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DESIGN, DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERES OF FUROSEMIDE BY MIXED SOLVENCY CONCEPT

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ABSTRACT
Furosemide, a potent loop diuretic, is used in the treatment of edema of hepatic, cardiac, pulmonary and renal failures and in chronic hypertension. The dose related adverse effects have been observed and the treatment with conventional tablets produced short period of maximum diuresis, which is inconvenient to the patients. The objective of present work is to develop a controlled release multiparticulate dosage form of the drug by the use of solvent evaporation technique and to explore the concept of mixed solvency. The aim is to enhance the solubility of furosemide in ethyl acetate and to make ethyl acetate a strong solvent for emulsification solvent evaporation process by the use of solubilizers and limit the use of toxic organic solvents since ethyl acetate is safer (class 3 solvent) than those generally employed for microsphere production i.e. methylene chloride (class 2 solvent). The aim to explore possibility of using ethyl acetate: petroleum ether as a combination of solvents to prepare hollow floating microspheres replacing dichloromethane: ethanol combination which is reported to produce hollow microspheres.

KEYWORDS- *Furosemide, renal failures, chronic hypertension, Floating microspheres, Mixed Solvency.*

INTRODUCTION

It has long been recognized that before an orally administered drug becomes available for absorption at specific sites within the GI tract, it must be dissolved in the GI fluid. Since both the dissolution rate and the maximum amount of a drug that can be dissolved are dictated by the solubility of the drug in the medium, aqueous solubility of a drug could be regarded as a key factor responsible for low oral bioa- vailability of poorly water-soluble drugs, thereby limiting their therapeutic potential. To achieve and maintain the drug concentration in the body within the therapeutic range required for a medication, it is often necessary to take conventional drug delivery system several times a day. This yields an undesirable 'seesaw' drug level in the body. A number of advancements have been made recently in the development of new techniques for drug delivery. These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drug to a specific tissue.

FLOATING DRUG DELIVERY- Floating drug delivery systems are classified depending on the use of two formulation variables: effervescent and non-effervescent systems.

1. Effervescent Floating Dosage Forms-

a. **Volatile liquid containing systems:** - The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contains a liquid e.g. ether, cyclopentane that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b. **Gas-generating Systems:** - The effervescent reactions between carbonate/ bicarbonate salts and citric/tartaric acid liberates CO_2 in this delivery system, which gets entrapped in the gelled hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float. These systems contain matrices prepared with swellable polymers like methocel, polysaccharides like chitosan. Other reported approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills etc.

2. Non-effervescent Floating Dosage Forms-

a. **Colloidal gel barrier system:**- These types of systems contain drug with gel forming hydrocolloids which allow them to remain buoyant on the stomach content. This system incorporates a high level of one or more gel- forming highly soluble cellulose

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type hydrocolloid as HPC, HEC, HPMC, polysaccharides and matrix-forming polymers such as polycarbophil, polyacrylate and polystyrene.

b. **Microporous compartment system: -** In this technology a drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed. This sealing prevents any direct contact of gastric surface with the undissolved drug. The floatation chamber containing entrapped air allows the delivery system to float over the gastric content, in the stomach. Gastric fluid enters through an aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

c. **Alginate beads:** - To develop multi-unit floating dosage forms, the freeze- dried calcium alginate has been used. Spherical beads can be prepared by the precipitation of calcium alginate by dropping sodium alginate solution into aqueous solution of calcium chloride.

d. **Hollow microspheres /Microballons:** - A novel emulsion solvent diffusion method has been used to prepare hollow microspheres loaded with drug in their outer polymer shelf. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer are poured into an agitated solution of poly vinyl alcohol (PVA). The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of microsphere of the polymer and drug.

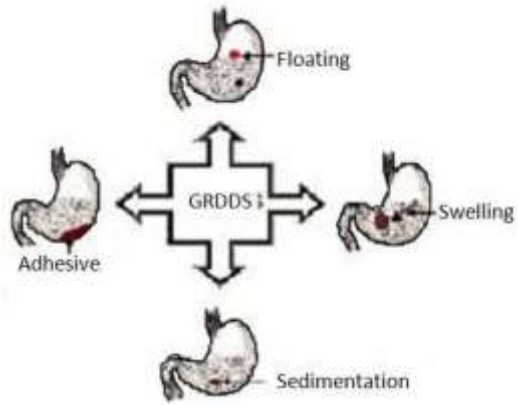

Fig 1. Techniques of GRDDS

Material and methods

Furosemide is benzoic-sulphonamide-furan. It is a diuretic with fast onset and short duration that is used for edema, hypertension and chronic renal insufficiency.

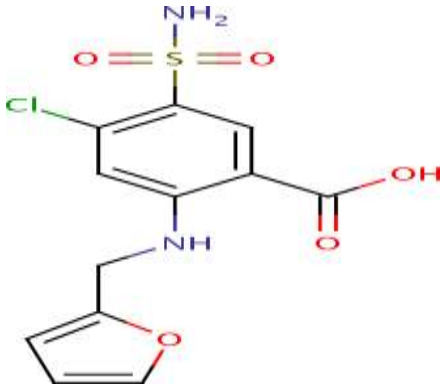

Fig 2: Chemical structure of furosemide

IUPAC name: 4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid.

3. Characterization of drug

1. MELTING POINT- The melting point of drug was determined by open capillary method. The capillary filled with drug powder was placed in Thiel's tube containing liquid paraffin. The tube was heated and the melting point of the drug powder was noted. The melting point range of furosemide drug sample was found to be 206-208°C.

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2. INFRARED STUDY OF FUROSEMIDE

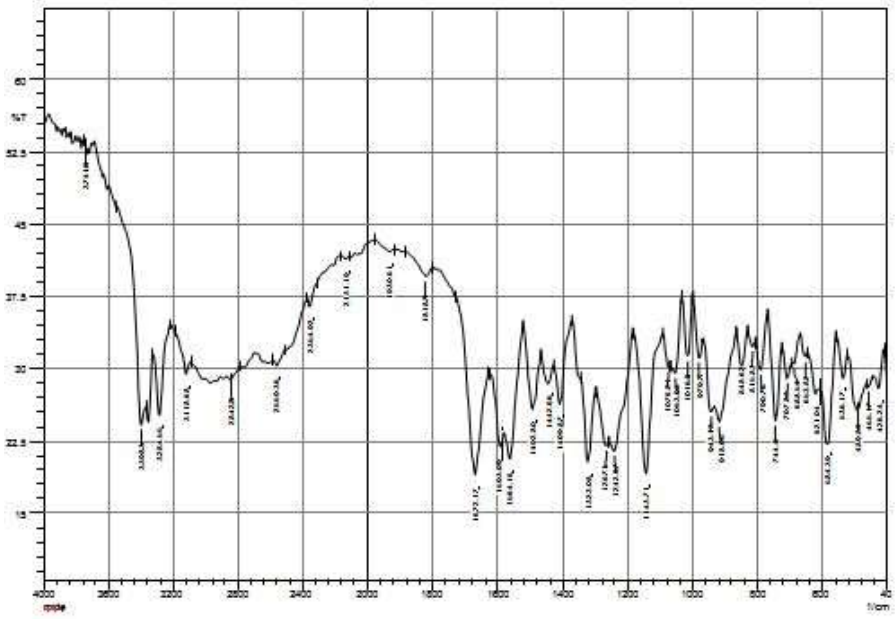

Fig 3: FTIR spectrum of furosemide

Interpretation of FTIR spectra*:* The principal peaks of furosemide were obtained at wave numbers: 3398.34 cm^{-1} (3500-3200 cm^{-1}) corresponds to NH_2 stretching vibration of Ar-$NHCH_2$, 3284.55 cm^{-1} (3500-3200 cm^{-1}) corresponds to stretching vibration of SO_2NH_2, 1672.17 cm^{-1} (1700-1500 cm^{-1}) corresponds to bending vibration of amino group, 1564.16 cm^{-1} (1700-1500 cm^{-1}) corresponds to asymmetric stretching vibration of carboxyl group, 1323.08 cm^{-1} corresponds to asymmetric stretching vibration of sulfonyl group.

3. UV SPECTRA OF FUROSEMIDE IN DEMINERALIZED WATER-

Twenty five mg of furosemide was weighed accurately and dissolved in 20 ml of methanol and volume was made upto 25 ml with methanol to prepare stock solution of 1000 µg/ml. This stock solution was suitably diluted with demineralized water to give solution of 20 µg/ml. The prepared solution was scanned and the UV spectra so obtained is shown in fig.

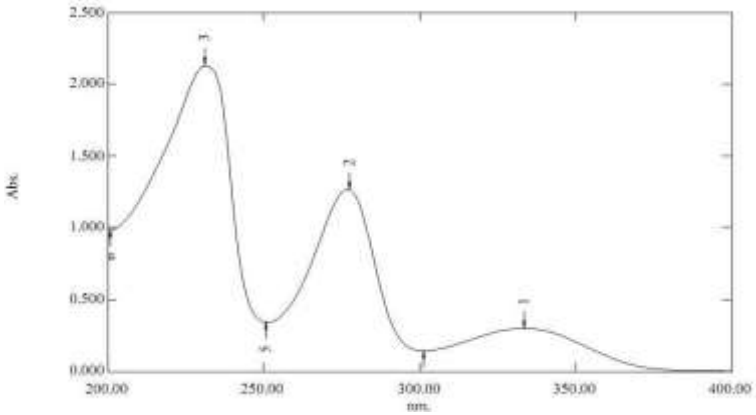

Fig 4: UV spectrum of furosemide in demineralized water

Calibration Curve of Furosemide In Demineralized Water- Twenty five mg of furosemide was weighed accurately and dissolved in about 20 ml of methanol and volume was made upto 25 ml with methanol to prepare stock solution of 1000 µg/ml. Appropriate dilutions were made with D.M. water so as to obtain a series of solutions in the concentration range of 10–80 µg/ml. The absorbances of these dilutions were measured on a double beam UV/Visible spectrophotometer (Shimadzu® 160A) at 333.3 nm against

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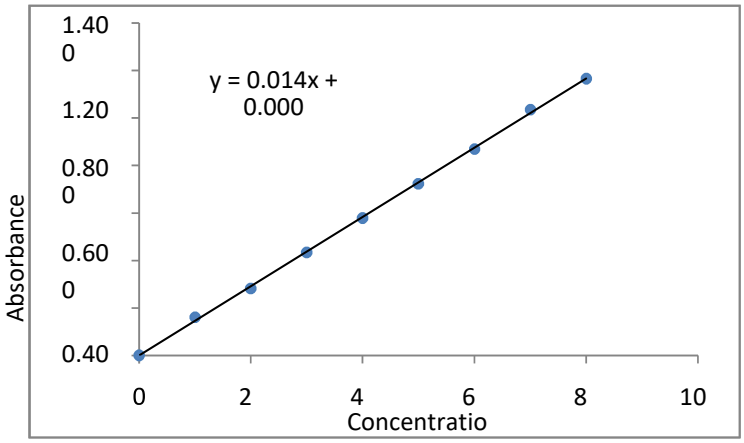
respective reagent blanks. The absorbance data obtained for various concentrations was subjected to linear regression analysis. The observations are recorded in the table1: Absorbance data for calibration curve of furosemide in D. M. water

S.No	Concentration (µg/ml)	Absorbance (at 333.3 nm)
1	0	0.000
2	10	0.162
3	20	0.283
4	30	0.435
5	40	0.578
6	50	0.724
7	60	0.870
8	70	1.036
9	80	1.165



DRUG-EXCIPIENT INTERACTION STUDY- This study was performed to determine any physical change in the drug when kept in contact with polymer under different storage condition for one month. Drug and polymer were mixed in 1:1 ratio and divided into three parts. These parts were sealed in vials and kept under different conditions. Two vials of each sample were kept at room temperature, in the oven at 40ºC and in refrigerator for one month period. After every fifteen days for one month, the vials were withdrawn and any change in physical appearance and color of the contents was observed. The observations are recorded in table

Table 6.7: Physical interaction studies of drug with excipients

S.No	Drug+Excipient	Initial observation	Final observation after one month		
			Room temperature	Refrigerator (2-8°C)	40°C
1	Furosemide + Eudragit RSPO	White powder	NC	NC	NC

PREPARATION OF MICROSPHERES- Emulsification solvent evaporation method was employed for preparation of microspheres of furosemide. Weighed amount of polymer Eudragit RSPO was dissolved in ethyl acetate. Drug was added to it and mixed with help of vortex, and resultant dispersion of drug was dissolved completely by addition of fixed amount of PEG 200 to it. To it, petroleum ether was added and again shaken with the help of vortex. The internal phase was then added in a stream, at once to external phase in a 250 ml long beaker containing demineralized water with PVA as stabilizer, while stirring using a mechanical lab stirrer (Remi, Mumbai). Stirring was continued for 2 h at room temperature until no detectable smell of ethyl acetate remained and microspheres were formed. Demineralized water was added to it to dilute the contents and the formed microspheres were filtered through Whatman grade 5 filter paper under vacuum using Buchner funnel. The residue was washed 3 times with 30 ml portions of demineralized water. The

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product was first kept at room temperature for 24 hours and then subjected to drying in oven at 65ºC to evaporate petroleum ether completely. The pores are formed inside microspheres due to removal of petroleum ether.

OPTIMIZATION OF EXTERNAL PHASE VOLUME-Because of high solubility of ethyl acetate in water, when internal phase was emulsified in demineralized water, polymer precipitates were formed. The volume of external phase, rather the ratio of internal: external phase volume played an important role in formation of microspheres. The inferences are as per table 7.2. Also, for efficient homogenization, based upon the beaker dimensions and position of blades of stirrer, external phase volume plays an important role.

Table 3 Effect of internal phase volume on microsphere formation

Sr No	Internal phase External Phase	Interference
1	1:4	Due to very less external phase, sufficient homogenization could not be obtained.
2	1:6	Optimum for microspheres, no precipitation or sticking
3	1:10	Sudden extraction of ethyl acetate into external phase, sticky clumps of polymer formed.

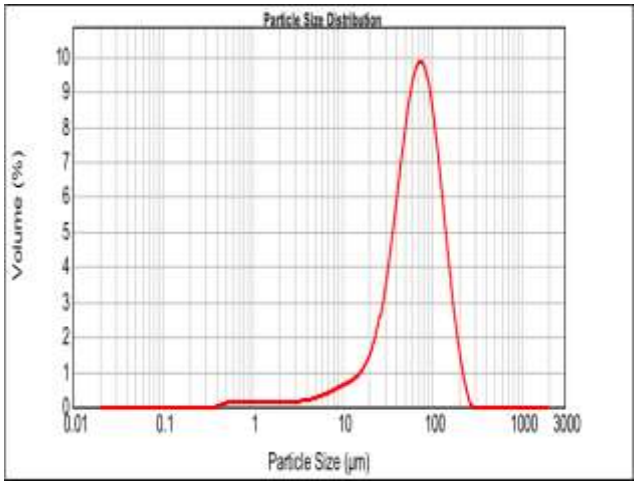
CHARACTERIZATION OF MICROSPHERES

ENCAPSULATION EFFICIENCY: Fifteen mg of drug loaded microspheres were accurately weighed and dissolved in 10 ml of methanol, sonicated for 15 min and then diluted five times with methanol. It was analysed at 341 nm on a double beam UV/Visible spectrophotometer (Shimadzu 160A). The percentage encapsulation efficiency was calculated as:

%Encapsulation Efficiency = (Actual drug loading/Theoretical drug loading) X 100

PARTICLE SIZE:- Particle size distribution of optimized batch of furosemide microsheres

Figure: 6 Particle size distribution of optimized batch of furosemide microsheres



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SURFACE MORPHOLOGY

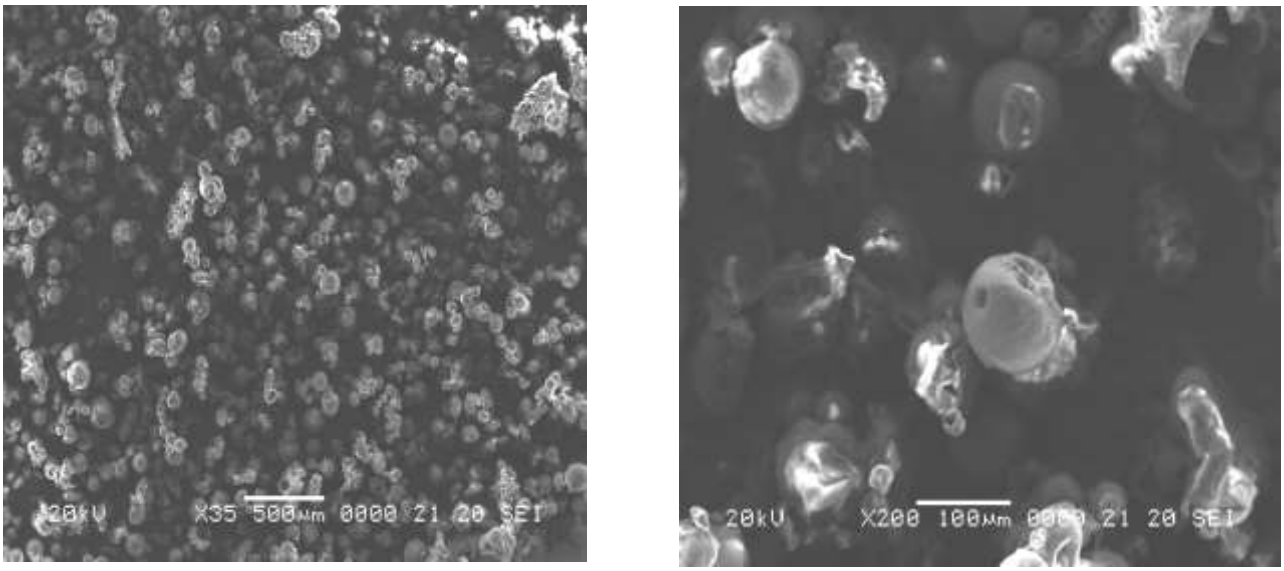

Fig: 7 Surface photographs of microspheres of furosemide, (a) at 200X and (b) at 35X

IN VITRO DRUG RELEASE:- Microspheres of furosemide were tested for their dissolution rate using U.S.P. XXIV (type II) dissolution test apparatus (Model TDT6P, Electrolab Mumbai, India) with paddle to rotate at 50 r.p.m. Nine hundred ml of 0.1 N HCl was taken as dissolution medium with temperature of 37±0.5°C. For maintaining sink conditions, a solubilizer was needed. Polysorbate 20 was added in dissolution medium to provide sink condition. Table 7.4 shows solubility of furosemide at different concentrations of polysorbate 20 in 0.1 N HCl needed for sink condition. At definite time intervals, 5 ml of the samples were withdrawn and were analyzed for drug content. Withdrawn samples were replaced with fresh dissolution media and calculations for the amount of drug were done using respective regression equation.

Table 4: Determination of polysorbate 20 concentration for sink condition

S.No.	Concentration of polysorbate 20 (% v/v)	Solubility of furosemide (% w/v)	Minimum volume required for 3 times the sink conditions (ml)
1	0	0.001778	13497.49
2	1	0.009783	2453.33
3	1.5	0.015955	1504.26
4	2	0.026913	891.76

PREPARATION OF PRE-OPTIMIZATION BATCHES:- Based on the literature, it was decided to first evaluate the effect of polymer to drug ratio or drug loading on microsphere properties. So based on literature studies, drug loading were shown to be varying from 10% to 30% of polymer. For the pre-optimization batches, internal phase volume was fixed to 8 ml based on studies reported in section7.7 and external phase volume to 50 ml. Drug amount was taken as 200 mg and amount of porogen was kept constant to 1.8 ml.

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Table 5 Pre-optimization batches based on drug to polymer ratio

Batch code	Drug: Polymer	Drug loading (%w/w of polymer)
P_1	1:10	10
P_2	1:5	20
P_3	1:3.3	30

EVALUATION OF PRE-OPTIMIZATION BATCHES:- Based on above formula, microspheres were prepared as per procedure mentioned previously. The batches were evaluated for their drug encapsulation efficiency and in vitro drug release. For in vitro release studies, a quantity of microspheres equivalent to 40 mg of furosemide was taken. The results are shown as per table 6 and table 7.

Table 6 Encapsulation efficiency of pre-optimization batches

Batch code	% Encapsulation efficiency
P_1	101.3
P_2	92.4
P_3	69.7

Table 7 In vitro release profile of pre-optimization batches

Time (hr)	% Cumulative release of drug from batches		
	P_1	P_2	P_3
0.5	11.87	26.15	35.50
2	26.82	47.76	61.73
3	32.82	58.45	71.42
4	36.72	63.67	76.69
6	37.99	67.09	80.37

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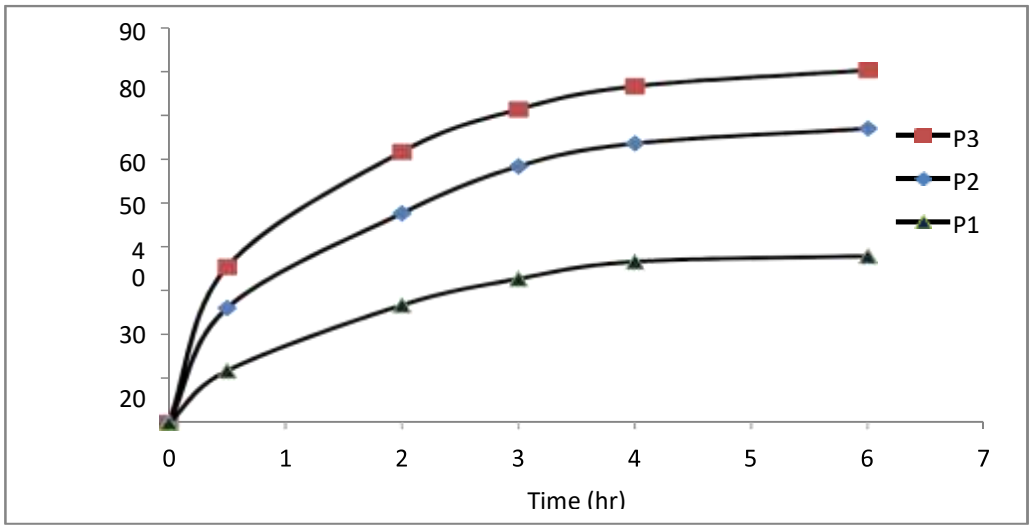

Fig. 8. In vitro release profile of pre-optimization batches

PREPARATION OF OPTIMIZATION BATCHES:- The Box-Behnken design with two center points provided a total of fourteen trial batches as per table 8 The microspheres of trial batches were prepared by the similar procedure which was described in section 7.7.1. The amount of drug was kept constant to 200 mg/batch and the volumes of internal phase and external phase were decided to be 8 ml and 50ml, respectively. The amount of PEG 200 required to solubilise the drug is as per table 9

Table no 8:- Box-Behnken experimental plan for optimization of microspheres:-

Formulation code	Independent variables		
	A: Polymer amount (mg)	B: Concentration of PVA (% w/v)	C:Porogen volume (ml)
FOB-1	800	0.2	1.8
FOB-2	1200	0.2	1.8
FOB-3	800	0.8	1.8
FOB-4	1200	0.8	1.8
FOB-5	800	0.5	1.5
FOB-6	1200	0.5	1.5
FOB-7	800	0.5	2.1
FOB-8	1200	0.5	2.1
FOB-9	1000	0.2	1.5
FOB-10	1000	0.8	1.5
FOB-11	1000	0.2	2.1
FOB-12	1000	0.8	2.1
FOB-13	1000	0.5	1.8
FOB-14	1000	0.5	1.8

Table no 9 Amount of PEG 200 required to dissolve drug in the polymer solution of ethyl acetate:

S. No.	Polymer amount (mg)	Amount of PEG 200 required (mg)
1	800	200
2	1000	120
3	1200	40

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EVALUATION OF OPTIMIZATION BATCHES:- The prepared microspheres optimization batches were evaluated for following parameters: particle size, encapsulation efficiency, floating nature and in-vitro drug release profile. The results of these evaluations are reported in table Cumulative percent release of optimization batches of furosemide microspheres

Formulation code	Percent cumulative release after					
	0.5 hr	2 hr	4 hr	6 hr	8 hr	12 hr
FOB-1	41.68	70.19	84.25	88.33	91.36	92.36
FOB-2	28.93	52.47	69.70	78.37	83.48	86.42
FOB-3	52.10	75.98	85.05	91.33	92.82	94.39
FOB-4	32.26	55.11	72.28	79.62	84.67	86.69
FOB-5	48.06	74.12	86.01	89.95	91.44	93.14
FOB-6	35.38	59.10	72.82	79.24	84.49	88.14
FOB-7	42.75	68.56	83.11	87.11	89.58	92.26
FOB-8	28.15	48.86	67.41	76.42	82.72	85.58
FOB-9	42.25	62.47	79.53	85.14	89.86	91.77
FOB-10	45.16	63.12	79.77	85.02	90.45	92.43
FOB-11	37.36	56.70	71.68	81.07	85.35	89.35
FOB-12	38.64	60.39	78.79	84.97	88.34	90.31
FOB-13	39.84	59.76	78.80	84.97	88.41	90.31
FOB-14	39.20	61.67	79.94	85.13	88.00	89.69

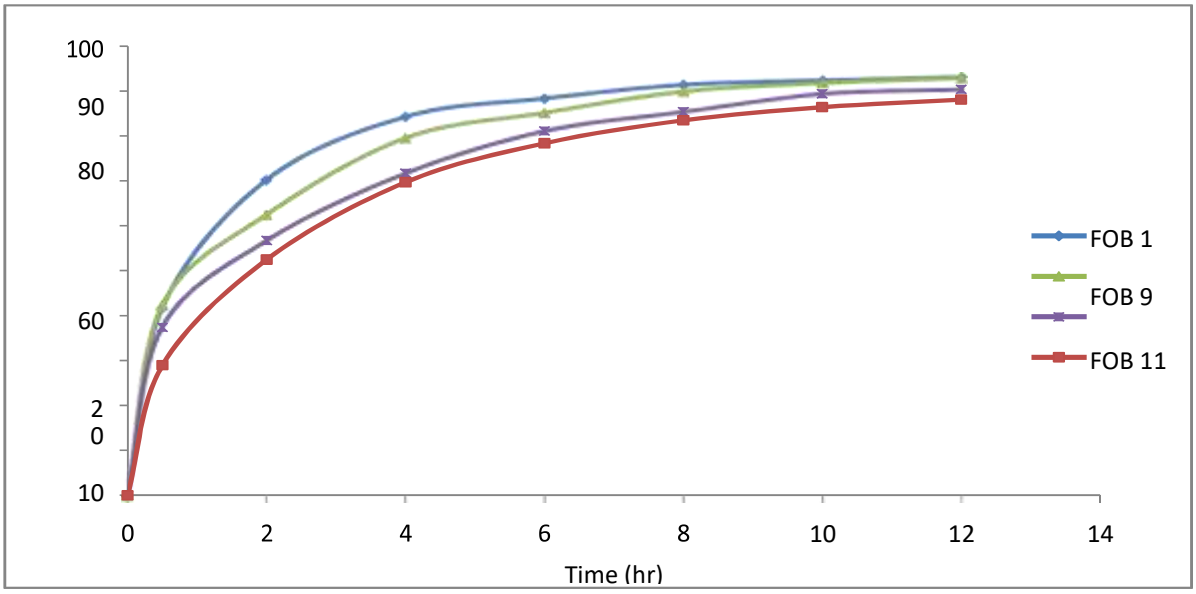

Fig 9 Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 1, 2, 9 and 11)

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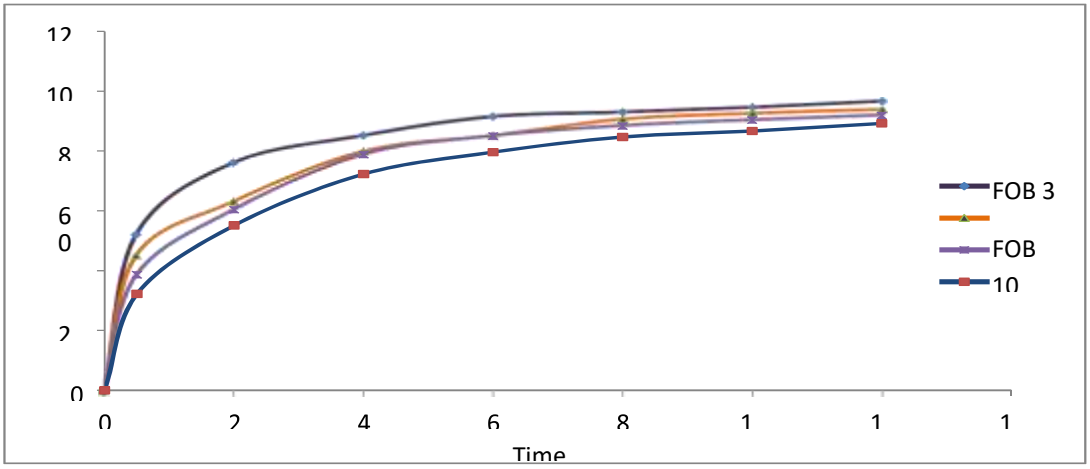

Fig 10 Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 3, 4, 10 and 12)

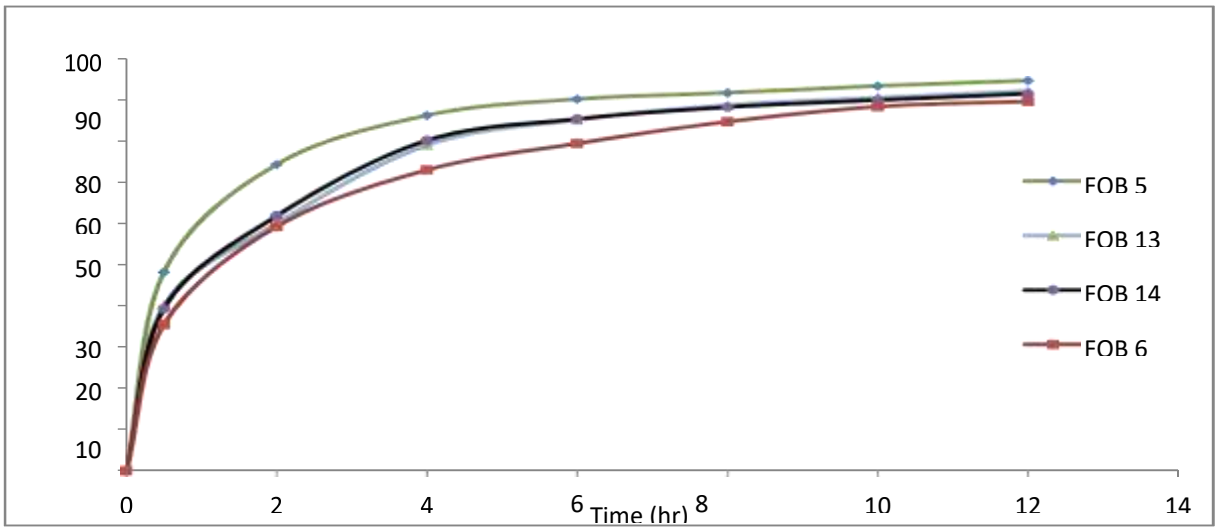

Fig 11 Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 7 and 8)

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Formulation code	Independent variables			Response variables			
	A: Polymer amount (mg)	B: Concentration of PVA (% w/v)	C:Porogen volume (ml)	% Floating after 8 hrs	% Encapsulation efficiency	Mean size (µm)	% Cumulative release after 8 hr
FOB-1	800	0.2	1.8	43.2	93.6	88	91.3
FOB-2	1200	0.2	1.8	72.2	99.1	124	88.0
FOB-3	800	0.8	1.8	39.5	94.2	58	92.8
FOB-4	1200	0.8	1.8	65.4	98.9	73	84.6
FOB-5	800	0.5	1.5	36.2	93.0	72	91.4
FOB-6	1200	0.5	1.5	61.1	98.4	97	84.5
FOB-7	800	0.5	2.1	52.8	93.6	72	89.5
FOB-8	1200	0.5	2.1	81.6	98.7	106	82.7
FOB-9	1000	0.2	1.5	48.2	96.3	103	89.8
FOB-10	1000	0.8	1.5	45.9	96.1	76	90.5
FOB-11	1000	0.2	2.1	65.7	96.1	107	85.3
FOB-12	1000	0.8	2.1	62.8	95.6	80	88.3
FOB-13	1000	0.5	1.8	56.2	95.0	86	88.4
FOB-14	1000	0.5	1.8	55.1	95.2	85	88.0

Table no 10 Evaluation of optimization batches of furosemide microspheres

X-RAY DIFFRACTION STUDIES-

The solid drug powder, eudragit RSPO and microspheres were analyzed for crystal arrangement and its crystalline nature by the virtue of diffraction pattern analyzed by Powder X-ray diffractometer (Bruker) at power: 4 KW, source: Cu K-α and wavelength: 1.5418 A˚. The X-ray diffractograms are shown from fig

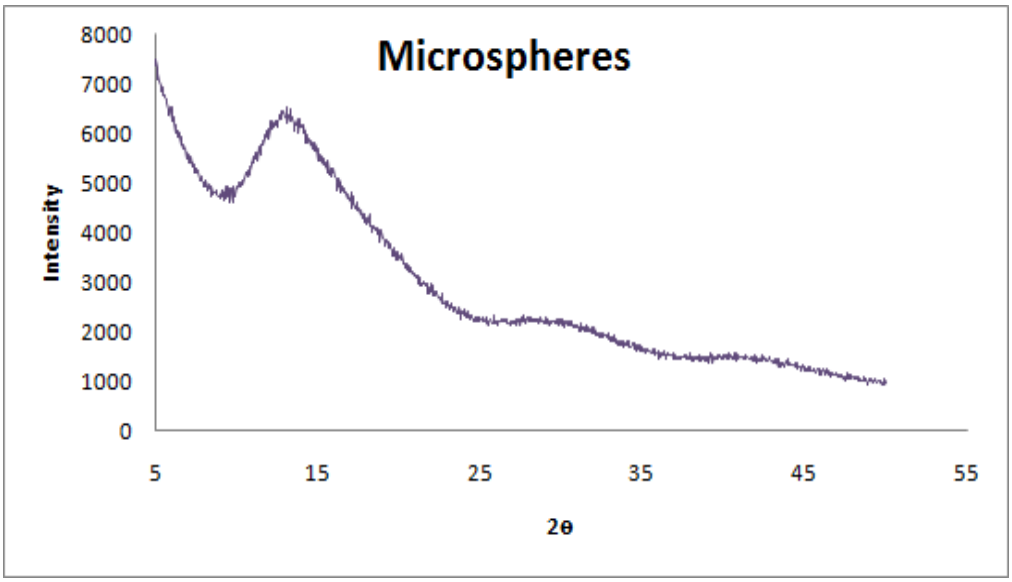

Fig 12 X-ray diffractogram of furosemide microspheres

EVALUATION OF OPTIMIZED FUROSEMIDE MICROSPHERES- Evaluation of optimized furosemide microspheres was carried out and results are recorded in table.

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Table 11 : Comparison of results predicted by software and those observed

Response Variable	Value predicted	Value obtained
% Floating after 8 hr	72.36 %	73.32
% Encapsulation efficiency	97.8 %	96.8%
Mean size	82.26 µm	66.97 µm
% Cumulative release after 8 hr	84.9%	85.3%

The microspheres were also characterized for their micromeritic properties. Four gm of microspheres were weighed and using 50 ml graduated measuring cylinder, tapped density, bulk density, compressibility index and Hausner's ratio were determined. Similarly, using 4 gm of microspheres and a glass funnel, angle of repose was determined. The results are recorded in table.

Table 12 : Micromeritic properties of optimized batch of microspheres

Formulation	Parameters				
	Bulk density (g/cc)	Tapped density (g/cc)	Compressibi -lity index (%)	Hausner's ratio	Angle of Repose
Optimized Batch	0.32	0.36	11.11	1.12	27.4°

The micromeritic properties of microspheres lied within range of values which indicated powder with good flow propereties.

IN VITRO RELEASE PROFILE OF FUROSEMIDE OPTIMIZED MICROSPHERES-

In vitro release from microspheres was studied by the same procedure mentioned in section 7.8.4. The percent cumulative release obtained was plotted against time. The % cumulative release data from microspheres is as per table 7.19 and release profile is shown in fig13

Table no 13 Percent cumulative release of drug from optimized microspheres

Time (hr)	0.5	2	4	6	8	10	12
% cumulative drug released	29.64	51.13	70.40	81.63	85.34	86.72	88.26

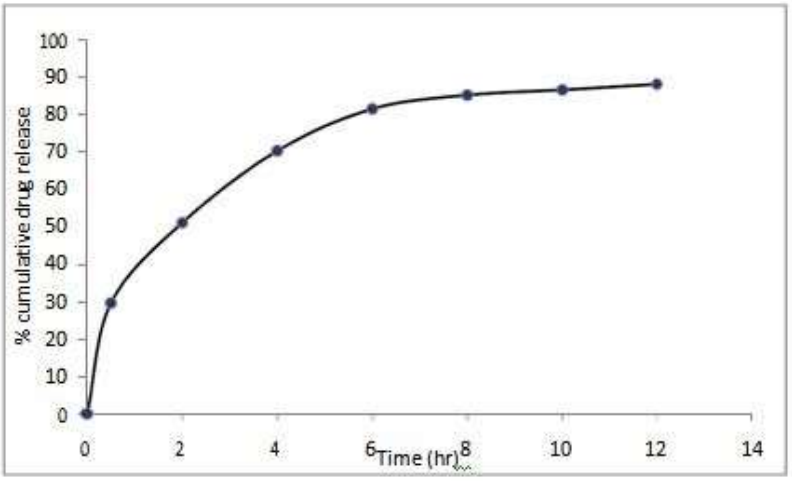

Fig 13 Cumulative % drug release v/s time plot of furosemide optimized microspheres

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STABILITY STUDIES- Furosemide microspheres (pre-optimization batch P_2) were kept at different storage conditions. Test samples were kept at room temperature and at 40ºC. Percent encapsulation efficiency of the formulation was determined initially which was found to be 92.4%. The samples were withdrawn at different time intervals and the drug contents were determined. The percent drug remaining is reported in table 7.20. The controlled release furosemide microspheres were found to be stable at the different storage condition for one month period.

Table 14: Stability data of furosemide microspheres

Condition	% Encapsulation efficiency after		
	7 days	15 days	30 days
Room Temperature	92.35	92.22	92.09
40°C	92.18	92.09	91.89

Summary & Conclusion- The main objective of present study was to explore mixed solvency concept in preparation of floating microspheres of furosemide using emulsification solvent evaporation method.

Microspheres were prepared by emulsification solvent evaporation method. Ethyl acetate was used as internal phase, eudragit RSPO as release rate controlling and matrix forming polymer, polyvinyl alcohol as emulsifier, PEG 200 was used as cosolvent to dissolve drug completely in internal phase and petroleum ether was used as porogen to form pores inside microspheres. Pre optimization studies were carried out to determine process parameters affecting microsphere formation. The factors studied were drug loading, internal phase volume, stirring speed and amount of porogen. Microspheres with drug loading 20% gave better release profile than with 10% and 30%.

Based on results of pre-optimization, optimization studies were performed using Design Expert 8.0.3 version (Stat-Ease Inc., Minneapolis, USA). Box-Behnken design with fourteen trial batches was used for optimization. Independent variables were selected based on results of pre-optimization study viz. polymer amount, amount of porogen and concentration of stabilizer. Response variables were selected as per desired characteristics of microsphers like % floating, encapsulation efficiency, mean size and % release after 8 hrs. The response variables of optimization batches were analysed statistically and response surface plots were generated. The software was made to generate a set of independent variables based on desired response variables with desirability of 0.764.

The optimized batch was evaluated using scanning electron microscopy, X-ray diffraction, and DSC. The results suggest complete encapsulation and miscibility of furosemide within the polymer.

The release data obtained from the dissolution study of the optimized validation batches were analyzed with respect to first order model, Higuchi model, Korsmeyer-Peppas model, and zero order models. It was found that the release data showed best fit in Higuchi model.

The stability study of microsphere formulation was performed for one month under different storage conditions. The developed formulation was found to be stable under the conditions of room temperature and 40ºC for one month stability study duration.

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