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Formulation and Evaluation of Floating Microspheres of Furosemide

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ABSTRACT:
Furosemide is a potent and commonly used loop diuretic. It is absorbed largely in the stomach and upper small intestine. This narrow absorption window results in its low (average of 50%) and variable (10-100%) bioavailability from conventional dosage forms. The objective of the present study was to develop an optimized controlled release floating microspheres of furosemide capable of floating on the gastric fluid and delivering the drug over a period of 12 h. The floating microspheres were prepared by solvent evaporation method. Preliminary studies were conducted and, drug loading and EC/HPMC ratio were identified as the most important factors affecting the desired response variables: drug release rate and buoyancy. The effects of drug loading and EC/HPMC ratio were further studied and optimized. Simultaneous optimization of buoyancy and release rate was performed using central composite design and the most desirable optimal point was obtained at release rate of 27h-1/2 and buoyancy of 58.45%, with corresponding levels of 344mg furosemide and 4.84 EC/HPMC ratio. Evaluation of the optimized formulation showed high yield, good flow property, extended release and buoyancy over a period of 12 h and excellent drug entrapment efficiency. Comparison of the release profiles of the three different batches of the optimized formulation confirmed that there was no statistically significant difference (p=0.302) in their lease profiles of the formulations.

KEYWORDS: Gastro-retentive floating microsphere, furosemide, ethyl cellulose, HPMC.

I. INTRODUCTION:

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm [1]. They are made of polymeric, waxy or other a protective material, that is biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations. Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range they have colloidal properties.

Glass microspheres are primarily used as a filler and volumizer for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology. Ceramic microspheres are used primarily as grinding media. Microspheres vary widely in quality, uniformity and particle size and particle size distribution. The appropriate microsphere needs to be chosen for each unique application. Floating systems have low density with maximum buoyancy to float on the gastric material and remain in the stomach for longer duration of time, the drug is released sustain with desired rate, which results in increased gastric retention time (GRT) by minimizing fluctuation [2].

SALIENT FEATURES OFMICROSPHERES [1,3]

1. Taste and odour masking.
2. Conversion of oil and other liquids, facilitating ease of handling.
3. Protaction of the drug from the environment.
4. Delay of volatilisation.
5. Freedom from incompatibilities between drug and excipients, the buffers.
6. Improvement of flow properties.
7. Safe handling of taste masking.
8. Dispersion of water insoluble substance in aqueous media.
9. Production of sustained release, controlled release and targeted medication.

Oral route of delivery is the most preferred route of administration of drug for systemic effect. The high level of taking oral dosage form is due to ease of administration, patient compliance and easy

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in handling form of formulation [4]. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric residence time and a better control of the fluctuation in plasma drug concentration [5]. Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups [6,7].

Furosemide drug has been classified as a class IV drug as per the biopharmaceutical classification system (BCS) as a result of its low solubility and oral bioavailability; one of the major causes of its low oral bioavailability is its solubility. Furosemide is absorbed mostly in the stomach and upper small intestine due to its weak acidic nature, pKa 3.8 [8]. This narrow absorption window is responsible for its low bioavailability of about 50%, and variable and erratic absorption [9]. Other reports indicate a poorer and highly variable oral bioavailability of 37-51% [4] or 10-100% [10]. Furosemide is given to help treat fluid retention (edema) and swelling that is caused by congestive heart failure, liver disease, kidney disease, or other medical conditions. It works by acting on the kidneys to increase the flow of urine.

II. MATERIALS AND METHODS:

Furosemide was a gift sample provided by Orchid Pharma, chennai, India & Other excipients used were of IP grades, all other chemicals were of analytical grade and were provided by the college.

2.1 Method of Preparation:

Preparation of Floating microspheres of Furosimide:

Floating microspheres are prepared by using water-in-oil-in-oil (w/o/o) double emulsion solvent diffusion method using different ratios of drug & polymers. The polymers is composed of Ethyl cellulose (F1-F4), Ethyl cellulose with Hydroxyl Propyl Methyl Cellulose (F5-F8), ethyl cellulose With Polyvinyl Pyrrolidine K30 (F9-F12).

Briefly drug and polymer mixture are dissolved in the mixed solvent system consisting of Acetone and Dichloromethane in a 1:1 ratio for F1 to F8, Acetone, Ethanol and Dichloromethane in a 1:1:1 ration for F9 to F12. The initial w/o emulsion is prepared by adding 4ml of water to the drug-polymer solution while stirring using a mechanical stirrer at 500 rpm for 5 min. This w/o primary emulsion is slowly added to 200ml of light liquid paraffin, the second a oil phase containing 0.1% span 80 as a surfactant while stirring at 1000 rpm. After 2 hr, 10ml of cyclohexane is added to harden the microspheres and the stirring is continued for a further 1 hr and the hardened microspheres are collected by filtration and washed with three portions of 50ml of cyclohexane and air dried for 12 hr. All the formulations are shown in table 1.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Furosimide	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
Ethyl cellulose	500 mg	1000 mg	1500 mg	2000 mg	250 mg	750 mg	1250 mg	1500 mg	250 mg	750 mg	1250 mg	1500 mg
HPMC	-	-	-	-	250 mg	250 mg	250 mg	500 mg	-	-	-	-
PVP K30									250 mg	250 mg	250 mg	500 mg
Eudragit S100												
PVP K90												
Liquid Paraffin	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml
Total weight	**1000 mg**	**1500 mg**	**2000 mg**	**2500 mg**	**1000 mg**	**1500 mg**	**2000 mg**	**2500 mg**	**1000 mg**	**1500 mg**	**2000 mg**	**2500 mg**

Table 1: Composition of Different Furosimide Formulations

III. RESULTS AND DISCUSSION:

3.1 CHARACTERIZATION OF FLOATING MICROSPHERES:

Percentage Yield: Increasing the polymer concentration lead to subsequent increase in its hydrophobicity consequently, it will react better with non solvent phase (liquid paraffin) leading to more efficient precipitation of the polymer at the droplet interface with subsequent higher yield. Increasing polymer ratio in the formulation led to

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increase the product yield. The low percent yield in some formulations may also due to microspheres lost during successive decantation during washing process. Results are in table 2.

Particle Size Analysis: Formulation F4(1:4), F8(1:4), F12(1:4), showed relatively larger particle size and formulation F1(1:1), F5(1:1), F9(1:1) showed relatively small particle size of floating microspheres. The polymer to drug ratio appears to influence the particle size distribution of floating microspheres, as shown in table 2. When the polymer to drug ratio was increased, the proportion of larger particles was high, because the viscosity of the primary emulsion was increased with increase of polymer to drug ratio. Due to this increased viscosity, large emulsion droplets were formed and it was difficult to break them and, hence, they were precipitated as such leading to an increase in the mean particle size of floating microspheres, as shown in table 2.

Drug Entrapment Efficiency: Drug entrapment efficiency was found to be 84.10%, 88.29%, 91.58%, 95.97%, 85.98%, 88.29%, 93.45%, 95.79%, 66.35%, 77.25%, 79.43%, 93.45%, 67.28%, 68.69%, 78.50%, 86.44%, 71.02%, 78.51%, 91.56% and95.75% for formulation F1(1:1), F2(1:2), F3(1:3), F4(1:4), F5(1:1), F6(1:2), F7(1:3), F8(1:4), F9(1:1), F10(1:2), F11(1:3), F12(1:4), respectively. Among the different drug polymer ratios investigated 1:4 (F4, F8, F12, drug polymer ratio had the maximum capacity for drug entrapment. Drug entrapment efficiency was increased with increasing polymer concentration in floating microspheres, as shown in table 2.

In-vitro Percentage Buoyancy Studies: The buoyancy percentage for all batches was almost above 60% which was studied for 12hrs, in dissolution medium (simulated gastric fluid pH 1.2) containing Tween 20 (0.02% w/v) without enzymes. The average buoyancy in percentage was found to be 62.06% to 82.77%. The highest percentage was obtained with formulation F4 (1:4), F8 (1:4), F12 (1:4). In general with increase in the amount of polymer blend (Ethyl cellulose + HPMC), there was an increased in buoyancy percentage. On increasing polymer concentration simultaneously percentage buoyancy also increased. Results are shown in table 2.

Formulations	Particle size (µm)	% yield	Entrapment efficiency (%)	% buoyancy
F1	521.3	76.27	84.10	62.06
F2	435.0	65.54	88.29	65.30
F3	430.0	66.15	91.58	66.07
F4	569.0	75.16	95.79	69.62
F5	666.0	74.00	85.98	68.66
F6	865.2	68.12	88.29	71.72
F7	858.0	83.56	93.45	77.91
F8	983.0	76.84	95.79	82.77
F9	447.8	66.80	66.35	66.54
F10	566.6	78.08	77.25	67.01
F11	603.6	79.95	79.43	69.20
F12	761.3	71.52	93.45	67.85

Table 2: Characterization of Floating Microspheres

In-Vitro Release Studies:

The cumulative percentage drug release after 12 hr was found to be 80.83%,74.70%, 65.98% and 66.63% for the formulations of F1 to F4, 82.24%, 76.26%, 74.56% and 68.13% for the formulations of F5 to F8, 77.78%, 72.65%, 71.68% and 69.49% for the formulations of F9 to F12, 77.78%, 72.65%, 71.68% & 69.46. It was found that the drug release was prolonged up to 12 hrs. It was also observed that as the polymer ratio increased the drug release was decreased. Results are shown in table 3, table 4, table 5 and figures 1, figure 2 & figure 3 respectively.

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Time (Hrs)	F1	F2	F3	F4
	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD
01	25.94 ± 1.25	24.11 ± 0.54	15.79 ± 0.51	17.84 ± 0.51
02	32.12 ± 1.60	29.73 ± 0.46	20.35 ± 0.31	22.27 ± 1.03
03	38.53 ± 2.25	35.41 ± 0.60	23.50 ± 0.27	24.81 ± 0.92
04	41.84 ± 1.32	40.51 ± 0.59	26.23 ± 0.50	29.90 ± 0.47
05	47.50 ± 0.81	45.64 ± 0.53	30.85 ± 0.51	34.25 ± 1.34
06	53.42 ± 0.44	46.94 ± 1.61	35.37 ± 0.83	38.85 ± 1.02
07	57.54 ± 1.05	54.56 ± 1.30	41.86 ± 0.54	41.86 ± 0.39
08	62.45 ± 3.49	58.64 ± 2.51	44.61 ± 1.66	45.90 ± 0.66
09	70.45 ± 1.65	63.73 ± 1.75	48.89 ± 0.84	51.22 ± 1.59
10	73.99 ± 1.46	68.54 ± 1.72	54.28 ± 0.95	55.13 ± 0.59
11	78.27 ± 1.51	71.98 ± 0.66	58.25 ± 0.64	58.92 ± 0.85
12	80.83 ± 0.92	74.70 ± 0.45	65.96 ± 0.43	66.63 ± 1.24

Table 3: Invitro Drug Release Data of formulations F1, F2, F3 & F4

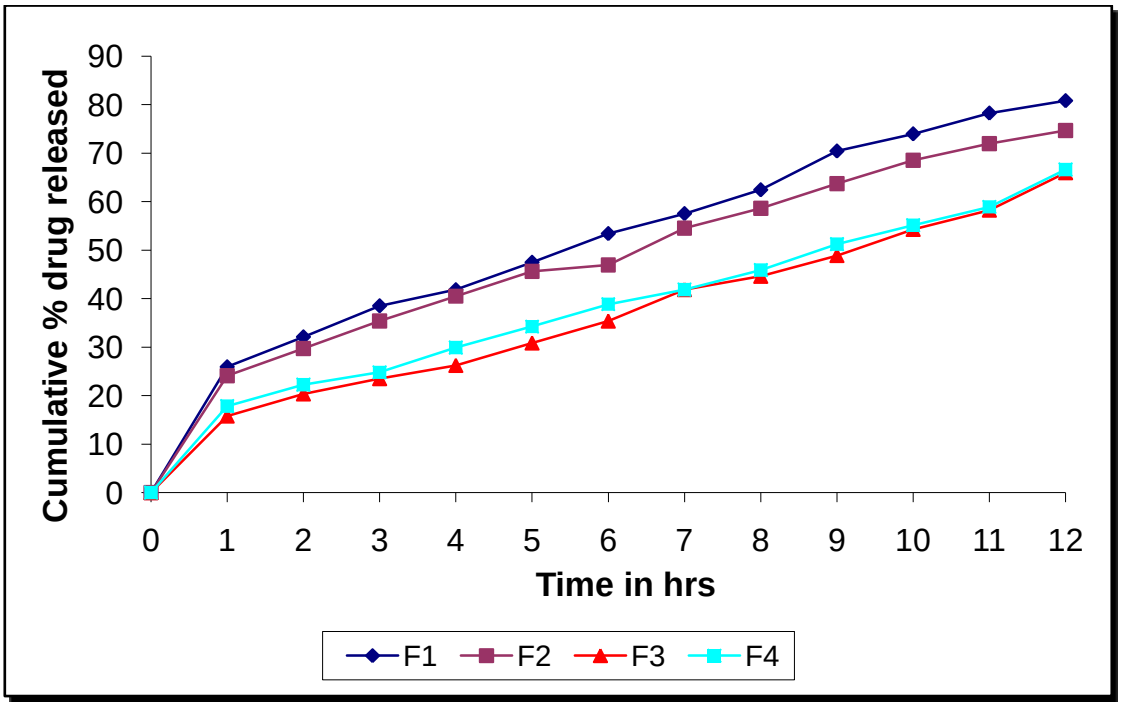

Fig 1: Invitro Drug Release curve of formulations F1, F2, F3 & F4

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Time (Hrs)	F5	F6	F7	F8
	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD
01	21.29 ± 0.58	19.29 ± 0.79	19.08 ± 0.76	18.17 ± 1.10
02	27.37 ± 2.05	22.38 ± 0.99	23.90 ± 0.52	22.49 ± 0.61
03	30.17 ± 0.59	25.77 ± 0.80	26.94 ± 1.03	25.69 ± 0.64
04	34.89 ± 0.47	28.87 ± 0.80	30.6 ± 0.55	29.59 ± 0.82
05	38.06 ± 0.98	31.52 ± 0.36	34.25 ± 1.06	33.94 ± 1.32
06	41.82 ± 1.15	35.37 ± 0.53	37.17 ± 0.81	38.04 ± 0.43
07	47.05 ± 0.60	39.14 ± 0.54	41.65 ± 0.87	41.53 ± 0.31
08	52.59 ± 1.43	42.97 ± 0.55	47.75 ± 0.40	45.42 ± 0.92
09	60.15 ± 1.13	47.21 ± 0.85	55.95 ± 1.60	49.03 ± 0.65
10	65.90 ± 0.98	53.89 ± 1.44	60.82 ± 0.63	53.54 ± 1.17
11	72.09 ± 1.40	62.11 ± 1.10	68.75 ± 1.62	59.51 ± 1.67
12	82.24 ± 0.11	76.26 ± 0.83	74.56 ± 1.40	68.13 ± 0.93

Table 4: Invitro Drug Release Data formulations F5, F6, F7 & F8

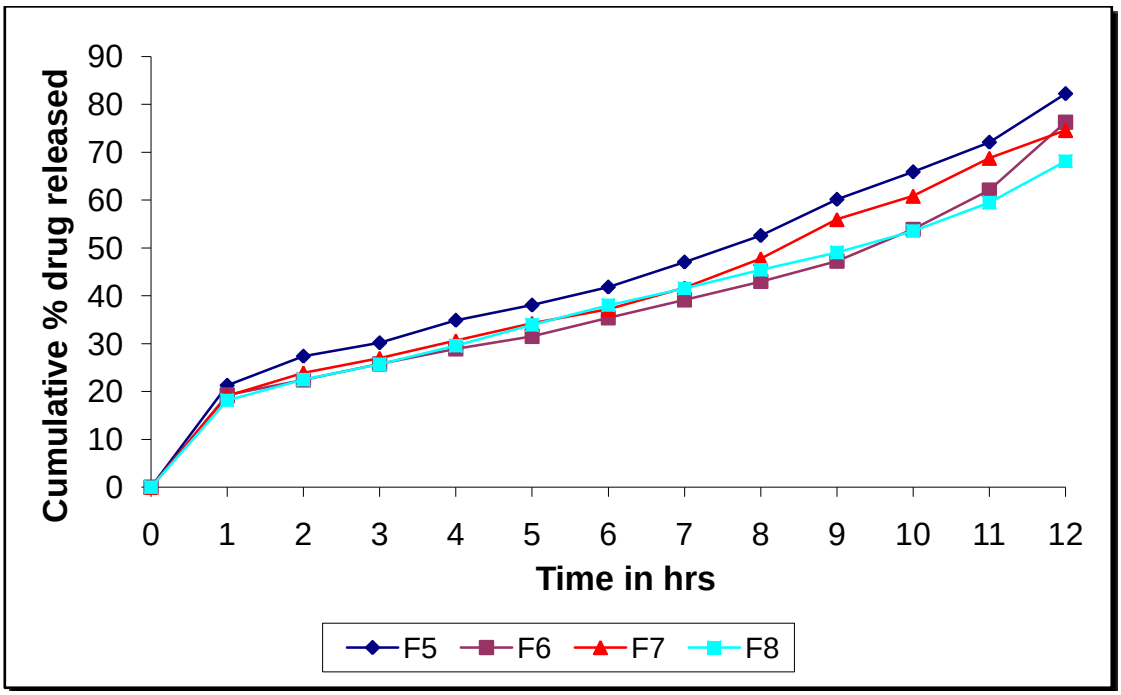

Fig 2: Invitro Drug Release curve of formulations F5, F6, F7 & F8

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Time (Hrs)	F9	F10	F11	F12
	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD	Cumulative* percent drug released ± SD
01	20.92 ± 1.02	20.73 ± 0.79	16.99 ± 4.59	17.88 ± 0.50
02	26.16 ± 1.09	25.93 ± 1.80	21.81 ± 0.54	22.15 ± 1.03
03	31.62 ± 1.38	28.33 ± 1.60	25.34 ± 0.56	25.19 ± 0.74
04	38.21 ± 1.64	32.70 ± 0.44	30.13 ± 0.87	28.58 ± 1.64
05	44.10 ± 0.70	36.77 ± 0.79	33.28 ± 0.84	32.08 ± 0.51
06	48.24 ± 0.63	40.38 ± 1.07	38.37 ± 0.58	36.48 ± 1.31
07	48.59 ± 0.48	45.28 ± 0.83	43.23 ± 0.39	39.74 ± 1.14
08	51.55 ± 1.16	49.24 ± 0.85	44.79 ± 1.76	43.93 ± 1.43
09	55.28 ± 0.40	53.61 ± 1.03	49.41 ± 0.17	48.53 ± 1.20
10	60.93 ± 0.62	58.54 ± 0.72	52.75 ± 0.41	53.90 ± 2.04
11	69.90 ± 0.71	64.13 ± 0.94	59.20 ± 0.48	62.11 ± 2.48
12	77.78 ± 1.22	72.65 ± 0.94	71.68 ± 0.62	69.46 ± 0.36

Table 5: Invitro Drug Release Data formulations F9, F10, F11 & F12

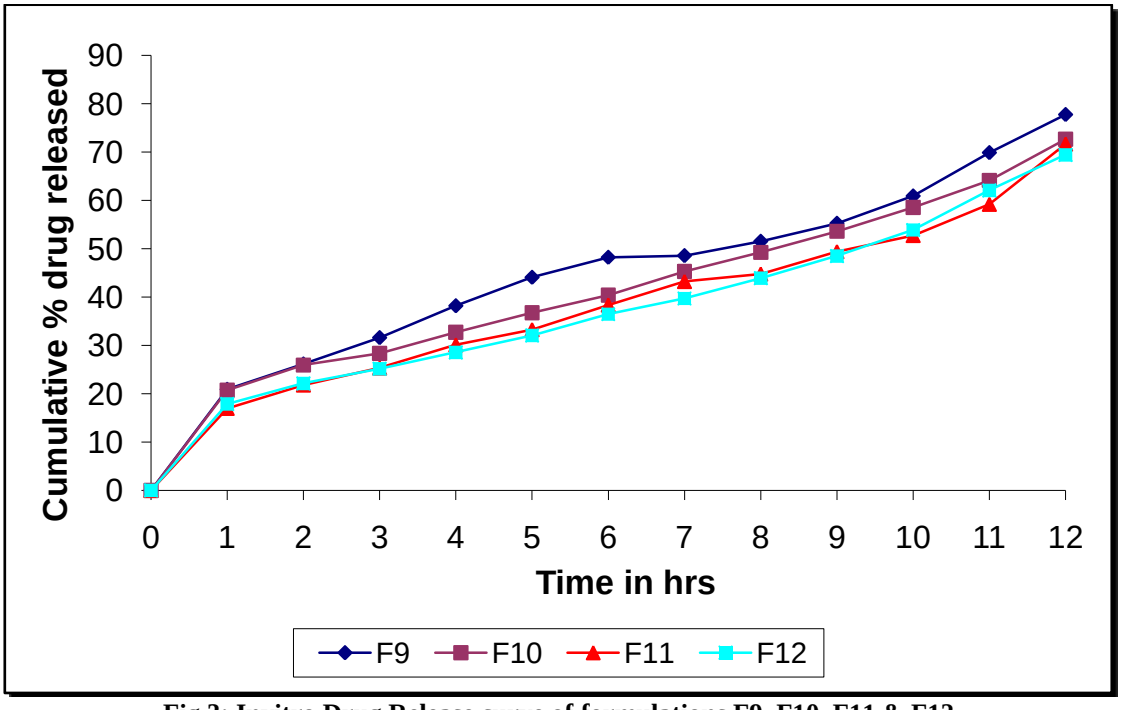

Fig 3: Invitro Drug Release curve of formulations F9, F10, F11 & F12

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IV. CONCLUSION:

- Furosemide is preferentially absorbed in the proximal tubule, gastrointestinal wall (narrow absorption window), the drug displays oral bioavailability problems in conventional dosage forms.
- The objective of the present investigation was to develop floating microspheres of Furosemide to achieve controlled release and prolongation of gastric retention time.
- Floating microspheres were prepared by double emulsification (w/o/o) solvent diffusion technique using different polymers such as Ethyl cellulose, Ethyl cellulose with HPMC, Ethyl cellulose with PVP K30, Ethyl cellulose with Eudragit S100 and Ethyl cellulose with PVP K90.
- The yield percentage of the produced microspheres is calculated for each batch by dividing the whole weight of product (M) by the total expected weight of drug and polymer (Mo).
- Particle size distribution was analyzed by sieving method.
- The Entrapment efficiency of prepared microspheres is calculated by using given formula Entrapment efficiency (%) = Experimental drug content/ Theoretical drug content x 100
- The floating microspheres are spread over the surface of the dissolution medium that is agitated by a paddle rotated at 100 rpm.
- The microspheres that floated over the surface of the medium and those settled at the bottom of the jar are recovered separately. After drying, each fraction of the microspheres is weighed and the buoyancy of the microspheres is calculated.
- The cumulative percentage drug release after 12 hr was found to 65.98% to 86.5%.It was found that the drug release was prolonged up to 12 hrs. Among all the formulations F8 (Ethyl cellulose +HPMC) had the better retardant effect (68.13% in 12 hours).
- It was also observed that, increase in the polymer ratio decreased the drug release. So, the controlled release of drug may be attributed to the slower rate of diffusion of dissolution medium into the microspheres due to increased density of the polymer matrix at higher concentration resulted in an increased diffusion path length.

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