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FORMULATION AND EVALUATION OF FLOATING MICROSPHERES FOR OEDEMA

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ABSTRACT

Oral gastroretentative dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. The purpose of present study was to formulate and develop a new gastroretentative controlled release diffusion of furosemide from the cellulose acetate floating microspheres. Furosemide is a widely used high-ceiling loop diuretic drug with low bioavailability (60-70 %) and shorter half-life (1-2 hrs). The microspheres were prepared by using o/w emulsion solvent evaporation method. The formulated floating microspheres were characterized for their micromeritic properties, surface morphology by SEM, in-vitro buoyancy studies, percentage drug entrapment efficiency and in-vitro drug release studies. Optimization studies were carried out by taking organic phase volume and drug: polymer ratio as independent variables and percentage drug entrapment efficiency and time percentage yield and size as responses using 3-level factorial design. The prepared microsphere formulations having percentage drug entrapment of 78.4%, and buoyancy of 89.42% with floating time up to 12 hours.

INTRODUCTION: Acute pulmonary edema (APO) is a life threatening emergency that requires immediate intervention with a management plan and an evidence based treatment protocol.

Presentations of acute pulmonary edema and acute heart failure to general practice require a coordinated and urgent response [1, 2].

Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours [3].

The floating or hydrodynamically controlled drug delivery systems are useful in such application.

In the present study, a gastroretentive Micro-particulate system of Furosemide, capable of floating on simulated gastric fluid for more than 12 hours was formulated by solvent evaporation technique [4]. Cellulose acetate, a biocompatible polymer was used to form microspheres of furosemide [5].

Approaches to increase the GRT include:

(i) Bioadhesive delivery system which adhere to mucosal surface [6]

(ii) Swellable drug delivery system, which increase in size after swelling and retard the passage through the pylorus [7] and;

(iii) Density controlled delivery systems, which either float or sink in gastric fluids [8]

The objective of the study is to prepare and evaluate furosemide containing floating microspheres for the treatment of pulmonary oedema associated with congestive heart failure.[9] It is a loop diuretic which inhibits water reabsorption in the nephron. Because the thick ascending limb is responsible for 25% of sodium reabsorption in the nephron [10]. Furosemide is a very potent diuretic [11].

Iannuccelli et al prepared air compartment multiple unit system for prolonged gastric residence. These units were composed of a calcium alginate core separated by an air compartment from membrane of calcium alginate. The porous structure generated by leaching of polyvinyl alcohol (PVA), which was employed as water soluble additive in coating composition, was found to increase the membrane permeability preventing the air compartment shrinkage. The ability of floatation increases with increase in PVA, molecular weight [12].

Loading the drug in floating microspheres causes less incidence of dose dumping. Hence, this increases the GRT of drug and increases its absorption through GIT.[13] This increases the bioavailability of the drug and leads to better treatment of the disease. Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping [14].

Various multiple unit floating systems have been developed in different forms and using principles such as air compartment multiple unit system; hollow microspheres prepared by emulsion solvent diffusion method [15], beads prepared by emulsion gelation method [16] and for preparing multiple unit FDDS. By this way objective is to formulate, optimize and characterize the Floating Microsphere of Furosemide and assess its performance *in-vitro* pharmacokinetically by suitable model [17].

MATERIALS AND METHODS:

Materials: Furosemide was obtained as a gift sample from Hem-Deep organics Pvt. Ltd., Ankleshwar. Cellulose Acetate was obtained as gift sample from Sulabh Chemicals, Baroda. Polyvinyl alcohol, Ethyl acetate, Acetone were purchased Sulabh Chemicals, Baroda All chemicals/reagents used were of analytical grade. A UV/Vis spectrophotometer (Shimadzu 1700 pharma spec) was used for drug analysis.

Preparation of Floating Microspheres: Floating microspheres loaded with drug was prepared using solvent diffusion evaporation method using cellulose acetate. Drug and polymer in different proportion was dissolved in 1:1 mixture of solvent system of ethyl acetate and acetone for cellulose acetate. This clear solution was poured slowly in a thin stream into the aqueous solution of 0.05% polyvinyl alcohol.

The emulsion was continuously stirred for 3 h at a speed of 500 rpm at room temprature. The floating microspheres was collected by decantation, while the non-floating microspheres was discarded. The microspheres was dried overnight at 40±2°C and stored in desiccator [18].

Process variables: Amount of Polymer: 500 mg; Stirring rate: 200, 400, 600 rpm; Temperature of the preparation:10, room temperature(RT), 50^{o}C; Volume of aqueous phase: 100, 300, 600ml.

Experimental Design: A 3 level 2 factors factorial design was employed to design Floating microspheres of Furosemide with the help of Design-Expert® 8 trial version software (Stat-Ease Inc., USA). The design was employed for cellulose acetate microspheres. The independent and dependent variables selected are as follows:

1. **Independent Variables**
   a. Drug: Polymer Ratio (X1)
   b. Organic phase volume (X2)
2. **Dependent Variables**
   a. % Yield (Y1)
   b. Particle Size (Y2)
   c. % Entrapment Efficiency (Y3)

Table 1: Experimental Design

Sr No.	Coded Value		Actual Value	
	Factor 1 Drug: Polymer (X_1)	Factor 2 Organic Phase volume (ml) (X_2)	Factor 1 Drug:Polymer (X_1)	Factor 2 Organic Phase volume (ml) (X_2)
1	-1	0	1:2	30
2	1	0	1:4	30
3	0	-1	1:3	20
4	1	1	1:4	40
5	-1	1	1:2	40
6	0	1	1:3	40
7	0	0	1:3	30
8	-1	-1	1:2	20
9	1	-1	1:4	20

Evaluation Methods:

1. **Process yield:** The prepared microspheres are to be collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres [19].

% Yield = (Actual weight of product / Total weight of excipient and drug) × 100

2. **Micromeritic properties:** The prepared microspheres were characterized by their micromeritic properties, such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose [20].

a. **Size and shape of Microspheres:** The size of microspheres was determined using microscope fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) was performed to characterize the surface of the formed microspheres. Microspheres were mounted directly onto sample stub and coated with gold film (~200 nm) under reduced pressure (0.133 Pa) [21, 22].

b. **Bulk Density:** The bulk density is defined as the mass of powder divided by bulk volume. The bulk density was calculated by dividing the weight of the samples in grams by the final volume in cm [23].

$$\text{Bulk Density} = \frac{\text{Mass of microspheres}}{\text{Bulk Volume of microspheres}}$$

c. **Tapped Density:** Tapped density is the volume of powder determined by tapping by using a measuring cylinder containing weighed amount of sample. The cylinder containing known amount of microspheres was tapped for about 1 minute on a tapped density apparatus until it gives constant volume [24].

$$\text{Tapped Density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

d. **Carr's Compressibility Index:** This is an important property in maintaining uniform weight. It is calculated using following equation,

$$\%\text{Compressibility Index} = \left(1 - \frac{\text{Tapped Density}}{\text{Bulk Density}}\right)$$

Lower the compressibility values indicate better flow [25].

e. **Hausner's ratio:** A similar index like percentage compressibility index has been defined by Hausner's. Values less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow. Added glidant normally improve flow of the material under study. Hausner's ratio can be calculated by formula,

$$\text{Hausner's ratio} = \left(\frac{\text{Tapped Density}}{\text{Bulk Density}}\right) \times 100$$

f. **Porosity:** Porosity (Ţ) was calculated using the equation:

$$Ţ = (1- Pp / Pt) \times 100$$

Where Pt and Pp are the true density and tapped density, respectively [26].

g. **Angle of Repose (θ):** Inter particle forces between particles as well as flow characteristics of powders are evaluated by angle of repose. Angle of repose is defined as the maximum angle possible between the surface and the horizontal plane. The angle of repose of each powder blend is to be determined by glass funnel method. Powders are to be weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel is so adjusted that the tip of the funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated using the following equation,

$$\tan \theta = \frac{h}{r}$$

Where, θ = angle of repose; h = height of the pile and; r = radius of the powder cone respectively.

Angle of repose affects particle size distribution, as larger the particle size, it will flow freely and vice-versa. It is a helpful parameter to monitor quality of powdered or granular pharmaceutical formulations. For good flowing materials then, angle of repose should be less than 30° [27].

3. **Drug content:** The drug content of Cellulose Acetate microspheres was determined by dispersing 50 mg formulation (accurately weighed) in 10 mL acetone, followed by agitation with a magnetic stirrer for 12 h to dissolve the polymer and to extract the drug. After filtration through a whatman filter, the drug concentration in the ethanol phase was determined spectrophoto-metrically at 271 nm (Schimadzu 1700, UV-spectrophotometer) by making desired dilution with 0.1N HCl. Cellulose acetate do not interfere under these conditions [28]. Each determination was made in triplicate. The percentage drug entrapment and yield are to be calculated as follows:

$$\% \text{ Drug loading} = \frac{\text{Actual drug content}}{\text{Weight of microspheres}} \text{ X } 100$$

$$\% \text{ Incorporation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

4. **Floating behavior:** Fifty milligrams of the floating microparticles were placed in 0.1 N HCl (100 mL) containing 0.02% w/v Tween 80. The mixture was stirred at 100 rpm in a magnetic stirrer. After 10 h, the layer of buoyant microparticles was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles [29].

$$\% \text{ Buoyancy} = \frac{W_f}{(W_f + W_s)} \times 100$$

Where, W_f and W_s are the weight of the floating and settled microspheres respectively.

5. ***In-vitro* Release:** The drug release study was carried out using USP rotating basket apparatus at 37 ± 0.5 ºC and at 100 rpm using 900 ml of simulated gastric fluid pH 1.2 containing 0.02 % Tween 20 as a dissolution medium. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through filter paper, diluted suitably and analyzed spectrophotometrically with UV-VIS Spectrophoto-meter at a wavelength of 271 nm. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample [30].

6. ***In vitro* Buoyancy:** Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 mL of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass

of the microspheres that remained floating and the total mass of the microspheres [31].

7. **Morphology:** The morphology of microsphere were studied by scanning electron microscopy (SEM) (Philips 505, Holland) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with platinum film. To investigate the internal morphology, the micrspheres were dissected with a blade [32].

8. **Data Analysis of Release Studies:** Four kinetic models including the zero order (Equation 1), first order (Equation 2), Higuchi matrix (Equation 3), and Peppas-Korsmeyer (Equation 4) release equations were applied to process the in vitro release data to find the equation with the best fit.

$R = k_1 t$ .....(1)

$\log UR = k_2 t/2.303$ .....(2)

$R = k_3 t_{0.5}$ .....(3)

$R = k_4 tn$ or $\log R = \log k_4 + n \log t$ .....(4)

Where *R* and *UR* are the released and unreleased percentages, respectively, at time (*t*); k_1, k_2, k_3, and k_4 are the rate constants of zero-order, first-order, Higuchi matrix and Peppas-Korsmeyer, respectively.[33]

9. **Stability:** The optimized formulation was stored in screw capped glass vials in stability chamber at accelerated stability condition $40^0C \pm 2^0C$ with 75%RH±5% for 3 months. Samples were analyzed for physical appearance, residual drug content after a period of 0, 1, 2 and 3 months. Initial drug content was taken as 100 % for each formulation. The log % residual drug content vs. time graph was also plotted for the optimized formulation in order to evaluate half-life and shelf life of formulations [34].

RESULTS AND DISCUSSION:

Effect of Temperature on Morphology: With increasing temperature, average size of microspheres was found to increase significantly. At 10^0C particles of irregular shape, with surface so rough as to crumble upon touching, are formed, whereas higher temperatures gradually improve the sphericity of microspheres. Surfaces of microspheres prepared at 50^oC were less rough than those of microspheres prepared at 10^0C or RT but some of them were broken. So, in subsequent experiments temperature of aqueous solution was kept at RT.

Effect of Stirring Rate: At higher speed, irregular microspheres were obtained probably because of increased incidence of collision of the dispersed phase and subsequent rupturing of microsphere. At lower speed sticking of the microsphere was noticed. The optimum rotation speed was 300rpm with respect to morphology and yield of microspheres.

Effect of volume of Processing Medium: Spherical microsphere was obtained at 100 ml volume of PVA. At smaller volume of PVA, particle size of the microspheres becomes smaller because at smaller volume of emulsifier, droplet size of the emulsion decrease and thereby particle size of the microspheres also decreases. Low volume of aqueous phase consumes less time and low volume of organic phase.

Effect of Organic solvent ratio: When acetone alone was used for preparation of cellulose acetate microspheres, fiber like aggregates was formed around the stirrer. This was because of fast diffusion of the acetone in the water before formation of the droplets. To control the diffusion rate of Acetone, ethyl acetate was added to the polymer solution. When acetone was totally replaced with Ethyl acetate microspheres were obtained with good sphericity and narrow size distribution but it took more time (3-4 hrs) for evaporation of the solvent. So co- solvents of the acetone and ethyl acetate in also affected the morphology of microspheres and best results with spherical shape were obtained when the ratio of Acetone and Ethyl acetate was 1:1. So this ratio was taken for further study.

TABLE 2: EXPERIMENTAL DESIGN

Sr No.	Batch Code	Factor 1 Drug: Polymer (X1)	Factor 2 Organic Phase volume (ml) (X2)	%Yield (Y1)	Size (Y2) µm	% entrapment efficiency (Y3)
1	F1	-1	-1	86.9	401	51.3
2	F2	-1	0	85	398	49.45
3	F3	-1	1	87.1	402	52.1
4	F4	0	-1	88.9	368	78.4
5	**F5**	**0**	**0**	**87.3**	**364**	**82.3**
6	F6	0	1	88.6	367	78.4
7	F7	1	-1	88.1	380	76.9
8	F8	1	0	86.3	379	75.9
9	F9	1	1	87.7	381	77.9

%Yield:

$Y1= 87.14+0.52X1-0.083X2-0.15X1X2-1.42X1^2 + 1.68X2^2$ …….(1)

Particle Size:

$Y2= 364.44-10.17X1+0.17X2+0.000X1X2+23.83X1^2+ 2.83X2^2$ …….(2)

%Encapsulation Efficiency:

$Y3= 79.33+12.98X1+0.30X2+0.050X1X2-15.78X1^2- 0.050X22$ …….(3)

Production Yield: Response surface plot (**Figure 1**) indicates the positive effect of drug-to-polymer ratio on the percent yield. With increase in the drug-to-polymer ratio, the percent yield also increases. This effect is also supported by Motlekar *et al.*, who reported that the increase in the percent yield may be due to the increased throughput of the polymer slurry and rapid evaporation of the solvent.

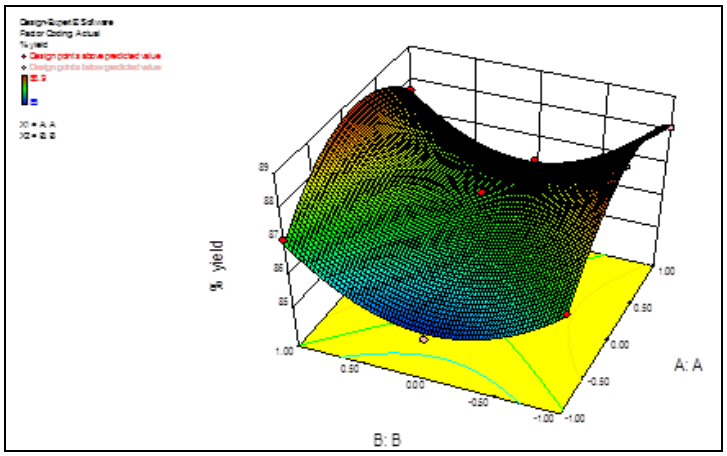

FIGURE 1: 3 D GRAPH OF PRODUCTION YIELD OF FLOATING MICROSPHERE

Entrapment Efficiency and Drug Loading: Response surface plot (**Figure 2**) indicates the positive effect of drug-to-polymer ratio on the Entrapment efficiency. Increase in the drug loading is due to increase in drug: polymer ratio, which in turn increases the efficiency during addition of the polymeric dispersion.

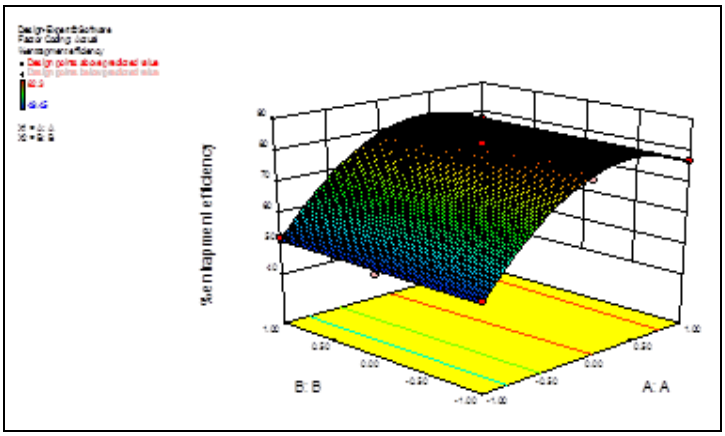

FIGURE 2: 3D GRAPH OF ENTRAPMENT EFFICIENCY AND DRUG LOADING OF FLOATING MICROSPHERE

Particle Size Analysis: Response surface plot also (**Figure 3**) indicates the negative effect of drug-to-polymer ratio on the percent yield. As the concentration of polymer increased the viscosity of the polymer solution increased resulting in the formation of larger polymer/solvent droplets. This results in larger particles.

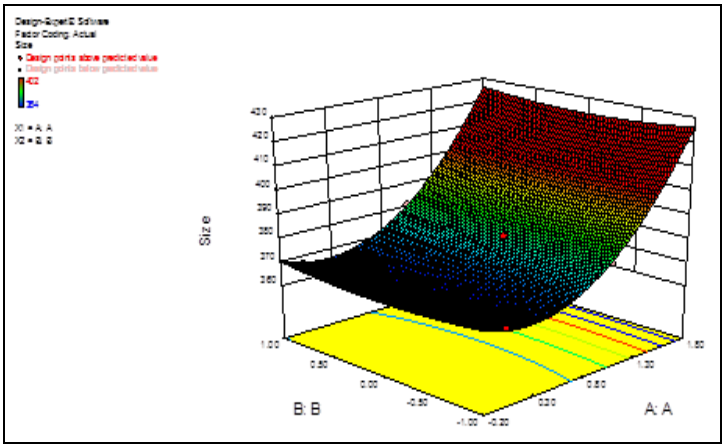

FIGURE 3: 3D GRAPH OF PARTICLE SIZE ANALYSIS OF FLOATING MICROSPHERE

Selection of Optimized Batch: The results of experimental design indicate that the quadratic model was significant for all response parameters investigated. The multiple linear regression analysis revealed that both the formulation variables analyzed had a significant influence on all response parameters. The results obtained indicate that optimum amounts of cellulose acetate and organic phase are essential to produce microspheres with desirable encapsulation and release characteristics. The factorial data suggests that an optimum ratio of drug to cellulose acetate and high level of organic phase (F5) play a significant role to produce microspheres were able to control release of the drug for a period of 12 h.

TABLE 3: RESULTS OF MICROMERITIC PROPERTIES OF OPTIMIZED FORMULATION OF FUROSEMIDE MICROSPHERES (F5)

Sr. no.	Micromeritic property	Value
1	Bulk Density	0.462
2	Tapped density	0.493
3	Carr's compressibility index	6.24
4	Hausner's ratio	1.06
5	Porosity	72%
6	Angle of response	25.34°
7	Size	368µm
8	%Yield	88.9%
9	% Entrapment Efficiency	78.4%
10	% Buoyancy	89.42%

***In vitro* Drug Release Studies:** As per the study of *in-vitro* release data of all the formulations, the comparative release studies of microspheres are graphically shown in **Figures 4, 5 and 6**. To obtain the values of the release constant and to understand the release mechanism the in vitro release data was fitted to various mathematical models as follows:

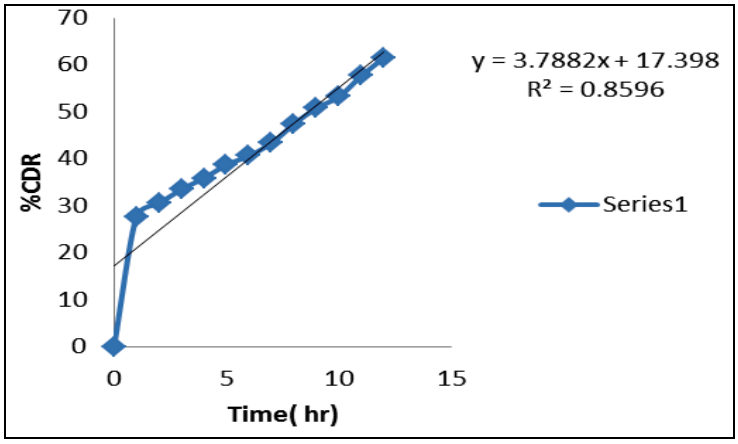

FIGURE 4: ZERO ORDER RATE KINETIC

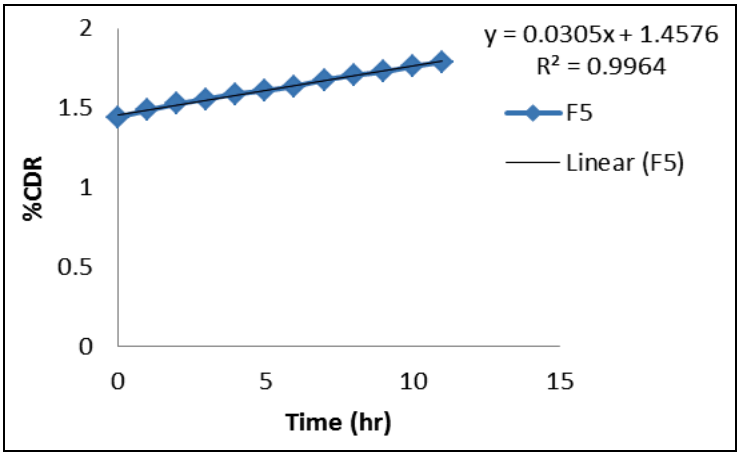

FIGURE 5: FIRST ORDER RATE KINETICS

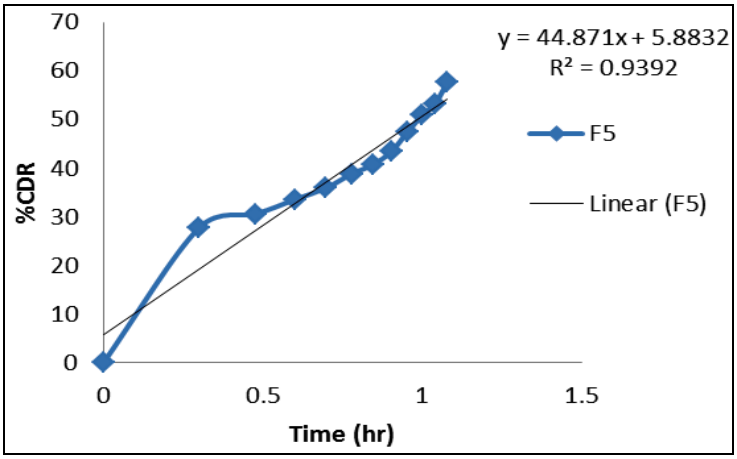

FIGURE 6: HIGUCHI MATRIX

TABLE 4: *IN-VITRO* CURVE FITS FOR VARIOUS RELEASE SYSTEMS FOR OPTIMIZED FUROSEMIDE-CELLULOSE ACETATE MICRO-SPHERES FORMULATION (F5)

Equation	Regression coefficient (r)	K value
Zero order	0.9725	2.9401
1st order	0.6375	0.0936
Matrix	0.9216	28.088
Peppas	0.7065	0.9665
Hixon Crowell	0.7932	0.0493

The correlation coefficients for the different drug release kinetic models are shown in **Table 4**. Models with the highest correlation coefficient were judged to be the most appropriate model for the in vitro release study.

Morphology:

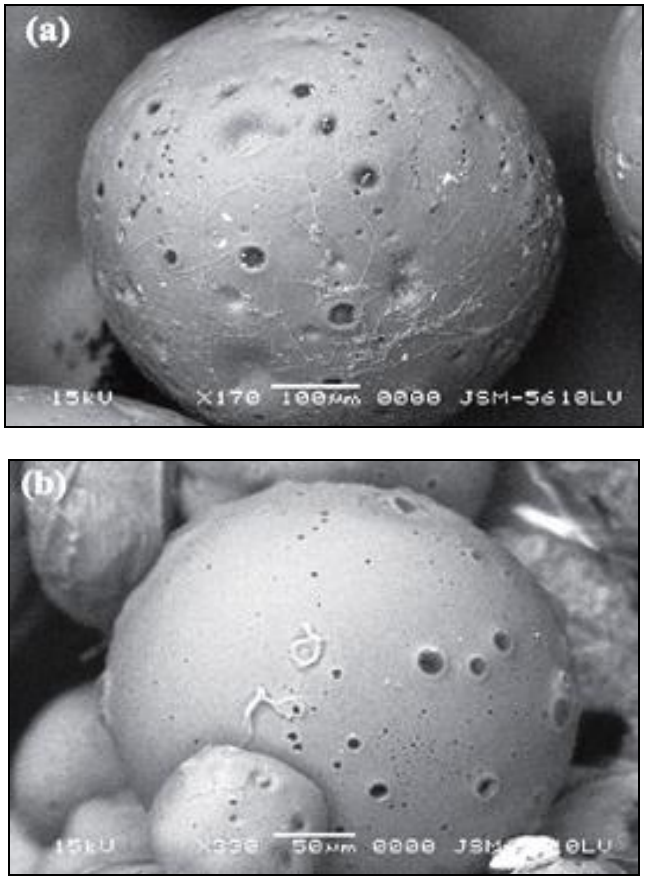

FIGURE 7: (A) MORPHOLOGY OF FLOTING MICROSPHERE OF FUROSEMIDE; (B) CROSS SECTIONAL VIEW OF FLOATING MICROSPHERE OF FUROSEMIDE

Stability Studies: Stability studies of the optimized formulation were carried out for accelerated stability testing at 40°C ±2°C with 75% RH ± 5% for a period of 3 months. The selected optimized formulations were packed in high density polyethylene containers, which were tightly plugged with cotton and capped. They were then stored for 6 months and evaluated for their physical appearance, % drug entrapment and t90% at specified intervals of time and the shelf life of the optimized microsphere formulation was predicted.

TABLE 5: STABILITY STUDIES DATA OF OPTIMIZED MICROSPHERES FORMULATION F5 FOR ACCELERATED STABILITY CONDITION (40°C±2°C WITH 75%RH±5%)

Months	% drug entrapment efficiency
0	100
1	99.79
2	99.47
3	99.32

The log % residual drug content vs. time graph was also plotted for the optimized formulation.

CONCLUSIONS: The present investigation involves the study of the process variables that affect morphology, yield and floating of the microspheres. Process variables studied are method of introducing polymer solution, Effect of volume of processing medium (Batches Vc1 to Vc3), Effect of Stirring Rate (Batches Sc1 to Sc3), Effect of organic phase volume (Batches T1 to T6), Effect of Temperature on Morphology (Batches Tc1 to Tc3). Cellulose acetate floating microspheres were characterized for mean particle size, percentage buoyancy, entrapment efficiency, drug release and production yield.

Entrapment efficiency and drug release of optimized batch F5 were found to be 82.3% and 63.042% respectively.

Mean particle size and production yield were found to be 364µm and 87.3% respectively. Percentage buoyancy was found to be 89.42%.

The optimization of floating and drug release behavior of Cellulose acetate Floating microspheres was done by applying Design Expert.

From kinetic modeling of the dissolution profile of the optimized formulation, it can be concluded that there is controlled release diffusion of furosemide from the cellulose acetate floating microspheres.

Stability studies of the optimized formulation were carry out for accelerated stability testing at 40°C ±2°C with 75% RH ± 5% for a period of 3 months and show that there was no major effect of temperature and relative humidity on % drug entrapment efficiency.

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