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Original Article

Gastro Retentive Microspheres Based Drug Delivery: Formulation and Evaluation

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ABSTRACT

The objectives of the present investigation was to formulate and evaluate Ramipril Microspheres by using different polymers such as HPMC K-4M, HPMCK-15M, HPMCK-100M and Ethyl Cellulose. The shape of microspheres were characterized by optical microspheres and surface morphology evaluated by scanning electron microscopy. Other evolutionary parameters such as Entrapment efficiency, Buoyancy study, In-vitro study was studied. The buoyancy study compliances the floating behavior of microspheres. In-vitro study shows prolonged sustained release pattern of drug release. Scanning electron microscopy showed that microspheres surface was sponge like structure with porous in nature. The prepared Floating microspheres of Ramipril might be used for prolonged drug relese in GIT, for better drug action and improved patient compliance.

Keywords: Ramipril, Microspheres, Scanning electron microscopy, Entrapment efficiency, Buoyancy study, In-vitro drug release, Sustained drug release

INTRODUCTION

Floating microsphere are gastro- retentive drug delivery system. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention time. Floating system are low density that have sufficiently bouncy to float over gastric fluid. After release of drug, the residual system is emptied from the stomach. Attempts are being made to develop a drug delivery system which can be provide therapeutically effective plasma drug concentration for longer period thereby reducing the frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a sustained manner.

MATERIAL AND METHOD MATARIAL

Ramipril is used as active pharmaceutical ingredients, HPMC K-4M, HPMC K-15M, HPMC K-100M, Ethyl Cellulose, Sodium alginate, Calcium chloride are of standard grade.

Table 01: Formula for Ramipril microspheres

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramipril	10	10	10	10	10	10	10	10	10
HPMC K -4M	30	50	70	---	---	---	---	---	---
HPMC K -15M	---	---	---	30	50	70	---	---	---
HPMC K -100M	---	---	---	---	---	---	30	50	70
Ethyl cellulose	10	10	10	10	10	10	10	10	10
Sodium alginate	3000	3000	3000	3000	3000	3000	3000	3000	3000
Calcium chloride	2000	2000	2000	2000	2000	2000	2000	2000	2000

U.V Scanning:

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

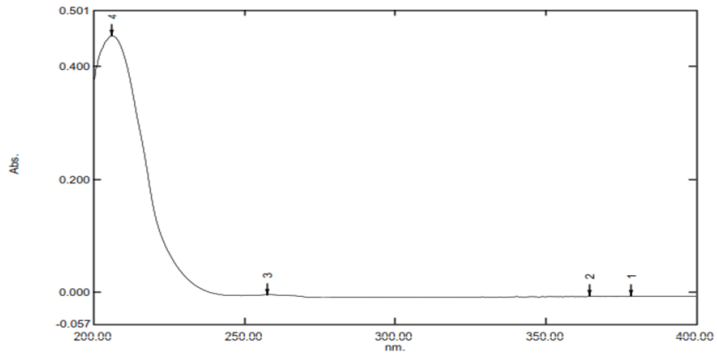

Figure No. 01: UV spectrum of Ramipril

λ_{max} of was found to be 206 nm in 1.2 acidic buffer of P^H 1.2. Hence further study was carried out at 206 nm in p^H 1.2 acidic buffer.

Standard calibration curves:

Table 02: Calibration curves in 0.1 N HCL

Sr.no.	Concentration (µg/ml)	Absorbance
1	00	00
2	02	0.096
3	04	0.180
4	06	0.268
5	08	0.365
6	10	0.447
7	12	0.540
8	14	0.643
9	16	0.719
10	18	0.818
11	20	0.916
12	22	1.035

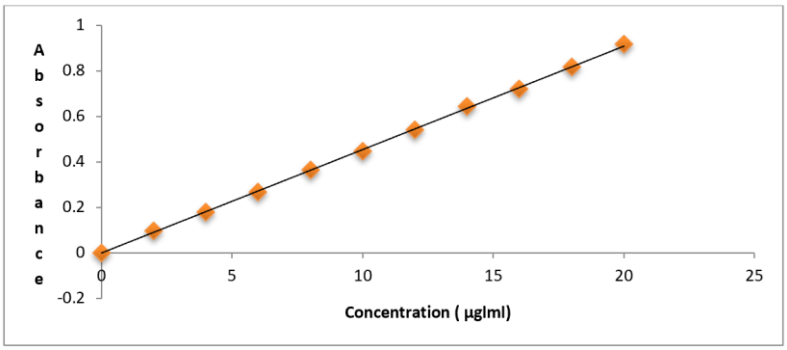

Figure No.02: Calibration curve of Ramipril in 0.1 N HCl

DSC:

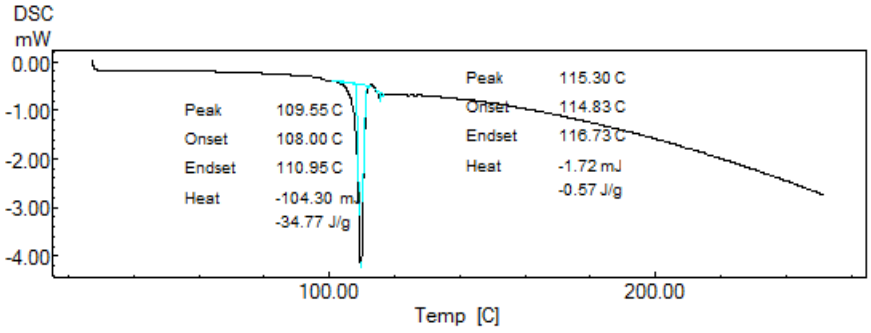

Figure No. 03: DSC of pure drug Ramipril

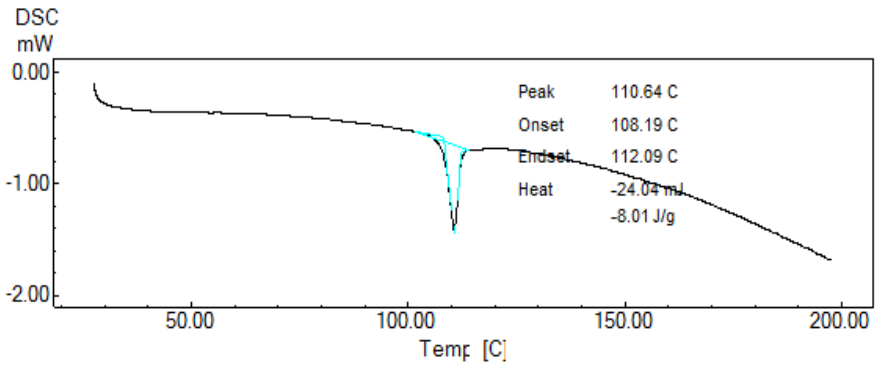

Figure No. 04: DSC of formulation

DSC Thermograms of pure Ramipril, blend of polymer with drug were determined. Pure Ramipril showed a sharp onset of peak at 109° C corresponding to its melting point. There was no appreciable change in the melting endotherms of physical mixture compared to that of pure drug Ramipril. Absence of any new endothermic peak or disappearance or shit of endothermic peak confirms that there is no any interaction and hence the polymers are compatible with drug.

SEM:

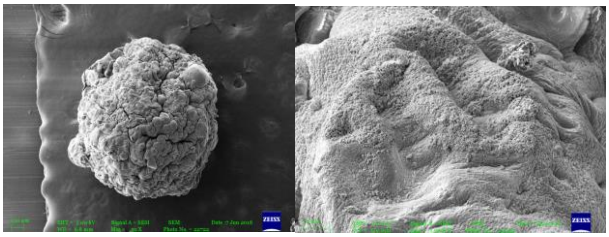

Figure No. 05: Figures of SEM of Microspheres

The microspheres were spherical and the external surface was smooth with slightly rough surface which could be due to drying. The internal surface of microspheres showed sponge like nature.

Evaluation Of Floating Microspheres For Floating Parameters:

Table 03: %Yield, mean particle size, angle of repose of microspheres

Formulation code	% yield	Mean particle size	Angle of repose
F1	92.83 ± 0.275	820 ± 1.520	26.12 ± 0.103
F2	94.43 ± 0.376	870 ± 1.007	28.07 ± 0.001
F3	90.23 ± 1.495	865 ± 2.065	19.65 ± 0.565
F4	82.10 ± 3.181	840 ± 3.105	12.95 ± 0.589
F5	88.63 ± 0.988	811 ± 4.187	16.52 ± 0.722
F6	89.88 ± 0.957	841 ± 0.174	16.12 ± 0.405
F7	95.75 ± 2.326	830 ± 5.0132	15.79 ± 0.400
F8	80.76 ± 0.668	865 ± 0.421	20.19 ± 0.182
F9	95.62 ± 0.490	841 ± 2.0174	16.59 ± 0.230

Table 04: entrapment efficiency, in vitro buoyancy, % drug release of ramipril microspheres

Formulation code	Entrapment efficiency	In-vitro buoyancy	% drug release
F1	89 ± 10.4	12+	85.74 ± 0.502
F2	85 ± 2.645	12+	80.31 ± 0.654
F3	85.66 ± 3.511	12+	82.41 ± 0.195
F4	83.66 ± 3.785	12+	86.04 ± 0.627
F5	86.66 ±1.527	12+	82.54 ± 0.401
F6	89.66 ± 21.45	12+	85.98 ± 0.598
F7	93.33 ± 0.577	12+	86.31 ± 0.185
F8	87 ± 15.099	12+	85.53 ± 0.697
F9	89.33 ± 9.865	12+	84.23 ± 2.081

Table 05: % Drug release study of ramipril microspheres (f1 –f5)

Time	% Release

(Hr)	F1	F2	F3	F4	F5
1	15.93 ± 0.109	22.57 ± 0.775	21.64 ± 0.775	21.64 ± 0.775	19.50 ± 1.216
2	27.36 ± 0.405	25.22 ± 0.995	25.22 ± 0.995	28.65 ± 1.028	31.70 ± 3.273
3	32.74 ± 0.334	36.45 ± 0.687	36.71 ± 0.687	36.71 ± 0.687	37.75 ± 0.401
4	37.94 ± 0.591	42.68 ± 0.385	42.88 ± 0.512	46.71 ± 0.687	42.22 ± 0.420
5	53.78 ± 0.975	52.69 ± 0.465	53 ± 0.675	54.62 ± 0.876	57.84 ± 0.450
6	60.62 ± 0.332	60.08 ± 0.681	59.88 ± 0.295	59.95 ± 0.225	59.89 ± 0.410
7	64.88 ± 0.327	64.06 ± 3.352	65.99 ± 0.687	63.65 ± 0.488	62.93 ± 1.276
8	70.27 ± 0.625	73.65 ± 0.390	75.07 ± 0.976	69.75 ± 0.700	73.87 ± 1.153
9	77.91 ± 0.226	77.57 ± 0.497	77.62 ± 0.845	77.47± 0.562	79.16 ± 0.405
10	79.29 ± 0.190	78.58 ± 0.594	80.72 ± 1.403	82.28 ± 1.460	81.31 ± 0.295
11	85.74 ± 0.502	80.31 ± 0.654	82.41 ± 0.195	86.04 ± 0.627	82.54 ± 0.401

Table 06: % drug release study of ramipril microspheres (f6 – f9)

Time (Hr)	% Release			
	F6	F7	F8	F9
1	19.83 ± 1.476	19.37 ± 1.072	21.91 ± 0.436	14.24 ± 0.780
2	24.57 ± 0.334	28.87 ± 1.203	28.65 ± 1.028	28.01 ± 0.900
3	37.48 ± 0.788	37.23 ± 0.519	37.23 ± 0.519	34.63 ± 2.439
4	41.87 ± 1.842	43 ± 0.300	43 ± 0.300	37.81 ± 0.190
5	51.37 ± 1.106	51.37 ± 1.106	54.62 ± 0.876	58.65 ± 1.350
6	61.71 ± 1.240	60.02 ± 0.195	59.89 ± 0.127	60.65 ± 1.350
7	64.04 ± 1.105	63.65 ± 0.488	64.35 ± 0.872	64.43 ± 1.144
8	68.71 ± 0.709	69.03 ± 1.170	71.81 ± 3.366	68.90 ± 1.001
9	78.64 ± 0.790	77.49 ± 2.619	76.50 ± 0.957	79.81 ± 0.740
10	81.31 ± 0.225	82.34 ± 1.409	81.37 ± 0.295	83.77 ± 2.361
11	85.98 ± 0.598	86.31 ± 0.185	85.53 ± 0.697	84.23 ± 2.081

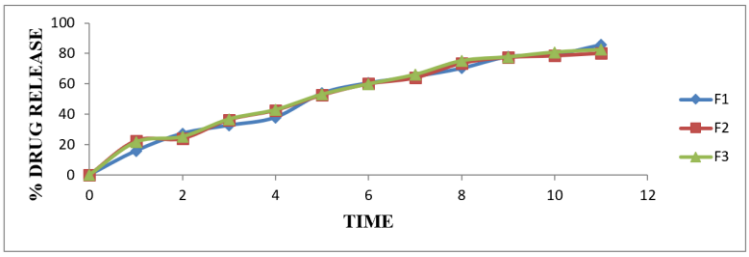

Figure No.06: % Release of drug of formulations (F-F3)

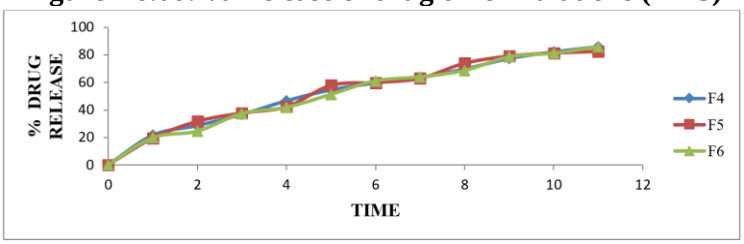

Figure No.07: % Release of drug of formulations (F4-F6)

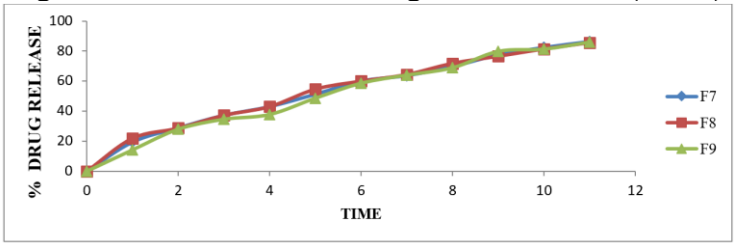

Figure No. 08: % Release of drug of formulations (F7-F9)

Stability Study:

Stability study of optimized best batch F7 at temperature 40 ± 2°C and relative humidity 75 ± 5%

Table 07: Stability study of best batch

Sr. no.	Time	Appearance	% drug entrapment	Floating	% drug release
1	0	White	93.33 ± 0.577	12+	86.31 ± 0.185
2	30 days	White	92.69 ± 1.684	12+	86.5 ± 0.400
3	60 days	White	93.32 ± .0.912	12+	86.96 ± 0.550
4	90 days	White	93.41 ± 0.167	12+	86.78 ± 0.436

CONCLUSION

Microspheres of Ramipril can be successfully prepared using various polymers such as HPMC , Ethyl cellulose. The % yield of all microspheres formulation was more than 75% suggesting that method used for encapsulation was effective. Particle size of all formulation was in range of 810 to 870 µm. The entrapment efficiency was good in all batches. The *in vitro* buoyancy was after 12 hrs indicated satisfactory performance of proposed formulation. The flow properties of of all prepared microspheres were good as indicated. The good flow properties suggested that the microspheres produced were no aggregated. The % release microspheres were found to be order F7< F4< F6. Among all formulations F7was found to best formulation in a sustained manner. SEM study of optimized batch was showed the porous nature of surface of microspheres. The surfaces of microspheres are sponge like structure. Hence, finally it was concluded that the prepared microspheres of Ramipril may proved to be potential candidate for safe and effective drug delivery over an extended period of time which can reduce dosing frequency.

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