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FORMULATION DEVELOPMENT AND INVITRO CHARACTERIZATION OF FLOATING TABLETS OF PERINDOPRIL

M. G. Niharika*[1], G. Mahesh[2], B. Madhavi[3]

[1,3]Department of Pharmaceutics, Avanthi Institute of Pharmaceutical Sciences, JNTUH, Telangana, India.

[2]Department of Pharmaceutical Chemistry, Avanthi Institute of Pharmaceutical Sciences, JNTUH, Telangana, India.

Abstract:

Floating drug delivery system is one of the novel drug delivery system. Perindopril is an anti hypertensive with elimination half life of perindopril is 2.5-3hrs . It was sought to increase gastric retention of perindopril by development of sustained release gastroretentive drug delivery system leading to reduced fluctuation in the plasma concentration and improved bioavailabilty. The floating microspheres were prepared using biocompatable polymers like HPMCK4M,sodium CMC,carbopol 934 by ionotropic gelation technique.Microspheres having lower densities exhibited good buoyancy effect and hence these could be retained in the gastric environment for more than 12 hours. SEM analysis showed that the surface of microspheres was completely uneven with rich complex network. The dissolution studies showed that the drug release followed first order kinetics and Higuchi's diffusion with some non – Fickian diffusion mechanism. The drug release was more controlled from the microspheres prepared with carbopol than those prepared with HPMC. The data obtained in this study thus suggest that floating microspheres of perindopril are promising for sustained drug delivery which improves oral bioavailability and can reduce dosing frequency.

Key words: *Perindopril, HPMC K4M, Sodium CMC, Carbopol, SEM, first order kinetics and Higuchi's diffusion*

Corresponding Author:

M. G. Niharika,
Assistant Professor,
Department Of Pharmaceutics, Avanthi
Institute Of Pharmaceutical sciences, Telangana, India.
niharika.girish888@gmail.com

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INTRODUCTION:

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system (GRDDS). Gasroretentive floating drug delivery system (GRFDDS) have a bulk density less than that of gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system floating on gastric contents, the drug is released slowly at a desired rate from system [1-10]. Both single and multiple unit systems have been developed, but the single unit system has the disadvantage that it's purpose would not be achieved if it fails to float or is rapidly emptied from the stomach since there is high variability of gastrointestinal transit time. On the other hand, floating system made up of multiple units may be better suited, because they are claimed to reduce intersubject variability in absorption and also lower the probability of dose dumping [10-20].

EXPERIMENTAL METHOD:

Materials used: perindopril, HPMC, Sodium CMC, carbopol, Sodium alginate, Calcium carbonate, Calcium chloride all the chemicals were lab grade.

Table 1: Formulation of perindopril Microspheres

Ingredients	perindopril (g)	HPMC (g)	Sodium CMC (g)	carbopol (g)	Sodium alginate (%)	Calcium carbonate(g)	Calcium chloride (%)
F1	0.5	0.25	-	-	3	0.5	1
F2	0.5	0.5	-	-	3	0.5	1
F3	0.5	1.0	-	-	3	0.5	1
F4	0.5	1.5		-	3	0.5	1
F5	0.5	2.0		-	3	0.5	1
F6	0.5	-	0.25	-	3	0.5	1
F7	0.5	-	0.5	-	3	0.5	1
F8	0.5	-	1.0	-	3	0.5	1
F9	0.5	-	1.5	-	3	0.5	1
F10	0.5	-	2.0		3	0.5	1
F11	0.5	-	-	0.25	3	0.5	1
F12	0.5	-	-	0.5	3	0.5	1
F13	0.5	-	-	0.1	3	0.5	1
F14	0.5	-	-	1.5	3	0.5	1
F15	0.5	-	-	2.0	3	0.5	1

Particle Size, Flow Properties of Microspheres, % Yield , % Entrapment Efficiency, Swelling Index (%) are the various tests performed for the prepared microspheres.\

RESULTS AND DISCUSSION:

Table 2: Standard Calibration Curve Of perindopril

Concentration (µg/ml)	Absorbance (in 0.1N HCl)
0	0
5	0.042
10	0.091
20	0.201
30	0.283
40	0.376
50	0.483
60	0.602

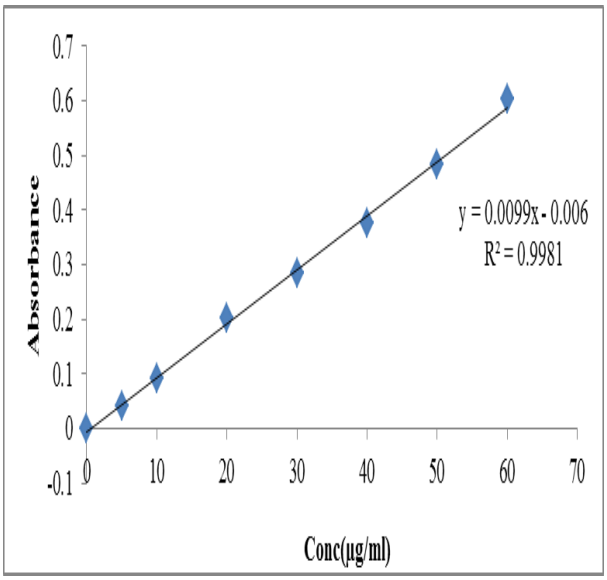

Fig 1: Standard Calibration Curve Of perindopril In pH 1.2 Buffer

Table 3: Average Particle Size Of perindopril Floating Microspheres

Formulation Code	Average Particle Size
F1	57.66
F2	87.45
F3	93.20
F4	62.46
F5	66.30
F6	85.52
F7	75.52
F8	78.32
F9	58.56
F10	79.56
F11	83.28
F12	86.46
F13	74.34
F14	84.36
F15	81.13

Flow Properties of Microspheres:

Table 4: Flow Properties of perindopril Microspheres of Formulations F1 – F15

S. No.	Formula-tion code	Bulk Density (Avg. ± S.D.) (n=3)	Tapped Density (Avg. ± S.D.) (n=3)	Angle of repose (Avg. ± S.D.) (n=3)	Carr's Index (Avg. ± S.D.) (n=3)	Hausners's ratio (Avg. ± S.D.) (n=3)
01	F1	0.372 ± 0.01	0.387 ± 0.01	17.103 ± 0.12	3.875 ± 0.01	1.040 ± 0.01
02	F2	0.416 ± 0.02	0.430 ± 0.02	16.921 ± 0.11	3.258 ± 0.02	1.034 ± 0.01
03	F3	0.327 ± 0.01	0.339 ± 0.01	16.537 ± 0.09	3.539 ± 0.01	1.037 ± 0.01
04	F4	0.383 ± 0.01	0.397 ± 0.01	16.909 ± 0.13	3.429 ± 0.02	1.036 ± 0.01
05	F5	0.406 ± 0.02	0.419 ± 0.02	16.812 ± 0.12	3.102 ± 0.02	1.032 ± 0.01
06	F6	0.307 ± 0.01	0.318 ± 0.01	21.170 ± 0.12	3.611 ± 0.01	1.037 ± 0.01
07	F7	0.386 ± 0.01	0.398 ± 0.01	17.181 ± 0.13	2.917 ± 0.02	1.031 ± 0.01
08	F8	0.417 ± 0.02	0.428 ± 0.02	16.926 ± 0.13	2.570 ± 0.01	1.026 ± 0.01
09	F9	0.318 ± 0.01	0.329 ± 0.01	17.108 ± 0.15	3.459 ± 0.02	1.034 ± 0.01
10	F10	0.373 ± 0.01	0.383 ± 0.01	20.120 ± 0.12	2.610 ± 0.01	1.026 ± 0.01
11	F11	0.291 ± 0.01	0.304 ± 0.01	23.942 ± 0.15	4.309 ± 0.03	1.045 ± 0.01
12	F12	0.351 ± 0.01	0.364 ± 0.01	20.321 ± 0.16	3.571 ± 0.02	1.037 ± 0.01
13	F13	0.363 ± 0.01	0.375 ± 0.01	20.162 ± 0.11	3.210 ± 0.01	1.033 ± 0.01
14	F14	0.290 ± 0.01	0.304 ± 0.01	22.371 ± 0.13	4.309 ± 0.02	1.048 ± 0.01
15	F15	0.282 ± 0.01	0.295 ± 0.01	22.461 ± 0.15	4.406 ± 0.01	1.046 ± 0.01

Evaluation Studies of Microspheres:

Table 5: Physical Evaluation Parameters Of perindopril Microspheres Of formulations F1 – F15

S. No.	Formulation code	% Yield (Avg. ± S.D.) (n=3)	% Entrapment Efficiency (Avg. ± S.D.) (n=3)	Swelling Index (%)
01	F1	90.13 ± 0.31	62.35 ± 0.21	1.1
02	F2	91.56 ± 0.43	65.81 ± 0.28	0.9
03	F3	86.30 ± 0.34	69.32 ± 0.32	0.2
04	F4	76.88 ± 0.32	78.43 ± 0.33	1.4
05	F5	83.01 ± 0.31	83.41 ± 0.37	0.7
06	F6	80.23 ± 0.33	87.52 ± 0.42	0.1
07	F7	92.21 ± 0.42	85.98 ± 0.40	1.2
08	F8	86.37 ± 0.34	86.41 ± 0.41	0.5
09	F9	83.15 ± 0.31	88.03 ± 0.43	0.1
10	F10	90.42 ± 0.41	77.83 ± 0.34	1.3
11	F11	88.34 ± 0.38	81.75 ± 0.37	0.8
12	F12	85.10 ± 0.35	86.53 ± 0.42	0.3
13	F13	88.91 ± 0.38	79.05 ± 0.30	1.2
14	F14	84.12 ± 0.33	83.78 ± 0.36	0.7
15	F15	82.66 ± 0.32	88.54 ± 0.42	0.2

Percent Buoyancy Of perindopril Floating Microspheres

Table 6: Percent Buoyancy Of perindopril Floating Microspheres

Formulation Code	Weight of Floating Microspheres Taken (mg)	Weight of Micro-spheres Floated (mg)	% Buoyancy
F1	300	260	86.67
F2	300	249	83.00
F3	300	238	79.33
F4	300	271	90.33
F5	300	253	84.33
F6	300	245	81.67
F7	300	262	87.33
F8	300	256	85.33
F9	300	240	80.23
F10	300	260	86
F11	300	260	81.5
F12	300	230	76.33
F13	300	222	74.67
F14	300	218	82.61
F15	300	212	70.33

***In-Vitro* Dissolution Studies:**

Table 7: Results of Dissolution Test Performed On perindopril Microspheres of Formulations F1to F3

S. No.	Time (min)	% drug dissolved (Avg. ± S.D.)		
		F1	F2	F3
1	0	0	0	0
2	15	91.87 ± 0.41	47.03 ± 0.21	18.71 ± 0.11
3	30	98.48 ± 0.46	76.98 ± 0.24	42.45 ± 0.20
4	45	-	82.21 ± 0.42	46.04 ± 0.26
5	60	-	92.67 ± 0.51	62.93 ± 0.32
6	90	-	97.88 ± 0.48	77.76 ± 0.38
7	120	-	-	84.72 ± 0.45

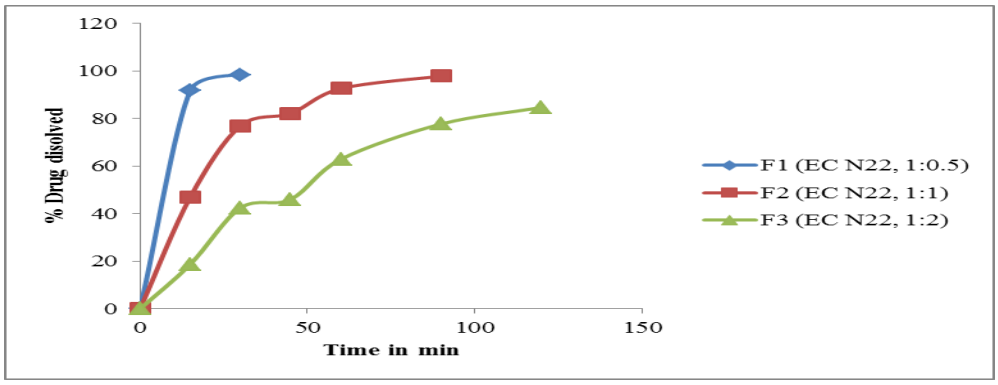

Fig 2 : Zero – Order Plots Of perindopril Microspheres Of Formulations F1 to F3

Table 8: Dissolution Kinetics Of perindopril Formulations F1 to F3

S.No.	Formulation	Regression coefficient (R^2) value			Dissolution rate constant (hr^{-1})	Peppasexponential constant (n)
		Zero – order	First – order	Higuchi's		
01	F1	0.894	0.984	0.945	0.112	0.099
02	F2	0.871	0.992	0.966	0.038	0.404
03	F3	0.958	0.991	0.947	0.015	0.711

Table 9: Results Of Dissolution Test Performed On perindopril Microspheres Of Formulations F4 to F6

S. No.	Time (min)	% drug dissolved (Avg. ± S.D.)		
		F4	F5	F6
1	0	0	0	0
2	30	43.24 ± 0.22	36.75 ± 0.12	22.19 ± 0.12
3	60	67.72 ± 0.21	52.24 ± 0.23	44.41 ± 0.14
4	90	82.42 ± 0.48	69.45 ± 0.32	52.68 ± 0.21
5	120	94.01 ± 0.51	80.23 ± 0.45	67.03 ± 0.25
6	150	-	89.06 ± 0.23	73.93 ± 0.38
7	180	-	92.16 ± 0.37	81.03 ± 0.43
8	240	-	97.47 ± 0.43	90.92 ± 0.21
9	300	-	98.41 ± 0.33	95.41 ± 0.33
10	360	-	-	96.36 ± 0.45
11	420	-	-	97.91 ± 0.46
12	480	-	-	98.79

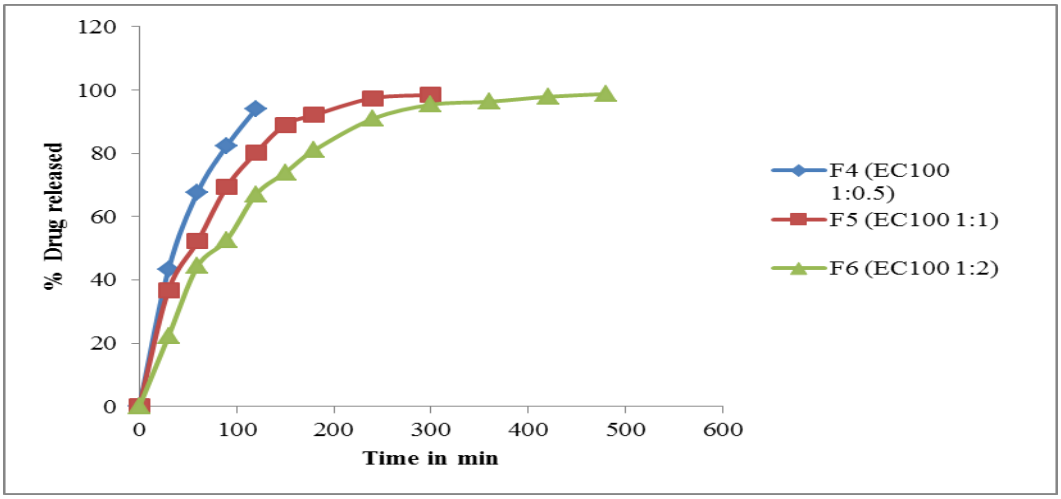

Fig 3: Zero – Order Plots of perindopril Microspheres of Formulations F4 to F6

Table 10: Dissolution Kinetics of perindopril Formulations F4 to F6

S.No.	Formulation	Regression coefficient (R^2) value			Dissolution rate constant (hr^{-1})	Peppas exponential constant (n)
		Zero – order	First – order	Higuchi's		
01	F4	0.9628	0.973	0.997	0.020	0.564
02	F5	0.8775	0.992	0.947	0.015	0.450
03	F6	0.8728	0.994	0.927	$9.212*10^{-3}$	0.507

Table 11: Results of Dissolution Test Performed On perindopril Microspheres of Formulations F7 to F9

S. No.	Time (min)	% drug dissolved (Avg. ± S.D.)		
		F7	F8	F9
01	0	0	0	0
02	30	48.71 ± 0.23	27.72 ± 0.12	13.9 ± 0.10
03	60	73.21 ± 0.32	40.97 ± 0.17	21.83 ± 0.14
04	90	83.93 ± 0.29	44.79 ± 0.21	39.32 ± 0.16
05	120	91.39 ± 0.43	49.53 ± 0.26	44.79 ± 0.23
06	150	94.69 ± 0.42	57.53 ± 0.30	49.06 ± 0.29
07	180	96.58 ± 0.43	70.07 ± 0.43	50.9 ± 0.25
08	240	98.35 ± 0.44	83.48 ± 0.25	54.71 ± 0.27
09	300	-	87.83 ± 0.42	66.96 ± 0.33
10	360	-	92.9 ± 0.45	71.88 ± 0.35
11	420	-	95.78 ± 0.46	82.09 ± 0.40
12	480	-	97.88 ± 0.46	85.67 ± 0.43
13	540	-	98.74 ± 0.47	87.83 ± 0.42
14	600	-	-	90.77 ± 0.46
15	660	-	-	94.67 ± 0.47
16	720	-	-	95.68 ± 0.42

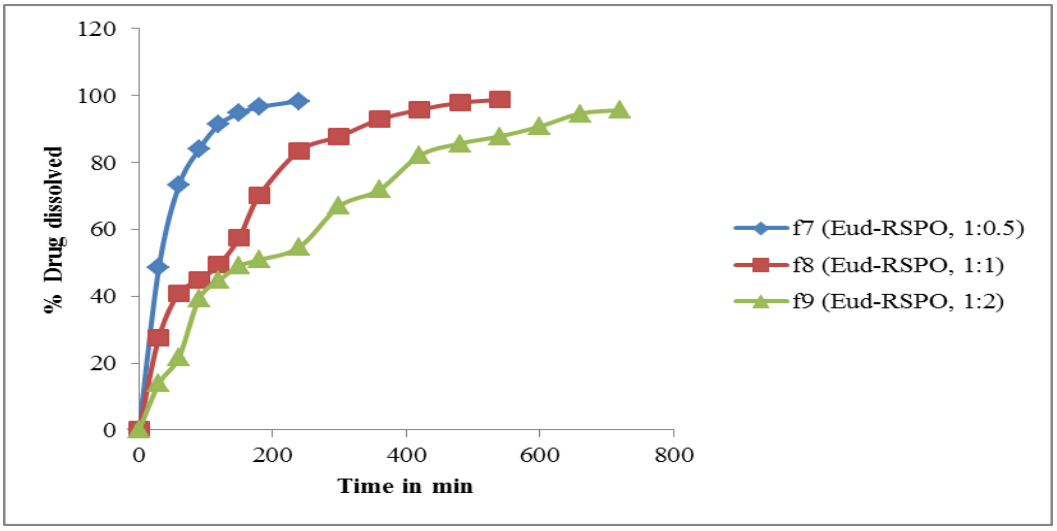

Fig 4: Zero – Order Plots of perindopril Microspheres of Formulations F7 to F9

Table 12: Dissolution Kinetics of perindopril Formulations F7 to F9

S. No.	Formulation	Regression coefficient (R^2) value			Dissolution rate constant (hr^{-1})	Peppas exponential constant (n)
		Zero – order	First – order	Higuchi's		
01	F7	0.8285	0.980	0.891	0.01704	0.336
02	F8	0.9195	0.986	0.967	$5.104*10^{-3}$	0.464
03	F9	0.9467	0.984	0.983	$5.258*10^{-3}$	0.579

Table 13 : Results Of Dissolution Test Performed On perindopril Microspheres Of Formulations F10 to F12

S. No.	Time (min)	% drug dissolved (Avg. ± S.D.)		
		F10	F11	F12
01	0	0	0	0
02	30	31.29 ± 0.14	29.10 ± 0.12	16.44 ± 0.13
03	60	51.01 ± 0.21	37.34 ± 0.17	25.53 ± 0.12
04	90	54.58 ± 0.22	38.63 ± 0.20	26.54 ± 0.14
05	120	70.34 ± 0.34	41.12 ± 0.20	33.85 ± 0.12
06	150	71.42 ± 0.34	47.38 ± 0.22	37.63 ± 0.18
07	180	85.54 ± 0.40	62.59 ± 0.31	47.35 ± 0.22
08	240	89.67 ± 0.39	68.74 ± 0.34	54.5 ± 0.25
09	300	94.87 ± 0.46	73.33 ± 0.34	67.34 ± 0.33
10	360	96.84 ± 0.47	81.25 ± 0.40	73.93 ± 0.34
11	420	-	87.12 ± 0.43	75.51 ± 0.32
12	480	-	91.68 ± 0.41	82.03 ± 0.41
13	540	-	93.97 ± 0.44	86.82 ± 0.44
14	600	-	95.43 ± 0.51	90.45 ± 0.41
15	660	-	97.18 ± 0.47	93.39 ± 0.45
16	720	-	-	95.53 ± 0.41

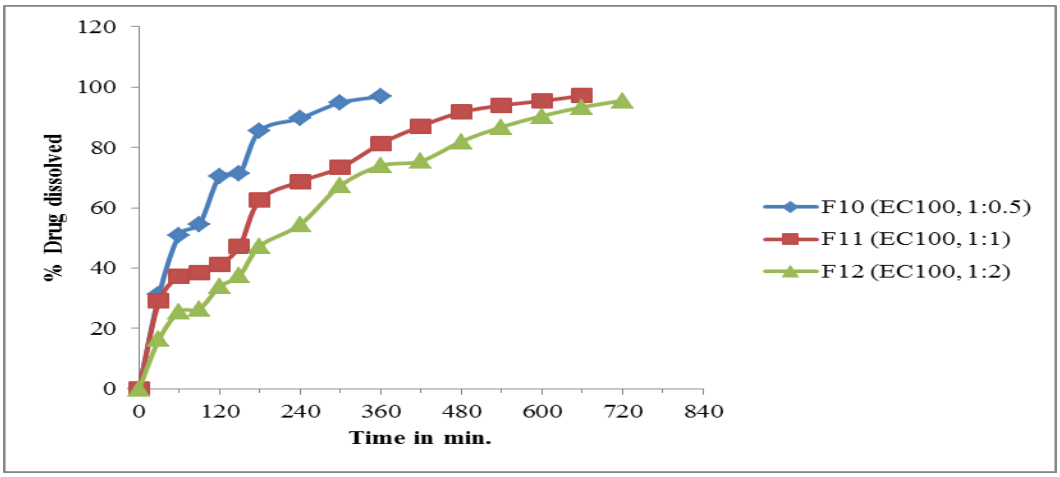

Fig 5: Zero – Order Plots of perindopril Microspheres of Formulations F10 to F12

Table 14: Dissolution Kinetics of perindopril Formulations F10 to F12

S.No.	Formulation	Regression coefficient (R^2) value			Dissolution rate constant (hr^{-1})	Peppas exponential constant (n)
		Zero –order	First- order	Higuchi's		
01	F10	0.8971	0.989	0.960	0.011	0.454
02	F11	0.9371	0.987	0.974	$2.994*10^{-3}$	0.434
03	F12	0.9649	0.982	0.983	$4.644*10^{-3}$	0.583

Table 15: Results of Dissolution Test Performed on perindopril Microspheres of Formulations F13 to F15

S. No.	Time (min)	% drug dissolved (Avg. ± S.D.)		
		F13	F14	F15
01	0	0	0	0
02	30	29.53 ± 0.15	18.71 ± 0.10	14.68 ± 0.11
03	60	42.05 ± 0.20	29.04 ± 0.15	22.19 ± 0.10
04	90	44.79 ± 0.21	40.84 ± 0.18	31.29 ± 0.15
05	120	53.44 ± 0.22	43.5 ± 0.25	36.61 ± 0.23
06	150	62.58 ± 0.35	54.91 ± 0.27	41.65 ± 0.24
07	180	71.75 ± 0.38	60.91 ± 0.33	48.71 ± 0.27
08	240	83.48 ± 0.42	67.93 ± 0.34	56.84 ± 0.39
09	300	89.23 ± 0.46	78.17 ± 0.32	61.36 ± 0.36
10	360	94.37 ± 0.42	80.85 ± 0.41	62.76 ± 0.37
11	420	95.96 ± 0.43	86.81 ± 0.44	67.86 ± 0.39
12	480	98.31 ± 0.41	91.81 ± 0.43	74.17 ± 0.35
13	540	-	93.39 ± 0.46	79.62 ± 0.38
14	600	-	94.81 ± 0.41	83.78 ± 0.40
15	660	-	96.45 ± 0.45	85.54 ± 0.43
16	720	-	98.82 ± 0.41	88.51 ± 0.46

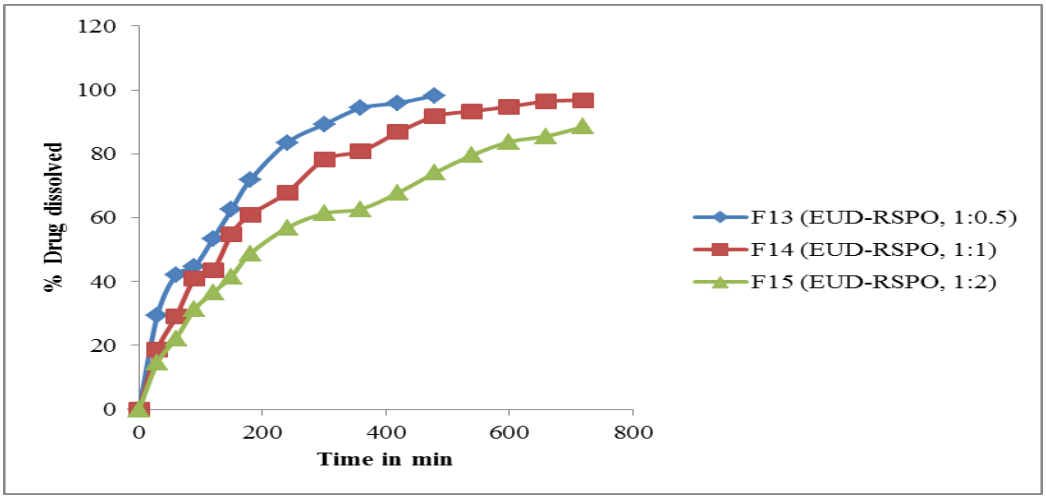

Fig 6: Zero-Order Plots of perindopril Microspheres of Formulations F13 toF15

Table 16: Dissolution Kinetics of perindopril Formulations F13 to F15

S.No.	Formulation	Regression coefficient (R^2) value			Dissolution rate constant (hr^{-1})	Peppas exponential constant (n)
		Zero – order	First – order	Higuchi's		
01	F13	0.9239	0.986	0.976	$8.982*10^{-3}$	0.461
02	F14	0.9198	0.996	0.968	$4.202*10^{-3}$	0.513
03	F15	0.9546	0.984	0.992	$3.051*10^{-3}$	0.554

CONCLUSION:

Studies have been carried out on the study of influence of formulation and drug release rate from perindopril microspheres. In this investigation, three different polymers viz. HPMC K4M, sodium CMC and carbopol 934, were studied for their influence at three different drug to polymer ratios . The nature of polymer influence the floating behaviour of the microspheres. SEM analysis of the microspheres prepared from carbopol 934 showed the surface of the microspheres was smooth, spherical and no pits were present on the surface.The dissolution studies showed that the drug release followed first order kinetics and Higuchi's diffusion with some non – Fickian diffusion mechanism.The drug release rate was found to be reduced upon increase in the concentration of the polymer.From the dissolution studies an interesting finding was observed that the drug release rate was found to be reduced upon increase in the viscosity of the polymer phase even at the same amount of the polymer.It was found that the drug release rate was more controlled upon increase in the molecular weight of the polymer,carbopol.The drug release was more controlled from the microspheres prepared with carbopol 934 than those prepared with HPMC K4M.Among all the formulations, F14 was found to be the best formulation as it release perindopril 96.82% in a sustained manner with constant fashion over extended period of time .Thus the major objectives of the present investigation were achieved and the results were appropriately placed.

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