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Formulation and evaluation of Multiunit floating drug delivery system of levofloxacin hemihydrate for Eradication of H. Pylori

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Abstract:
The objective of the present study was to develop floating microspheres of Levofloxacin hemihydrate for the treatment of peptic ulcer disease caused by Helicobacter pylori (H. pylori). Levofloxacin hemihydrate was chosen as a model drug because it preferentially absorbed from the upper part of the gastrointestinal tract. The floating microspheres were prepared by the emulsion solvent evaporation method using polymers hydroxypropylmethylcellulose (HPMC K4M) in fixed ratio and Ethylcellulose in variable ratios, in the mixture of acetone and ethanol at ratio of (1:1), with tween80 as the surfactant. 2^3 factorial design was adopted to optimize the formulation variables. The floating microspheres were evaluated for Particle size analysis, %buoyancy, drug entrapment efficiency, % yield and *in vitro* drug release. All the results were found to be in acceptable limit. The optimized formulation were subjected to different release kinetic model like zero order, First order, Higuchi, korsemeyer peppas and Hixon-crowell. The korsemeyer peppas model was accepted due to its highest value of slop (n) (0.9890). The optimized formulation again subjected to stability studies as per the ICH Guideline. The formulation was found to be stable under the provided condition of temperature and humidity.

Keywords: Floating microspheres, Levofloxacin hemihydrate, Helicobacter pylori, drug entrapment efficiency.

Introduction

Historically, oral drug delivery systems are the most popular drug delivery system but these systems have some, limitation such as, patient incompliance due to frequent drug administration, undesirable side effect due to fluctuating plasma drug level, inability to maintain adequate drug concentration in plasma for therapeutic effect, larger dose than required dose [(1)]. This limitation can be overcome by modifying existing drug delivery systems (DDSs). An appropriately designed sustained release (SR) or controlled release DDS can be a major step toward solving the problem associated with conventional DDSs[(2)]. Oral controlled release (CR) dosage forms (DFs) have been developed for the past three decades due to their considerable therapeutic advantages [(3)]. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine. This is due to the relatively short transit time of the DF in these anatomical segments. Thus, after only a short period of less than 2-3 h, the CR-DF has already left the upper gastrointestinal tract and the drug is released in non absorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability. The medications that are included in the category of

narrow absorption window are mostly associated with improve absorption at the jejunum and ileum due to their enhanced absorption properties, e.g. huge surface area [4]. It was suggested that preparing narrow absorption window drugs in a unique pharmaceutical DF with gastro retentive properties would enable an extended absorption phase of these drugs [5]. The major objectives of the study are to formulate and evaluate the levofloxacin floating microspheres with the help of hydroxypropyl methyl cellulose (HPMC K4M) and release-retarding hydrophobic polymer ethyl cellulose to control the release of highly water soluble levofloxacin hemihydrates for the systemic as well as local delivery for eradication of H. Pylori.

MATERIALS AND METHODS

PREPARATION OF FLOATING MICROSPHERES

Floating Microspheres were prepared by a Non-aqueous Solvent Evaporation method. HPMC K4M and EC (14cps) were mixed in the mixture of acetone and ethanol at 1:1 ratio. The slurry was slowly introduced into 50 ml of liquid paraffin containing 1% Tween 80 while being stirred at 1000 rpm using mechanical stirrer equipped with five bladed propellers at room temperature. The solution was stirred for 2 h and allowed the solvent to evaporate completely and filtered by using filter paper (Whatman filter paper). The microspheres obtained were washed repeatedly with petroleum ether (40-60°C) until free from oil. The collected microspheres were dried at room temperature and subsequently stored in desiccators. Same procedure was repeated for all the batches [6].

EVALUATION OF FLOATING MICROSPHERES

Size distribution and morphology

The floating microspheres were examined by optical and scanning electron microscopy (SEM). A freshly prepared suspension of microspheres in 0.1% Tween 80 was examined on an optical microscope. The size of the microspheres was measured using a photo microscope [7]. Around 100 particles from each formulation were measured and the observed data of each formulation are presented in Table 1.

Table 1: Mean particle size of different formulation of Levofloxacin loaded floating microspheres.

S. No.	Formulation code	Mean particle size(µm)
1	F-1	318.24±0.0012
2	F-2	347.21±0.0032
3	F-3	323.31±0.043
4	F-4	349.57±0.0051
5	F-5	334.25±0.0030
6	F-6	357.32±0.0048
7	F-7	329.26±0.056
8	F-8	354.27±0.0011

n =3, ± SD

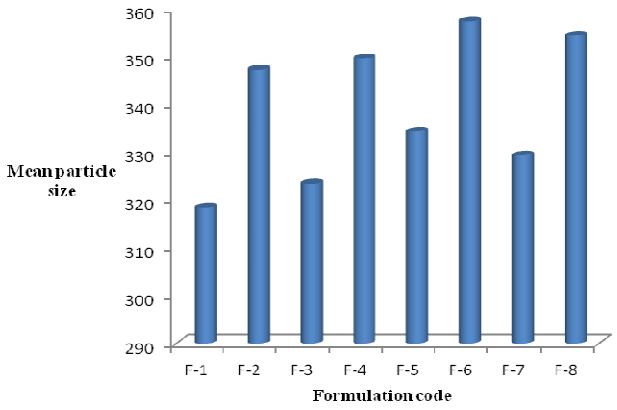

Figure 1: Mean particle size vs. Formulation

The surface morphology of microspheres was visualized by scanning electron microscopy. The samples for SEM were prepared by lightly sprinkling the microspheres particles on a double adhesive tape which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300°A using a sputter coater.

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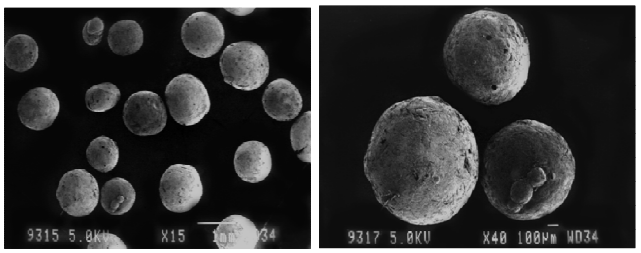
These samples were than randomly scanned and photomicrographs were taken which are shown in Fig. 2 (A & B).



A B

Figure 2: SEM of floating microspheres: A.X15 B.X40

Microspheres of the drug with combination of ethyl cellulose and HPMCK4M were porous, rough, and grossly spherical. The surface topography reveals that the microspheres were highly porous due to the rapid escape of the volatile solvents during formulation.

Very less particulate matter of the drug were seen on the surface of the microspheres indicating uniform distribution of the drug in the polymeric network. The microspheres are retained in the stomach by virtue of their buoyancy due to the pores and hydrophobic nature of ethyl cellulose.

Flow Properties

The flow properties of all the formulations were found out by measuring the angle of repose and compressibility index. The results are shown in table 2. The values of angle of repose were between 23^0 to 34^0, which are within the normal acceptable range of 20^0 to 40^0.

The porous microspheres thus showed reasonably good flow potential. The values of Compressibility index (I) was in the range 20 to 28, indicating good flow characteristics of the microspheres. This also implies that the microspheres are non-aggregated. Thus they can be easily handled and filled into a capsule8, 9. Therefore, capsules loaded with microspheres can be suggested as a floating micro particulate drug delivery system. Moreover the soft gelatine capsules easily absorb water and disintegrate and do not hinder with the floating capability of the microspheres [10, 11].

Table 2: Micromeritics parameters of different batches of floating microspheres

Formulation	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's compressibility index	Hausner ratio	Angle of repose (Θ)
F-1	1.59±0.0016	0.48±0.0013	28±0.017	1.45±0.124	34±0.034
F-2	1.48±0.006	0.43±0.0021	26±0.0048	1.35±0.034	33±0.023
F-3	1.52±0.0031	0.46±0.031	22±0.0037	1.81±0.054	25±0.0017
F-4	1.44±0.0012	0.41±0.0023	20±0.018	1.31±0.098	26±0.0028
F-5	1.62±0.0014	0.52±0.0015	25±0.0023	1.45±0.101	32±0.0043
F-6	1.54±0.0062	0.46±0.0071	23±0.0019	1.62±0.167	33±0.0029
F-7	1.64±0.0026	0.47±0.0042	21±0.028	1.39±0.051	27±0.042
F-8	1.53±0.0032	0.44±0.0056	20±0.0013	1.05±0.096	23±0.0011

n = 3, ± SD

Estimation of drug incorporation efficiency and % yield

The values of total drug content and % incorporation efficiency are shown in table 3. High incorporation efficiencies are seen with higher concentrations of ethylcellulose. Comparison of total incorporation efficiencies is shown in Fig.2. F-8 shows the highest incorporation efficiency (89.06%) while F-3 shows the least (74.86%).

Table 3: Percentage yield, percentage encapsulation efficiency and percentage buoyancy (after 12hrs) of floating microsphere of Levofloxacin hemihydrates

S. N.	formulation	%yield	%DEE	%buoyancy after 12hrs.
1	F-1	55.928±0.012	78.3±0.016	64.2±0.032
2	F-2	50.571±0.031	76.28±0.027	82.5±0.071
3	F-3	56.586±0.007	74.86±0.052	66.32±0.19
4	F-4	50.928±0.042	77.426±0.120	76.72±0.071
5	F-5	56.167±0.016	78.417±0.231	58.64±0.065
6	F-6	58.3±0.034	82.53±0.051	80.06±0.043
7	F-6	59.546±0.061	79.83±0.046	61.23±0.071
8	F-8	59.76±0.023	89.06±0.061	82.47±0.01652

n =3, ± SD

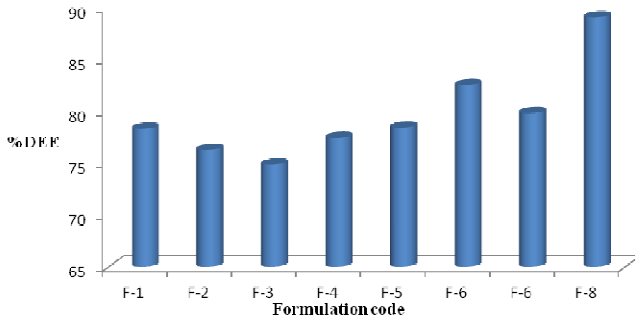


Fig.3: Percentage DEE vs. Formulation

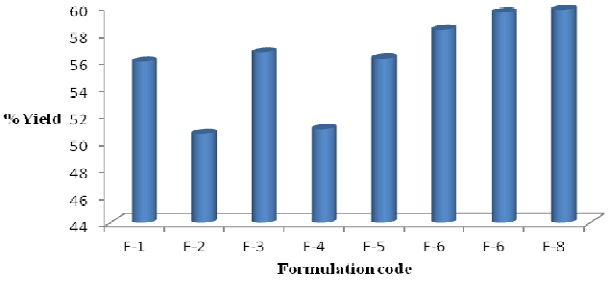


Fig.4: Percentage yield vs. Formulation

In vitro buoyancy studies

The purpose of preparing floating microsphere was extend the gastric residence time of a drug, the in vitro floating behavior was investigated in the acidic medium containing a small amount of surfactant Tween 20 (0.02% w/v), agitated with a paddle at 50 rpm was used to simulate the wetting action of gastric fluid under movement. The results are shown in table 3. In vitro buoyancy studies reveal that in spite of stirring the dissolution medium for more than 12 hours about 58-82.47% of microspheres were still continued to float without any apparent gelation, thus indicating that microspheres exhibit excellent buoyancies which can be attributed to the pores and lower density of polymer12. Comparison of % buoyancy of different formulation is shown in Fig.5.

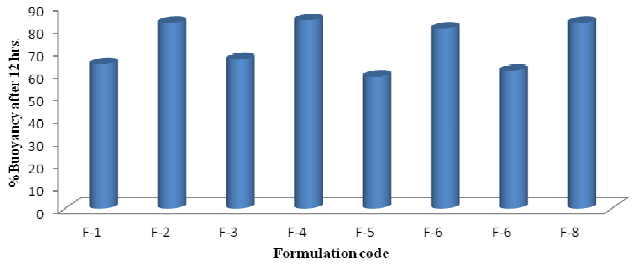


Fig. 5: %buoyancy after12hrs vs. Formulation

The percentage buoyancies increase with increase concentration of ethyl cellulose. So the microspheres having higher polymer (Ethylcellulose) concentrations were more buoyant (F8; 82.47%) than those with lower polymers (ethylcellulose) concentrations (F5; 58.64%).

In vitro drug release studies

Dissolution studies on all the eight formulations of Levofloxacin hemihydrates floating microspheres were carried out using a USP XXIII Type II i.e., Paddle Type dissolution apparatus. As the microspheres floated in the stomach and

released the drug, SGF (pH 1.2) was used as the dissolution medium.

A combination of polymer was used for the current study to design a perfect gastro retentive delivery system which released most of the drug in upper part of gastrointestinal tract. As the amount of ethyl cellulose used in the preparation was increased the release of the drug was decreased due to hydrophobic nature of ethyl cellulose13.

The In vitro drug release data for each of the formulations is shown in tables 4 to table 11. The cumulative percent drug release after 8 hours was found to be 90.527±0.0420, 88.874±0.0036, 89.866±0.0027, 86.065±0.0361, 91.662±0.0063, 85.569±0.0021, 88.874±0.0047, 87.221±0.0052% for the formulations F-1 to F-8 respectively. The initial fast release may be due to the release of surface adsorbed drug. It indicates a period that the drug release is prolonged over a period of 8 hours in case of Levofloxacin hemihydrates in which ratio of HPMCK4M and EC were 1:9.

It may be concluded from this in vitro drug release study that the release rate can be controlled by varying the polymer: polymer ratio and the dosage form could be designed to give the release in a controlled fashion at the desired site. As for Levofloxacin hemihydrates, the site of absorption is upper GI tract, the formulation F-8 can serve the needs of a controlled release in upper GIT.

Table 4: Drug release profile of F1

S. N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.152	70.588	0.0706	63.529	63.529	25.411±0.0016
3	60	0.213	98.592	0.0986	88.733	88.803	35.521±0.0011
4	90	0.284	131.186	0.131	118.067	118.167	47.267±0.0024
5	120	0.335	154.599	0.155	139.139	139.271	55.708±0.016
6	180	0.476	219.329	0.219	197.396	197.550	79.020±0.008
7	240	0.517	238.151	0.238	214.336	214.555	85.822±0.0019
8	300	0.542	249.628	0.249	224.665	224.903	89.962±0.021
9	360	0.543	250.087	0.250	225.078	225.328	90.133±0.006
10	420	0.545	251.005	0.251	225.905	226.155	90.462±0.013
11	480	0.546	251.465	0.251	226.318	226.569	90.627±0.015

Dilution factor=15, dose 250 mg, n=3, ± SD

Table 5: Drug release profile of F2

S. N.	Time (min.)	absorbance	Conc. (µg/ml)	Conc. (mg/ml)	Conc. (mg)	Cum. drug release	% release
1	0	0	0	0	0	0	0
2	30	0.137	63.702	0.064	57.332	57.332	22.932±0.0036
3	60	0.163	75.638	0.077	68.075	68.138	27.255±0.0014
4	90	0.197	91.247	0.091	82.122	82.197	32.879±0.006
5	120	0.267	123.382	0.123	111.044	111.135	44.454±0.016
6	180	0.332	153.223	0.153	137.900	138.023	55.209±0.0046
7	240	0.391	180.308	0.180	162.277	162.430	64.972±0.046
8	300	0.435	200.507	0.201	180.456	180.636	72.254±0.009
9	360	0.479	220.707	0.221	198.636	198.836	79.535±0.056
10	420	0.498	229.429	0.229	206.486	206.706	82.683±0.0116
11	480	0.536	246.873	0.247	222.187	222.415	88.966±0.0096

Table 6: Drug release profile of F3

S. N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.147	68.293	0.068	61.463	61.463	24.586±0.0019
3	60	0.213	98.592	0.099	88.733	88.801	35.520±0.003
4	90	0.264	122.0051	0.122	109.804	109.903	43.961±0.015
5	120	0.327	150.926	0.151	135.834	135.956	54.382±0.006
6	180	0.432	199.129	0.199	179.216	179.367	71.747±0.0046
7	240	0.497	228.969	0.229	206.072	206.272	82.508±0.0081
8	300	0.509	234.479	0.235	211.031	211.259	84.503±0.0066
9	360	0.533	245.496	0.2454	220.947	221.181	88.472±0.062
10	420	0.539	248.251	0.2482	223.426	223.671	89.468±0.005
11	480	0.542	249.628	0.2496	224.665	224.913	89.965±0.0082

Dilution factor=15, dose 250 mg, n=3, ± SD

Table 7: Drug release profile of F4

S.N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.127	59.112	0.059	53.200	53.200	21.280±0.009
3	60	0.173	80.229	0.081	72.2061	72.265	28.906±0.001
4	90	0.204	94.460	0.094	85.0144	85.094	34.037±0.030
5	120	0.243	112.364	0.112	101.128	101.223	40.488±0.0072
6	180	0.322	148.632	0.149	133.768	133.880	53.552±0.0051
7	240	0.387	178.471	0.178	160.624	160.772	64.309±0.0034
8	300	0.449	206.934	0.206	186.240	186.419	74.567±0.0071
9	360	0.497	228.969	0.228	206.072	206.279	82.512±0.006
10	420	0.514	236.774	0.23677	213.096	213.325	85.330±0.004
11	480	0.519	239.069	0.23906	215.162	215.399	86.159±0.0036

Dilution factor=15, dose 250 mg, n=3, ± SD

Table 8: Drug release profile of F5

S. N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.157	72.883	0.072	65.595	65.595	26.238±0.026
3	60	0.195	90.329	0.090	81.295	81.368	32.548±0.007
4	90	0.214	99.0512	0.099	89.146	89.236	35.694±0.016
5	120	0.253	116.955	0.117	105.259	105.358	42.143±0.022
6	180	0.322	148.632	0.149	133.768	133.885	53.554±0.0031
7	240	0.407	187.653	0.187	168.887	169.036	67.614±0.008
8	300	0.469	216.116	0.216	194.504	194.691	77.876±0.021
9	360	0.507	233.560	0.234	210.204	210.420	84.168±0.0042
10	420	0.534	245.955	0.245	221.360	221.593	88.637±0.019
11	480	0.542	249.628	0.249	224.665	224.911	91.962±0.002

Dilution factor=15, dose 250mg, n=3

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Table 9: Drug release profile of F6

S. N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.137	63.702	0.063	57.332	57.332	22.932±0.0052
3	60	0.185	85.738	0.085	77.164	77.228	30.891±0.008
4	90	0.214	99.051	0.099	89.146	89.231	35.693±0.0021
5	120	0.253	116.955	0.117	105.259	105.358	42.144±0.003
6	180	0.322	148.631	0.149	133.768	133.885	53.554±0.0047
7	240	0.397	183.062	0.183	164.756	164.904	65.962±0.0051
8	300	0.419	193.161	0.193	173.845	174.028	69.611±0.004
9	360	0.467	215.198	0.215	193.677	193.871	77.548±0.0076
10	420	0.504	232.183	0.232	208.965	209.180	83.672±0.001
11	480	0.516	237.692	0.238	213.923	214.155	85.662±0.036

Dilution factor=15, dose 250 mg, n=3, ± SD

Table 10: Drug release profile of F7

S. N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.149	69.211	0.069	62.290	62.290	24.916±0.007
3	60	0.205	94.9196	0.095	85.427	85.496	34.198±0.011
4	90	0.264	122.005	0.122	109.804	109.899	43.953±0.0021
5	120	0.313	144.499	0.145	130.049	130.171	52.069±0.008
6	180	0.392	180.766	0.181	162.690	162.834	65.134±0.003
7	240	0.417	192.243	0.192	173.019	173.200	69.280±0.0026
8	300	0.469	216.116	0.216	194.501	194.696	77.878±0.06
9	360	0.507	233.560	0.234	210.204	210.420	84.168±0.0044
10	420	0.524	241.365	0.241	217.228	217.462	86.984±0.0031
11	480	0.536	246.873	0.247	222.186	222.427	88.971±0.006

Dilution factor=15, dose 250 mg, n=3, ± SD

Table 11: Drug release profile of F8

S. N.	Time (min.)	absorbance	Conc.(µg/ml)	Conc.(mg/ml)	Conc.(mg)	Cum.drug release	% release
1	0	0	0	0	0	0	0
2	30	0.129	60.0297	0.060	54.026	54.026	21.610±0.0032
3	60	0.145	67.375	0.067	60.637	60.697	24.278±0.0058
4	90	0.184	85.279	0.085	76.751	76.818	30.727±0.0091
5	120	0.213	98.592	0.098	88.732	88.818	35.527±0.0051
6	180	0.262	121.087	0.121	108.978	109.077	43.630±0.006
7	240	0.317	146.336	0.146	131.702	131.824	52.729±0.0012
8	300	0.369	170.208	0.170	153.187	153.334	61.334±0.009
9	360	0.427	196.835	0.197	177.151	177.321	70.928±0.002
10	420	0.484	223.002	0.223	200.701	200.898	80.359±0.0031
11	480	0.526	242.283	0.2423	218.054	218.278	87.311±0.0019

Dilution factor=15, dose 250 mg, n=3, ± SD

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Table 12: *In-vitro* drug release profile of different batches of floating microspheres

Time (min.)	% cum. drug releaseF1	% cum. drug release F2	% cum. drug release F3	% cum. drug releaseF4	% cum. drug releaseF5	% cum. drug releaseF6	% cum. drug releaseF7	% cum. drug releaseF8
0	0	0	0	0	0	0	0	0
30	25.412 ±0.0016	22.932 ±0.0024	24.586 ±0.020	21.280 ±0.019	26.238 ±0.027	22.932 ±0.032	24.916 ±0.0052	21.610 ±0.0012
60	35.493 ±0.010	32.188 ±0.032	35.493 ±0.0042	28.882 ±0.002	32.518 ±0.018	30.865 ±0.0062	34.171 ±0.0072	29.213 ±0.0016
90	47.227 ±0.0017	40.616 ±0.0012	43.921 ±0.0022	34.005 ±0.014	35.658 ±0.013	35.658 ±0.0034	43.921 ±0.0051	35.658 ±0.0022
120	55.655 ±0.0017	49.375 ±0.014	54.334 ±0.0032	40.451 ±0.0022	42.103 ±0.042	42.104 ±0.032	52.019 ±0.0018	43.756 ±0.021
180	78.959 ±0.0026	61.770 ±0.022	71.687 ±0.0029	53.507 ±0.028	53.507 ±0.0013	53.507 ±0.0025	65.076 ±0.021	55.160 ±0.0026
240	85.735 ±0.014	74.165 ±0.0046	82.429 ±0.0052	64.249 ±0.0021	67.555 ±0.013	65.902 ±0.0038	69.208 ±0.0076	65.902 ±0.0042
300	89.866 ±0.0042	79.950 ±0.0038	84.412 ±0.041	74.496 ±0.0052	77.801 ±0.0048	69.538 ±0.0082	77.80167 ±0.019	74.496 ±0.0032
360	90.031 ±0.021	85.073 ±0.0054	88.378 ±0.027	82.429 ±0.0019	84.081 ±0.0081	77.471 ±0.0032	84.08184 ±0.0644	80.776 ±0.0323
420	90.362 ±0.030	86.395 ±0.0142	89.370 ±0.0037	85.239 ±0.0065	88.544 ±0.0029	83.586 ±0.0134	86.89139 ±0.0042	85.238 ±0.0031
480	90.527 ±0.0420	88.874 ±0.0036	89.866 ±0.0027	86.065 ±0.0361	91.662 ±0.0063	85.569 ±0.0021	88.87460 ±0.0047	87.221 ±0.0052

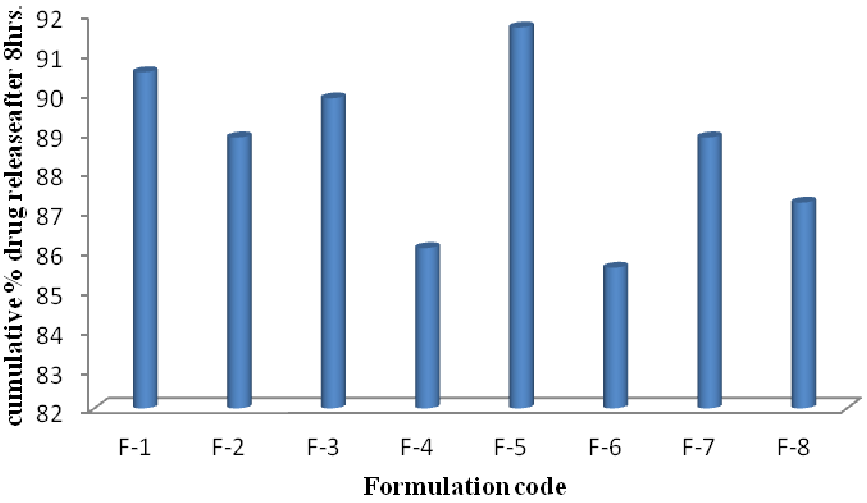

Fig. 6: Cumulative % drug released vs. Formulation code

DATA ASSESSMENT FOR OPTIMIZATION OF ORMULATIONS: EFFECT OF POLYMER ON % BUOYANCY

Positive value of β_1 (9.80) showed that the factor X_1 (quantity of EC) have positive effects on % buoyancy (Y). As the value of this factor increases, there will be increase in the % buoyancy as observed from results. Same thing was found with factor X_2 (quantity of tween-80) as positive value of β_2 showed a significant positive effect on % buoyancy. On the other hand factor X_3(quantity of drug) showed negative effect on % buoyancy as observed from the results. Value for β_o was found 72.39 for % buoyancy optimization. Mathematically, response (dependent variable) for % buoyancy can be shown by equation-

$$Y=72.39+9.80X_1+1.043X_2+1.792X_3-0.145X_1X_2-0.870X_1X_3-0.2075X_2X_3-0.09X_1X_2X_3$$

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Table 13: Value of predicted and Experimental responses (% buoyancy)

Formulation	Predicted response (%buoyancy)	Experimental response (%buoyancy)	Result of t-test
F1	58.62	64.2	Null Hypothesis = 0 a = 95% df=14 t stat = 0.05929 t critical = 1.7613 conclusion: For a given df (14), t stat value is less than the t critical value (table value) so null hypothesis was accepted that means there is no difference between predicted and experimental mean value.
F2	81.12	82.5	
F3	62.97	66.32	
F4	82.05	76.72	
F5	64.36	58.64	
F6	82.51	80.06	
F7	66.32	61.23	
F8	83.71	82.47	

KINETIC MODELLING

The correlation coefficients for the different drug release kinetic models are shown in Tables 14. Models with the highest correlation coefficient were judged to be the most appropriate model for the dissolution data14, 15.

The results of in vitro drug release studies were treated with zero order, first order kinetics, Higuchi, Hixson Crowell and Korsmeyer Peppas model.

As clearly indicated in Table 14, the formulations F2.F4, F5, F6, F7 and F8 follow a zero order release with highest r^2 value from 0.9642 to 0.9108 respectively. Only formulation F5 (r^2=0.9178) follows first order release pattern.

In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2= 0.9231 to 0.9929). To confirm the diffusion mechanism, the data were fitted into Korsmeyer Peppas model. All formulations F1 to F8 showed high linearity (R^2= 0.9669 to 0.9946), with slope (n) values ranging from 0.5013 to 0.9890. This indicates that coupling of diffusion and erosion mechanism so called anomalous diffusion. It might be concluded that the drug release is controlled by more than one mechanism i.e. diffusion coupled with erosion mechanism.

Table 14: Release model

Formulation\model and parameter	Zero order(r2)	First order(r2)	higuchi (r2)	Korsemeyer peppas (r2)/n	Hixon crowell (r2)
F1	0.7852	0.2100	0.9231	0.9941,0.5207	0.4957
F2	0.9108	0.8188	0.9742	0.9872,0.5138	0..8550
F3	0.8466	0.7609	0.9254	0.9669,0.5836	0.7938
F4	0.9560	0.8869	0.9758	0.9902,0.9668	0.9161
F5	0.9642	0.9178	0.9801	0.9736,0.5251	0.9372
F6	0.9646	0.8927	0.9929	0.9933,0.5013	0.9223
F7	0.9202	0.82130	0.9686	0.9891,0.5623	0.8594
F8	0.9553	0.8731	0.9602	0.9946,0.9890	0.9067

Table 15: Release mechanism with variation of n*values

'n'	Mechanism
<0.5	Fickian diffusion
0.5 < n < 1	Non Fickian diffusion or anomalous release
>1	Case II Transport

*The diffusional exponent is based on Korsmeyer Peppas equation, $Mt/M\infty = Kt^n$

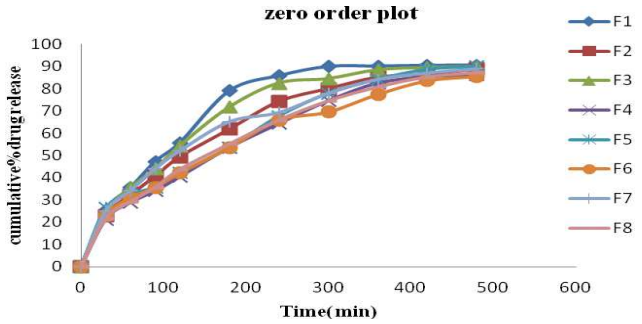

Fig.7: Cumulative % drug release vs. Time

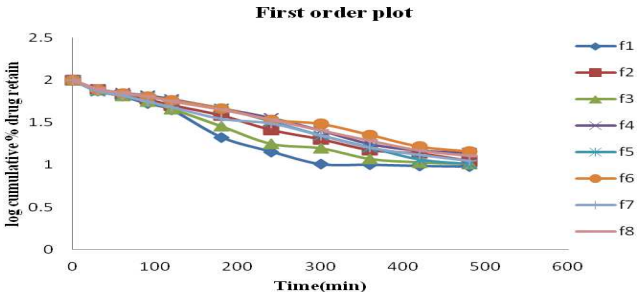

Fig. 8: Log cumulative % drug retain vs. Time

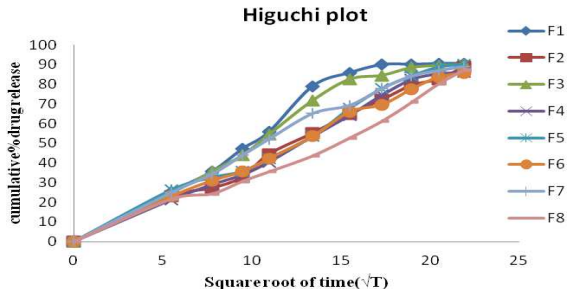

Fig. 9: Cumulative % drug release vs. √T

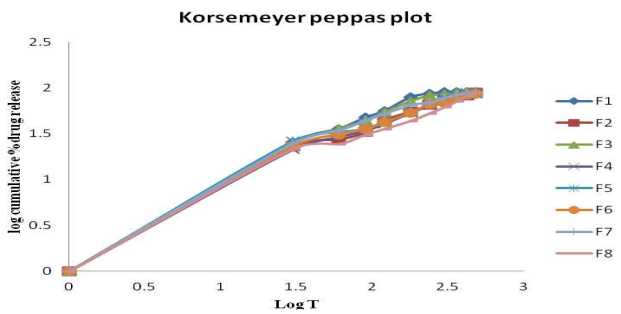

Fig. 10: Log cumulative % drug retain vs.log Time

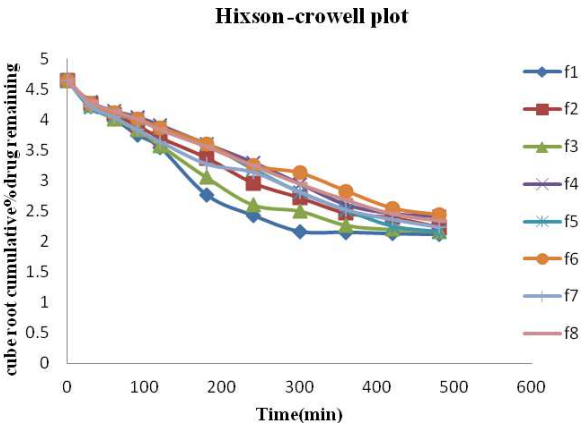

Fig. 11: Cube root cumulative % drug remaining vs. Time

STABILITY STUDIES OF OPTIMIZED FORMULATION

The optimized formulation **(F 8)** was subjected to stability studies at a room temperature / 60 % RH and 40^{0}C / 75% RH for one month. The optimized formulation was evaluated for their appearance, drug content, % buoyancy after 12 hrs and in-vitro release study. Negligible change was seen in different physicochemical parameters at a room temperature as well as 40^{0}C/75 % RH. .(see table 16 & 17) There was no significance difference in in-vitro release after one month stability study at both room temperature and accelerated conditions which was further confirmed by similarity factor (f2) calculation(Table 18 & 19).

Table 16: Physical characteristics of levofloxacin hemihydrate Tablet of Formulation F8 kept at room temperature for 30 days

Physical parameters	Formulation code F8		
	0 days	15 days	30 days
%buoyancy after 12hrs.	82.47 ± 1.44	82.29 ± 1.13	82..24 ± 1.49
Percentage drug content	89.06 ± 0.51	88.93 ± 0.62	88.99 ± 0.52
% cumulative drug release	87.221 ± 0.0052	88.07 ± 0.0305	86.792 ± 0.0132

n=3, ± SD

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Table 17: Physical characteristics of levofloxacin hemihydrate Tablet of Formulation F8 kept at 40^{0}C/75 % RH for 30 days

Physical parameters	Formulation code F8		
	0 days	15 days	30 days
%buoyancy after 12hrs.	82.47 ± 1.44	81.89 ± 0.03	82..16 ± 1.18
Percentage drug content	89.06 ±0.51	89.98 ± 0.042	90.06 ± 0.02
% cumulative drug release	87.221± 0.0052	88.97 ± 0.033	87.86 ± 0.092

n=3, ± SD

Table 18: *In-vitro* release data of floating microspheres of levofloxacin hemihydrate of batch F8 in 0.1N HCL kept at Room temperature/ 60 % RH for 30 days

S. No.	Initial % drug release (F8)	%drug release after (30days) (F8)	Result of similarity factor (f2)
1	21.6	23.01	f_2= 51.7831 **conclusion:** The f_2 value is within the range (i.e. 50-100), so no significant difference between the released pattern of floating microspheres before and after the stability studies.
2	29.2	27.678	
3	35.7	33.821	
4	43.8	45.387	
5	55.2	54.13	
6	65.9	66.19	
7	74.5	73.214	
8	80.8	81.538	

Table 19: *In-vitro* release data of floating microspheres of levofloxacin hemihydrate of batch F8 in 0.1N HCL kept at 40^{0}C/ 75 % RH for 30 days

S. No.	Initial % drug release (F8) (Reference)	%drug release after (30days) (F8) (Test)	Result of similarity factor (f_2)
1	21.6	20.09	f_2= 51.7918 **conclusion:** The f_2 value is within the range (i.e. 50-100), so no significant difference between the released pattern of floating microspheres before and after the stability studies.
2	29.2	28.17	
3	35.7	33.921	
4	43.8	44.237	
5	55.2	53.392	
6	65.9	64.62	
7	74.5	73.814	
8	80.8	81.768	

Results and Discussion

All formulations were subjected to evaluation parameter studies like % buoyancy, entrapment efficiency, % yield and drug release profile and following results were found: The % buoyancy of all the formulation (F1-F8) was found to be in the range of 58.64-82.5. The formulation F2 and F8 were found to have best % buoyancy i.e. 82.5 and 82.47 respectively. The drug entrapment effiency of all the formulation (F1-F8) were found to be in the range of 74.86-89.06. The formulation F6 and F8 were found to have best drug entrapment effiency i.e. 82.53 % and 89.06 % respectively. The % yields of all the formulation (F1-F8) were found to be in the range of 50.571-59.76. The formulation F7 and F8 were found to have best % yield i.e. 59.546 and 59.76 respectively. The drug release profiles of all the formulation (F1-F8) were found to be in the range of 85.569±0.0021 - 91.662±0.0361. The formulation F4 and F8 were found to have best % drug released profile i.e. 86.06505±0.0361 and 87.22193±0.0052 respectively. From the above results i.e. % yield, % DEE, % buoyancy and % drug released, the formulation F8 was consider as an optimized formulation.

Conclusion

Multiunit floating drug delivery system (microspheres) for levofloxacin hemihydrate was prepared by emulsion solvent evaporation method with the help of hydroxypropyl methyl cellulose (HPMC K4M) and release-retarding hydrophobic polymer ethyl cellulose (14 cps). Prepared formulation showed the acceptable % yield, % DEE, % buoyancy and % drug released.

As the ratio of ethyl cellulose increase, the % DEE, % buoyancy increase and % drug released was decreased. Optimized formulation followed the Higuchi kinetics while the drug release mechanism was found to be anomalous types

(case II transport) or non- Fickian type, controlled by diffusion through the swollen matrix. In vitro drug release studies showed a biphasic release pattern for all formulations with an initial burst affect which may be attributed to the drug present on the surface. The *in vitro* release profiles of drug from optimized formulation could be best expressed by Higuchi's equation. To confirms the diffusion mechanism; the data was fitted into Korsmeyer Peppas model. The (n) value indicates that drug release followed the coupling of diffusion and erosion mechanism so called anomalous diffusion. Optimized formulation was found to be stable at all stability conditions.

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