8	54.36
4	C4	1.34	5.5	10.26	18.18	24.84	33.82	42.66	51.84
5	E1	7.56	14.42	24.62	31.86	42.03	50.9	59.74	62.82
6	E2	6.36	12.24	18.84	26.82	37.36	48.96	55.26	60.8
7	E3	1.53	7.92	12.96	18.21	27.9	36.36	46.44	52.02
8	E4	0.80	4.32	9.12	16.56	24.48	32.04	41.76	47.7
9	S1	8.46	14.95	24.3	32.01	46.40	57.96	61.42	66.24
10	S2	7.02	11.7	18.9	25.02	38.88	48.96	55.6	64.08
11	S3	4.68	10.8	18.4	30.24	37.08	46.98	53.04	62.52
12	S4	1.2	7.22	14.22	21.24	32.54	44.46	50.01	57.41
13	SH1	10.8	15.48	24.3	30.42	42.52	49.5	57.96	62.64
14	SH2	8.82	12.96	15.3	26.28	37.26	46.16	56.16	60.48
15	SH3	3.78	10.98	14.76	20.88	39.1	41.94	36.62	54.36
16	SH4	1.08	4.81	12.24	18.9	28.16	33.12	42.66	46.98

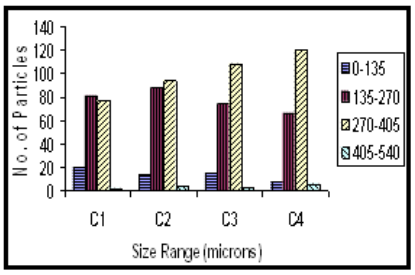


Figure 3(a) Particle size distribution of chitosan microspheres

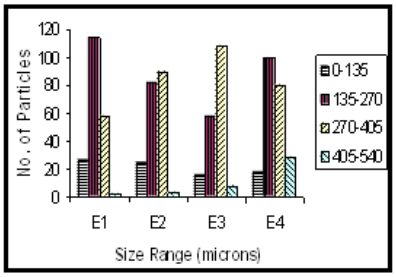


Figure 4(b) Comparative dissolution profile of Ethyl cellulose microspheres

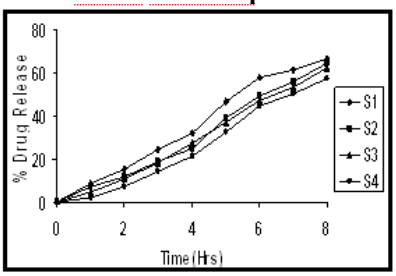


Figure 4(c) Comparative dissolution profile of Sodium alginate microspheres

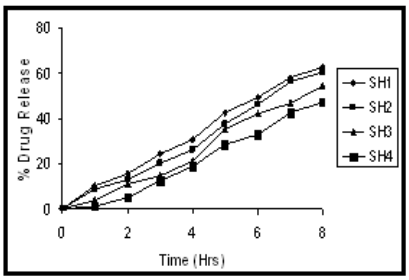


Figure 4(d) Comparative dissolution profile of Sodium alginate+ HPMC microspheres

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