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Formulation and evaluation of microspheres loaded with enalapril

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ABSTARCT

In the present work, microspheres of Enalapril using Sodium alginate along with Carbopol 934, HPMC as copolymers were formulated to deliver Enalapril via oral route. The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Enalapril microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers usedThe invitro drug release decreased with increase in the polymer and copolymer concentration. Analysis of drug release mechanism showed that the drug release from the formulations followed first order kinetics with higuchis model of drug release. Based on the results of evaluation tests formulation coded F3 was concluded as best formulation.

Key words: Enalapril , Sodium alginate, Carbopol 934 and HPMC

INTRODUCTION

Microencapsulation

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation is arbitrarily differentiated from macrocoating techniques in that the former involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size.[6] Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials.

Microenacapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded or enclosed, by an intact shell. Two major classes of microencapsulation methods have evolved i.e. chemical and physical.

The first class of encapsulation method involves polymerization during the process of preparing the microcapsules. The second type involves the controlled precipitation of a polymeric solution where in physical changes usually occur.[7, 8]

Microencapsulation process

Basic microencapsulation processes can be divided into chemical and mechanical.

Chemical processes involved

- Complex coacervation
- Polymer-polymer compatibility
- Interfacial polymerization in liquid media
- In-situ polymerization

- In-liquid drying
- Thermal and ionic gelation in liquid media

Mechanical processes involved

- Spray drying
- Spray coating
- Fluidized bed coating
- Electrostatic deposition
- Centrifugal extrusion
- Spinning disk or rotational suspension separation
- Polymerization at liquid-gas or solid-gas interface
- Pressure extraction or spraying into solvent extraction bath.[9, 10]

AIM AND OBJECTIVE

Aim of the study is to formulate Enalapril microspheres using different polymers by ionotropic gelation method

The objective of the present study is

- To conduct preformulation studies by analytical methods.
- To develop dosage forms whose bio availabilities of drugs are significantly greater than those observed from conventional solid forms such as tablets and capsules.
- To formulate the Enalapril microspheres using different polymers like sodium alginate, HPMC, carbopol 940, Guar gum, Xanthum gum in different ratios.
- To evaluate the prepared mucoadhesive microspheres.
- To choose the better formulation among the prepared formulations based on better release.

METHODOLOGY

Method of preparation

Ionotropic gelation method

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (50 ml) to form a homogeneous polymer mixture. The API, Enalapril were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (2% w/v) aqueous retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried

Table No1: Prepared Formulation of Microspheres

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug: polymer	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2
Muco adhesive Polymer ratio	--	1:1	1:1.5	1:2	0.5:1	0.5:1	--	2:1	1.5:1	1.5:2
Carbopol	1%	1%	1%	1%	0.5%	0.5%	1.5%	1.5%	1.5%	1.5%
HPMC K100	--	1%	1.5%	2%	--	--	--	0.75%	1%	2%
Xanthum gum	--	--	--	--	1%	--	--	--	--	--
Guar gum	--	--	--	--	--	1%	--	--	--	--
Na-Alginate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Water	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml
Calcium Chloride (2%)	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

RESULTS AND DISCUSSION

Drug excipient compatibility studies

The From the IR spectral data of ideal formulation F3, it is clearly evident that there were no interactions of the drug.

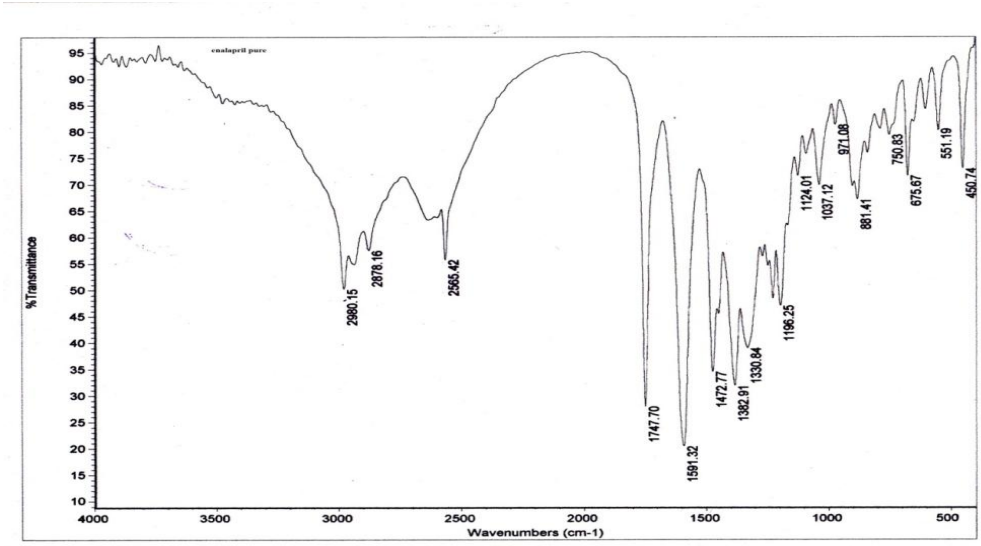

Figure No 1: FTIR Spectra of Enalapril pure drug

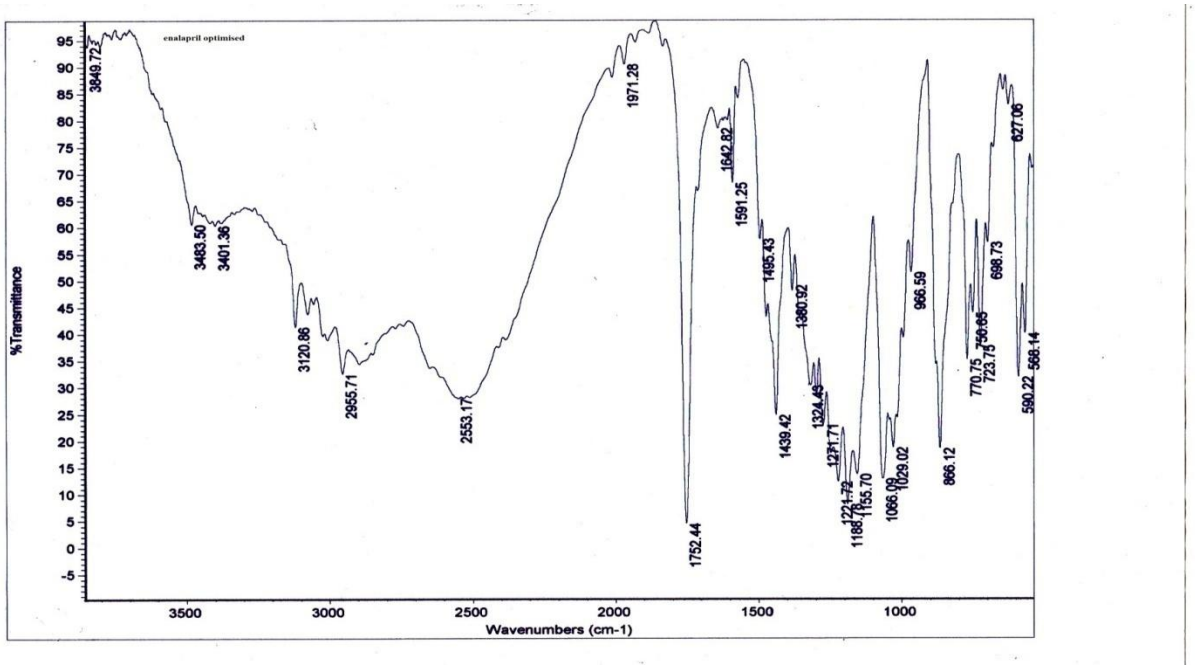

Figure No 2: FTIR Spectra of Enalapril optimized formulation

Evaluationand characterisation of microspheres

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The

percentage yield was found to be in the range of 87.6 to 95.1% for microspheres containing sodium alginate along with carbopol 940 and HPMC as copolymers, around 90.1% for microspheres containing sodium alginate along with Xanthum gum as copolymer and 95.1% for microspheres containing sodium alginate along with Guar gum as copolymer.

Drug entrapment efficiency

The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 2, and displayed in Figure 4.

Table No 2: Percentage yield and percentage drug entrapment efficiency of the prepared Microspheres

S.No.	Formulation code	% yield	%Drug entrapment efficiency	% Muco adhesion
1	F1	93.8	70.1	68.6
2	F2	87.6	83.4	88.1
3	F3	94.8	91.8	90.6
4	F4	95.0	90.4	92.4
5	F5	90.1	71.7	80.5
6	F6	95.1	64.3	74.8
7	F7	96.9	73.6	83.5
8	F8	95.1	91.8	90.2
9	F9	94.2	90.6	93.6
10	F10	90.6	88.2	96.4

DISCUSSION

Formulation F3 containing blend of carbapol and HPMC K100maximum percentage of drug loading about 91.8%.Formulation F1 contianing carbapol percentage of drug loading about 70% because these microspheres are small in size which results more loss of drug from surface during washing of microspheres.

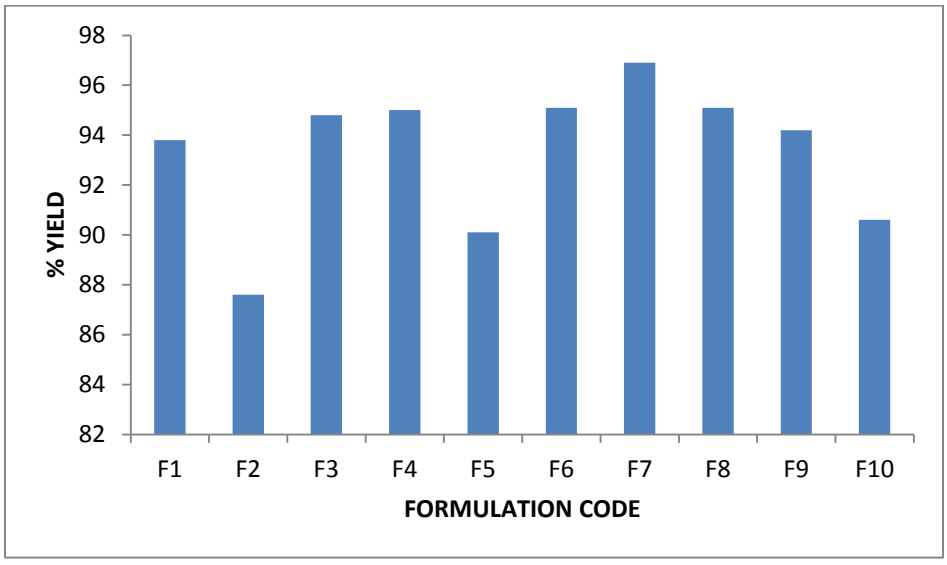

Figure No 3: Graphical representation of percentage yield of formulations F1-F10

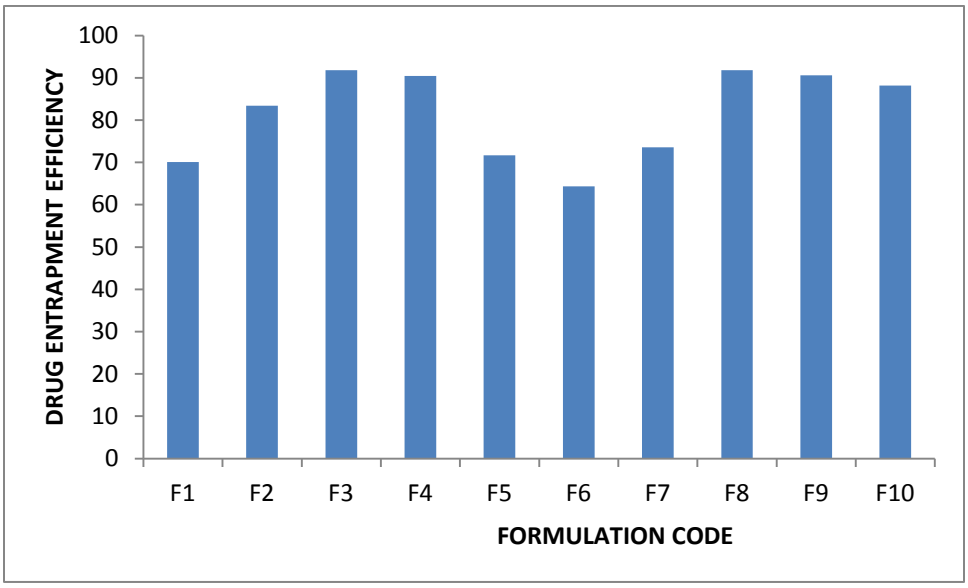

Figure No 4: Graphical representation of percentage drug entrapment efficiency of formulations F1-F10

Scanning electron microscopy

The SEM photography revealed that the drug loaded microsphere are spherical .Microspheres prepared containing higher amount of polymer exhibited smoother surface than those prepared with a low amount of polymer Irregular surfaces and large sizes of microspheres were observed for those prepared with the lower amount of polymer >This has greatly affected the Morphological Characteristics of the microspheres. As the drug –to-polymer ratio was increased more spherical microspheres with smooth surfaces were obtained.

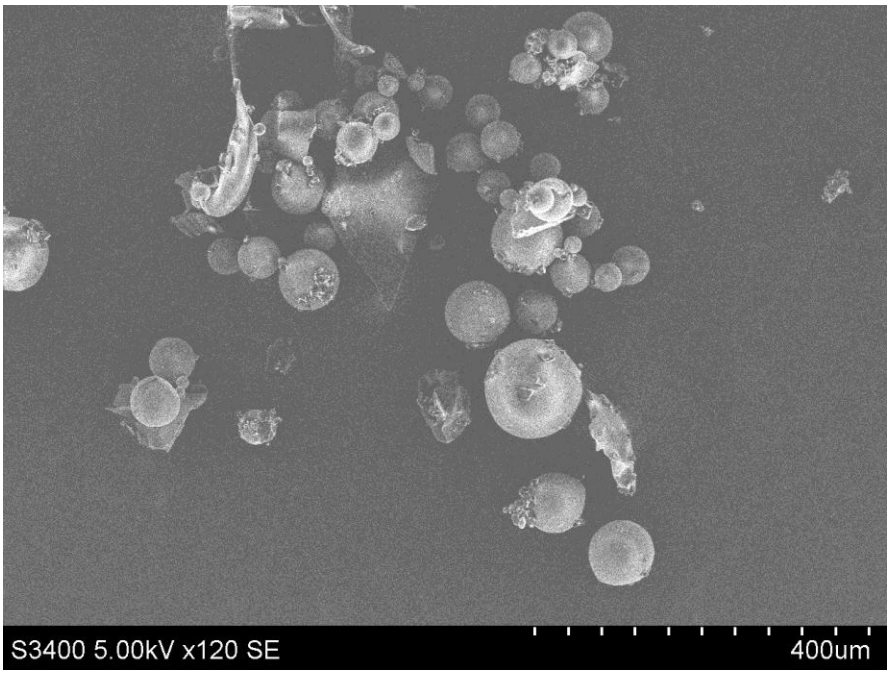

Figure No 5: SEM of Enalapril

Particle size analysis

The mean particle size and size distribution of the mucoadhesive microspheres of enalapril with different drug/polymer ratio were studied and found to be in the range of 642µm -740 µm. The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Table No 3: Average Particle Size analysis for formulation F1-F10

Formulation code	Average particle size(µm)
F1	642
F2	617
F3	611
F4	717
F5	642
F6	792
F7	834
F8	664
F9	702
F10	740

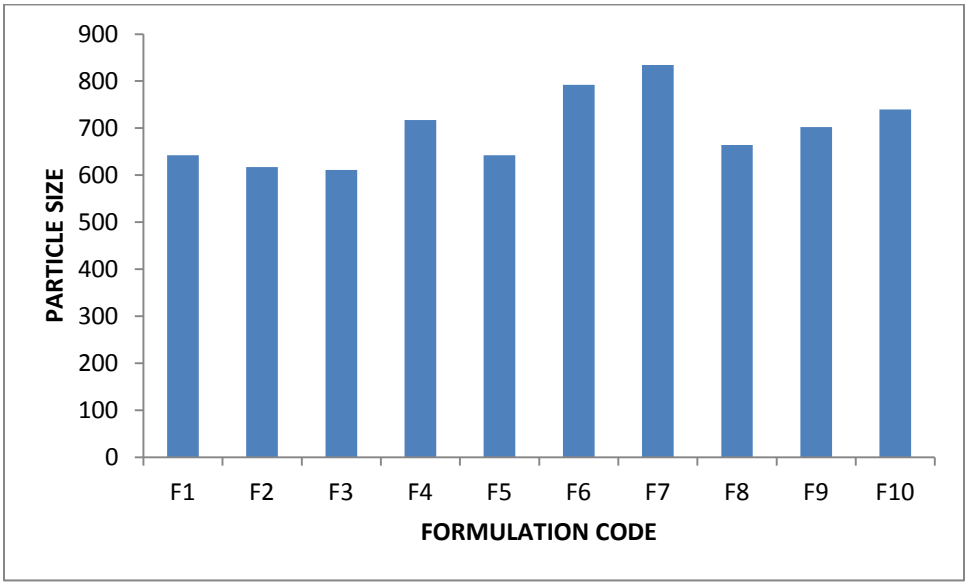

Figure No 6: Graphical representation of average particle size for formulations F1-F10

Swelling study

Table No 4: Percentage Swelling of the Prepared Microspheres

S.NO.	FORMULATION CODE	PERCENTAGE SWELLING
1	F1	90.3
2	F2	105.8

3	F3	106.4
4	F4	91.8
5	F5	93.1
6	F6	94.6
7	F7	95.1
8	F8	101.4
9	F9	116.8
10	F10	120.3

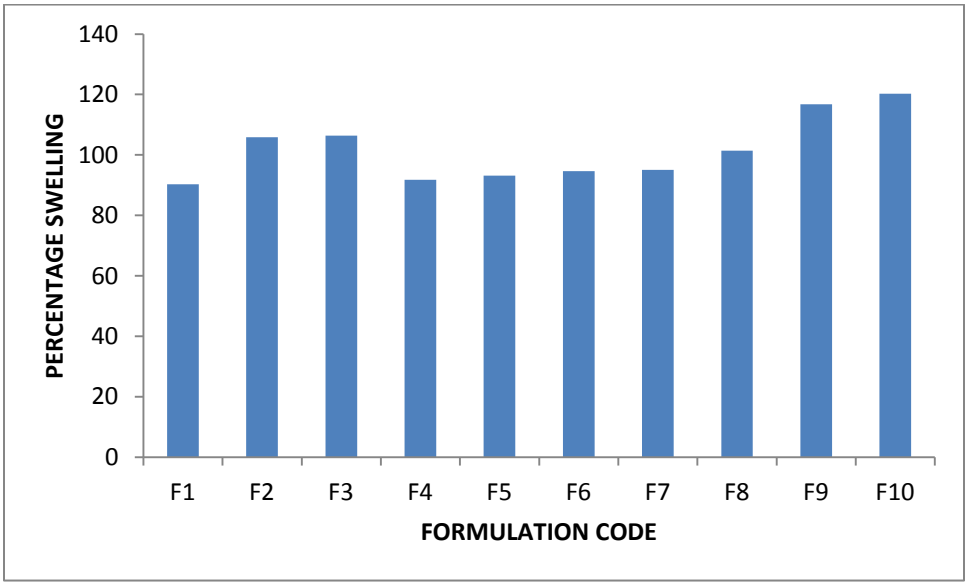

Figure No 7: Graphical representation of Percentage swelling index of formulations F1-F10

In-vitro drug release studies

The invitro release studies of all the extended release tablets formulated (F_1-F_{10}) were performed using USP II dissolution apparatus at 37.5±0.5 in 0.1N HCL and samples were withdrawn and analyzed by using UV spectrophotometry at 212nm.

Release studies of Enalapril mucoadhesive microspheres formulations F_1-F_{10}

The release profile of formulations F_1-F_{10} comprising various polymers like Carbopol, HPMC K 100,Xanthum gum ,sodium alginate with different l concentrations were shown in **table 11, 12 and fig 12, 13**. Formulations F_1, F_2, F_3 and F_4 exhibits release rates of 88.7%, 85.4%, 91.0%, 90.0%, 86.0%, 69.1%, 87.6%, 88.0%, 85.1%, 72.6%.

The results of the in-vitro dissolution studies of formulations F_1 to F_{10} and shown in table no.11-12.The plots of Cumulative percentage drug release Vs Time. Figure 12-13 shows the comparison of % CDR for formulations F_1 to F_{10}.

Table No 5: In-Vitro drug release data of Enalapril microspheres

TIME (h)	Cumulative Percent Of Drug Released				
	F1	F2	F3	F4	F5
0	0	0	0	0	0

0.5	10.5	6.7	11.5	10.4	11.5
1	21.3	10.3	20.8	18.1	20.6
2	30.8	19.1	31.2	28.6	30.1
3	45.7	29.8	46.8	31.8	44.7
4	60.4	40.1	61.8	40.6	49.8
5	71.8	52.1	73.1	58.6	56.3
6	88.7	60.3	79.4	65.8	66.9
8	--	79.8	83.5	73.6	70.6
10	--	85.4	86.9	80.3	81.5
12	--	--	91.0	90.1	86.0

DISCUSSION

Among all the formulations F3 Containing carbopol, HPMC and sodium alginate showed maximum release at 12 hours. This shows that more sustained release was observed with the increase in percentage of polymers.

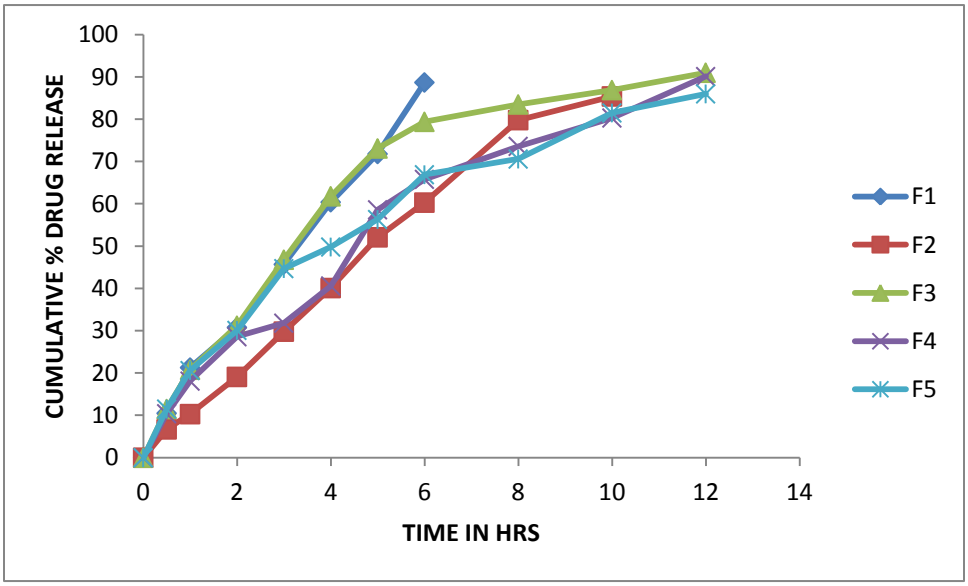

Figure No 8: Comparison of In-Vitro drug release profile of Enalapril microspheres (F1 – F5)

Table No 6: In-Vitro drug release data of Enalapril microspheres

TIME (h)	Cumulative Percent Of Drug Released				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
0.5	10.5	11.5	11.5	10.4	7.6
1	15.3	20.6	20.8	18.1	15.2
2	26.4	30.1	31.2	28.6	25.9
3	32.4	44.7	46.8	31.8	33.8
4	40.6	59.8	61.8	40.6	45.6

5	49.2	70.4	73.1	58.6	50.3
6	51.3	87.6	79.4	65.8	56.2
8	60.7	--	86.2	73.6	61.6
10	62.4	--	88.0	80.3	69.2
12	69.1	--	--	85.1	72.6

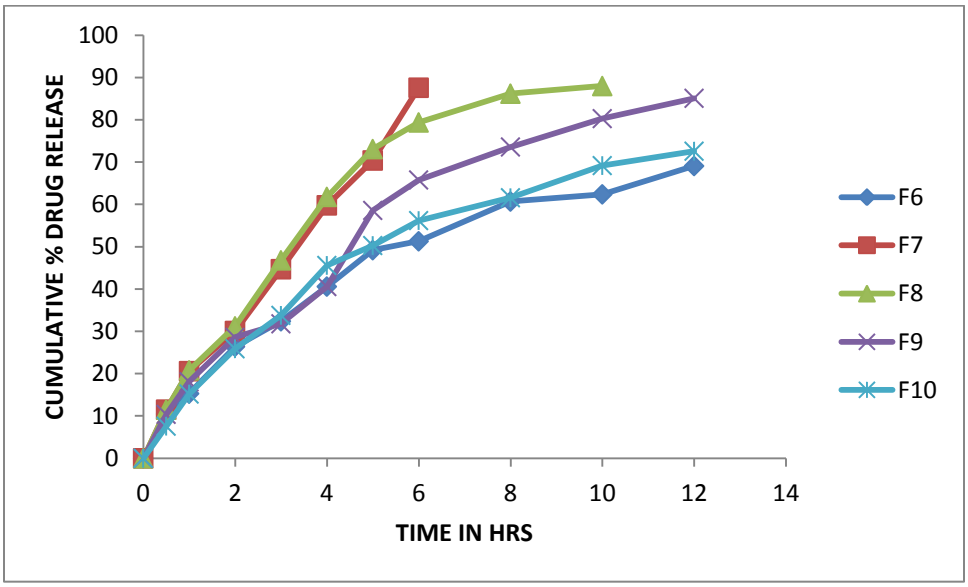

Figure No 9: Comparison of In-Vitro drug release profile of Enalapril microspheres (F5-F10)

In-vitro drug release kinetics

Table No 7: Release Kinetics Studies of the Prepared Formulations

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.274488491	-0.14046354	31.43943102	1.37238628
Intercept	9.643606138	2.20149929	-12.2709975	0.703967511
Correlation	0.950160504	-0.92487055	0.966554763	0.876716503
R 2	0.902804983	0.855385541	0.93422811	0.768631826

Stability studies

Time	Assay		Cumulative % drug release at 12 hrs	
	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH
First day	100	97	90.3	90.5
30 days	101.88	99.18	89.8	89.1
60 days	100.85	98.75	88.84	88.63
90 days	99.30	100.50	88.76	88.22

DISCUSSION

Micromeritic studies revealed that the mean particle size of the prepared optimized microspheres was in the size range of 611µm and are suitable for microspheres for oral administration. Increase in the polymer concentration lead to increase in % Drug entrapment efficiency, Particle size, % swelling. The invitro drug release decreased with increase in the polymer and copolymer concentration. Analysis of drug release mechanism showed that the drug release from the formulations followed first order kinetics with higuchis model of drug release. Based on the results of evaluation tests formulation coded F_3 was concluded as best formulation.

CONCLUSION

The Sustained released tablets containing Mebeverine SR tablets were successfully prepared by direct compression method. The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index. The prepared powdered blend were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F6 which releases the Mebeverine in sustained manner in 1^{st} hour it releases 8.7 % but the remaning drug release was sustained up to 24 hours.

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