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Research Article

# APPLICATION OF NOVEL CONCEPT OF MIXED SOLVENCY IN THE DESIGN AND DEVELOPMENT OF FLOATING MICROSPHERS OF FUROSEMIDE

**RAJESH KUMAR MAHESHWARI[1], VIKRAM URJIT KARAWANDE[1]**

[1]Department of Pharmacy, Shri G.S. Institute of technology and Science, Indore (M.P.), India. Email: vickky619@gmail.com

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**ABSTRACT**

Ethyl acetate (class III solvent) has been used to prepare oral floating microspheres replacing methylene chloride (class II). The concept of mixed solvency has been utilized to increase the solubility of drug in the internal phase. One step emulsification solvent evaporation technique (o/w) was used to prepare microspheres. Internal phase consisted of solution of drug in ethyl acetate containing dissolved polymer i.e. Eudragit RSPO. The solubilizer i.e. PEG 200 along with polymer aided to dissolve the drug completely in internal phase. Petroleum ether was used as porosity generator. The microspheres with good floating ability (73% floating after 8 hrs on simulated gastric fluid) and controlled release (85% cumulative release after 12 hrs *in-vitro*) were successfully prepared. Average particle size of microspheres was in micron range ($D_{0.5}$ = 67µm) with 1.703 as polydispersity index. Floating microspheres using safer solvents i.e. ethyl acetate (class 3) were prepared replacing generally used solvent methylene chloride (class 2). Buoyancy of microspheres was increased with increasing amount of petroleum ether. Drug release was decreased with increasing polymer: drug ratio. Encapsulation efficiency was also enhanced with increasing polymer: drug ratio.

**Keywords:** Hydrotropy, Mixed Solvancy, Ethylacetate, Floating Microsphere, Furosemide, Eudragit

## INTRODUCTION

Oral drug delivery is the most desirable method of administering therapeutic agents mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy with an acceptable level of safety to the patient. However, the potential for oral dosage form development is sometimes limited for therapeutic agents that are poorly absorbed in the gastrointestinal (GI) tract and unstable. The overall process of oral delivery is frequently impaired by several physiological and pharmaceutical challenges that are associated with the inherent physicochemical nature of the drugs and/or the variability in GI conditions.

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.

Gastro retentive systems also called as floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. Singh and Kim [1] reviewed various techniques of floating drug delivery system. They depicted various approaches for gastro retention such as swelling systems, high density system, effervescent and non effervescent systems etc. Microspheres have been used as a means of gastric retention.

Kawashima and coworkers [2] prepared hollow microspheres ('microballoons') with drug loaded in their outer shells by an emulsion-solvent diffusion method. The ethanol-methylene chloride solution of drug and enteric acrylic polymer was poured into an aqueous solution of polyvinyl alcohol (PVA) that was maintained at 40°C. The latter solution was constantly stirred to form emulsion droplets. Yasunori and coworkers [3] prepared microballoons of five different drugs using enteric polymers dissolved in a mixture of methylene chloride and ethanol which constituted the internal phase. They also concluded that the affinity of drug towards polymer, which depends upon drug characteristics, decides the encapsulation efficiency and also release of drug from the formulation.

In the present investigation, furosemide was selected as a model drug. Klausner and coworkers [4] investigated pharmacokinetic and pharmacodynamic properties of furosemide in male volunteers. They found that 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. These adverse effects were traced to the fact that furosemide is absorbed and metabolized mostly at the gastric level and, to a lesser extent, at the level of the upper section of the intestine. The treatment with sustained release tablets produced the same diuretic effect as produced by conventional tablets eliminating brief and intense diuresis. Thus they concluded that use of sustained release tablets are well tolareted due to the avoidance of discomfort associated with the short period of maximum diuresis and marked drug absorption variability.

Acrylic polymer (Eudragit RSPO) was used as release controlling polymer since it has shown to have good affinity for furosemide. Aceves and coworkers [5] prepared controlled release systems of furosemide and showed that furosemide changes its crystalline structure to amorphous state in solid dispersions with Eudragit. Petroleum ether was used as a pore forming agent which would after evaporation form pores inside microspheres. Petroleum ether was used as an alternative to heptane which has been used as a porogen. Yang and coworkers [6] used n-heptane as non solvent to prepare microspheres of aspirin. During the drying stage, evaporation of heptane produced pores inside microspheres.

Maheshwari is of opinion that all the substaces whether solids, liquids or gas have solubilizing power [7]. Various examples of mixed solvency concept can be found in literature [8, 10-11]. Furosemide solubility has also been shown to be increased in ethanol using various solubilzers [9]. Examples include solubilization of diclofenac sodium (melting point 284°C) in molten ibuprofen (melting point 78°C). The concept of mixed solvency was used to increase the solubility of drug into internal phase so as to prepare a homogeneous drug solution required to achieve homogeneous distribution of drug throughout polymer matrix. The drug furosemide had limited solubility in internal phase (14.89 mg/ml in ethyl acetate). To increase the drug solubility, PEG 200 was used. The addition of polymer in ethyl acetate further improved the solubility of furosemide in ethyl acetate, which confirms that even solid substances possess solubilizing power.

## MATERIALS AND METHODS

### Materials

Furosemide was obtained from Ipca Laboratories Pvt. Ltd., Ratlam. Eudragit gift sample from Evonik Degussa India Pvt Ltd, Mumbai, India. All other reagents and solvents used were of analytical grade.

### METHOD

### Determination of Solubility of Furosemide in Various Solutions of Solubilizers in Ethyl Acetate

Accurately measured 5 ml of a particular solution of solubilizer in ethyl acetate was taken in a 10 ml vial and excess amount of drug was added and mechanically shaken (to saturate the solution). The vials were sealed with rubber closure and aluminium cap and shaken on mechanical shaker for 12 hrs so that equilibrium solubility can be achieved and solution was allowed to equilibrate for 24 hrs. Then solution was centrifuged at 2000 r.p.m. for 5 minutes in ultra-centrifuge and then solution was filtered through Whatman grade 5 filter. Aliquotes were suitably diluted with ethyl acetate and analyzed using UV spectrophotometer at 344.7 nm against respective reagent blanks. The results are shown in **table 1**.

**Table 1: Solubility enhancement in various solutions of solubilizers in ethyl acetate**

| Solubilizing agent employed (%w/w) | Solubility enhancement ratio |
|---|---|
| Ethyl acetate | 1.000 |
| Camphor (20%) | 2.573 |
| Camphor (10%) | 1.261 |
| PEG 200 (20%) | 7.232 |
| PEG 200 (10%) | 2.827 |
| PEG 400 (20%) | 5.769 |
| PEG 400 (10%) | 2.070 |
| Menthol (20%) | 3.239 |
| Menthol (10%) | 2.252 |
| Dichloromethane | 1.957 |
| Vanillin (10%) | 2.921 |
| Eudragit RSPO (20%) | 5.107 |
| Eudragit RSPO (15%) | 3.367 |
| Eudragit RSPO (10%) | 1.756 |

Based on above results, PEG 200 was selected as a solubilizer to dissolve the furosemide in internal phase. The polymer eudragit RSPO itself also aided in increasing the solubility of furosemide in ethyl acetate.

### Procedure for Preparing 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 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 stirring speed

Both the shape and size of the particles depend heavily on the stirring speed. Rapid rotation (> 1700 rpm) of the stirrer resulted in heavy foaming, and vigorous agitation of contents with smaller particle size. However, agglomeration was observed when stirring speed was kept low (700-900 rpm). Finally 1300-1500 rpm stirring speed was selected for preparation of microspheres at which encapsulation efficiency was found to be satisfactory. The observations are as per **table 2**

**Table 2: Effect of stirring speed on microsphere formation**

| RPM | Observation |
|---|---|
| 700-900 | Agglomerates formed |
| 1300-1500 | Good round microspheres |
| 1700-1900 | Foaming and vigorous agitation |

### Optimization of Formulation Variables

From the results of pre-optimization studies it was concluded that many factors such as drug to polymer ratio, porogen amount and PVA concentration affected microsphere properties. So these were selected as independent variables and formulation was optimized using Design Expert software. Box-Behnken design (BBD) was used to generate experimental runs based on independent variables as shown in **table 3.** BBDs are a class of rotatable or nearly rotatable second-order designs based on three-level incomplete factorial design. It permits: (i) estimation of the parameters of the quadratic model; (ii) building of sequential designs; (iii) detection of lack of fit of the model; and (iv) use of blocks.

The response variables were selected on the basis of desired characteristics of microspheres. Percent floating after 8 hrs, encapsulation efficiency, mean size and percent cumulative release at 8$^{th}$ hr were selected as response variables. They are as per **table 4.**

### Preparation of Optimized Batches

The Box-Behnken design with two center points provided a total of fourteen trial batches as per **table 5**. The microspheres of trial batches were prepared by the similar procedure which was described in previous section. 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 50 ml, respectively. The amount of PEG 200 required to solubilise the drug is as per **table 6.**

**Table 3: Independent variables selected for optimization studies**

| Code | Variable | Unit | Type | Low Level | Middle Level | Upper Level |
|---|---|---|---|---|---|---|
| A | Polymer Amount | mg | Numeric | 800 | 1000 | 1200 |
| B | Concentration of PVA | % | Numeric | 0.2 | 0.5 | 0.8 |
| C | Amount of porogen | ml | Numeric | 1.5 | 1.8 | 2.1 |

**Table 4: Response variables selected for optimization studies**

| Response Variable | Units | Code |
|---|---|---|
| Microspheres floating after 8 hrs | Percent | $Y_1$ |
| Encapsulation efficiency | Percent | $Y_2$ |
| Mean size | µm | $Y_3$ |
| Cumulative release after 8$^{th}$ hr | Percent | $Y_4$ |

**Table 5: 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 6: 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 |

**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 7.** The release profiles are shown as per **fig. 1-4.**

**Table 7: Evaluation of optimization batches of furosemide microspheres**

| 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 |

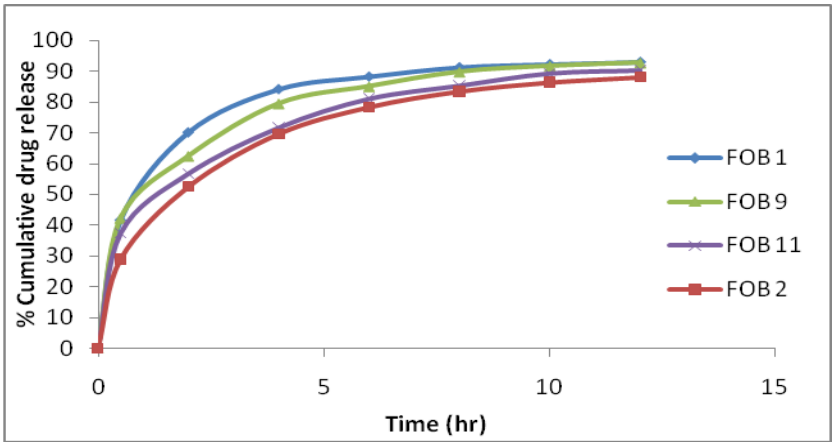


**Fig. 1: Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 1, 2, 9 and 11)**

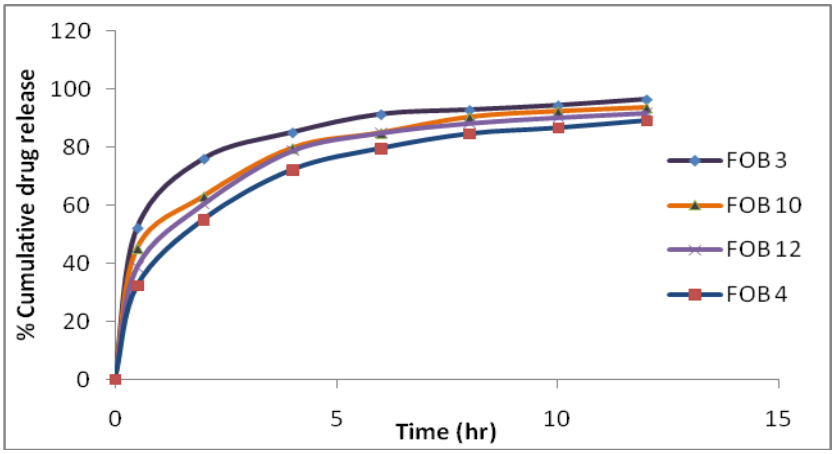


**Fig. 2: Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 3, 4, 10 and 12)**

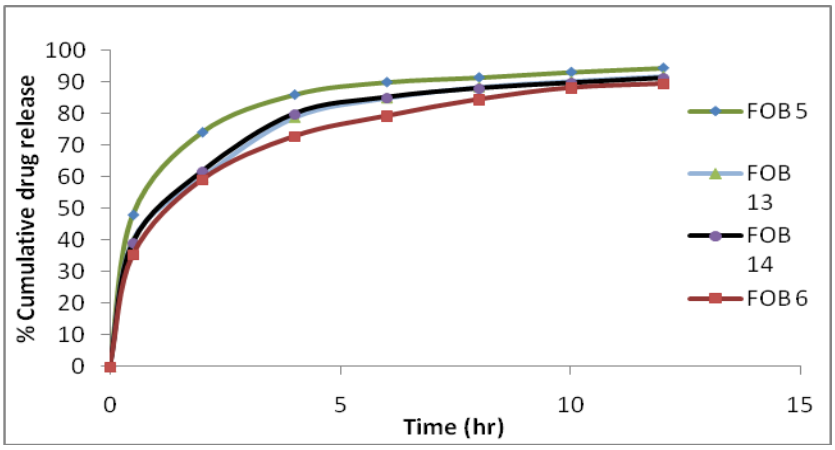


**Fig.3: Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 5, 6, 13 and 14)**

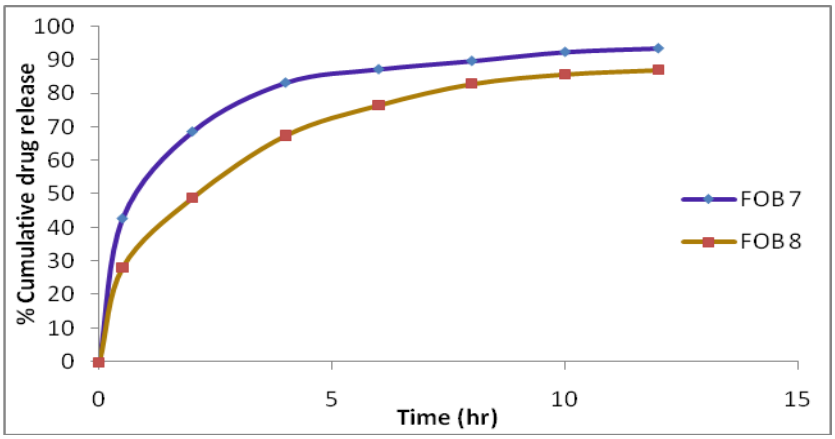


**Fig. 4: Cumulative % drug release v/s time plot of furosemide microspheres (optimization batches 7 and 8)**

**Prediction of Optimized Microspheres Formulation of Furosemide**

For optimized batch, the desired characteristics of microspheres were decided as follows: (a) % floating after 8 hrs, maximized between 60% to 80%, (b) % encapsulation efficiency maximized between 95% to 99%, (c) mean size minimized between 60 µm to 100 µm and (d) % cumulative release after 8 hrs set to target 85%. Based on these criteria, the software predicted ten solutions. The solution with maximum desirability as 0.764 was selected as optimized batch. The desirability area amongst the formulations is shown by response surface plot in **fig 5.** The formula predicted by software is depicted in **table 8.**

**Table 8: Formula predicted by Design Expert software**

| Independent Variable | Quantity |
|---|---|
| Eudragit RSPO amount | 1136.2 mg |
| PVA concentration | 0.8% |
| Porogen amount | 2.1 ml |

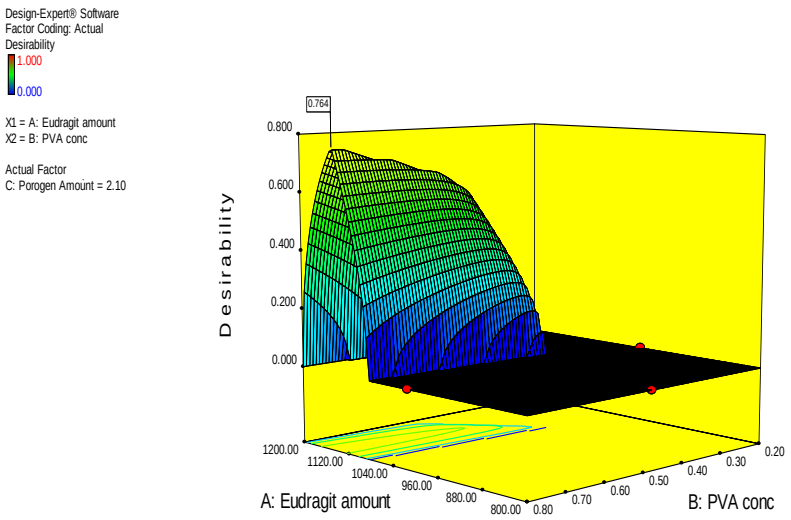


**Fig. 5: Response surface graph 3D showing desirability of optimized batch**

**Evaluation of Optimized Formulation**

**Particle Size Analysis**

Particle size of microspheres was determined by laser diffraction based particle size analyzer (Malvern mastersizer 2000, UK). Microspheres were suspended in a 1% aqueous solution of polysorbate 80 and sonicated for 2 min prior to particle size determination. Polydispersity index was calculated by the following formula:

Polydispersity index = $(D_{0.9}-D_{0.1}) / D_{0.5}$

Where $D_{0.9}$, $D_{0.5}$, and $D_{0.1}$ are the particle diameters determined at the 90th, 50th, and 10th percentile of undersized particles, respectively.

The particle size distribution of optimized batch is shown as per **fig 6.** D0.5 was found to be 66.97 µm and polydispersity index was found to be 1.703.

**Surface Morphology**

Morphology of the microspheres was studied by scanning electron microscopy. Dried samples were mounted on metal stubs with double side tape. Metal stub was examined under SEM (Jeol JSM 6100, Japan) at 20 kv. The photographs as per **figure 7(a) and 7(b)** clearly reveal presence of pores on microsphere surface.

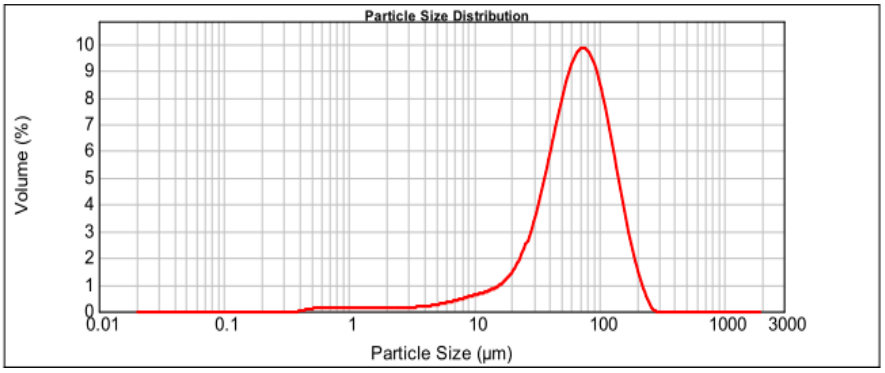


**Fig. 6: Particle size distribution of optimized batch of furosemide microsheres**

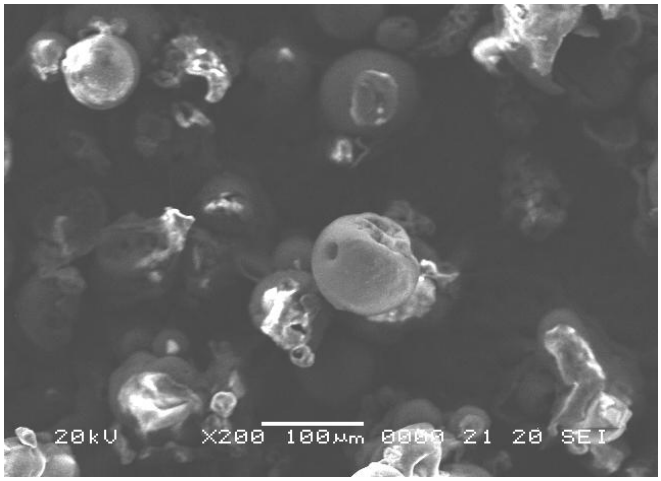


**Fig. 7 (a)**

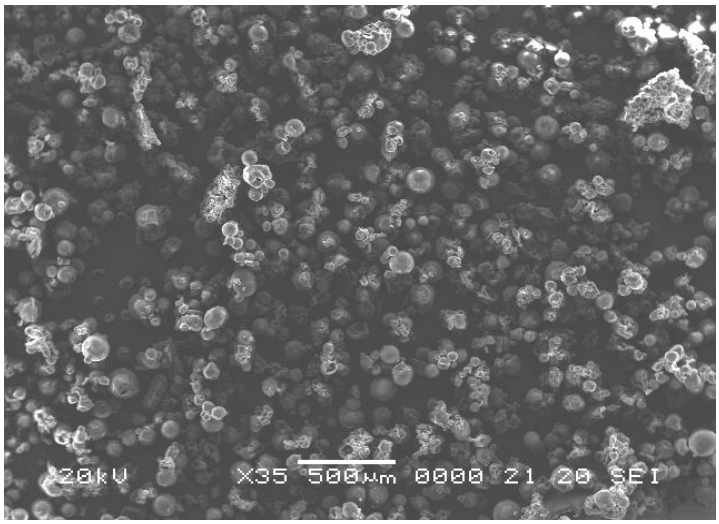


**Fig. 7 (b)**

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

**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 **figure 8** to **10.**

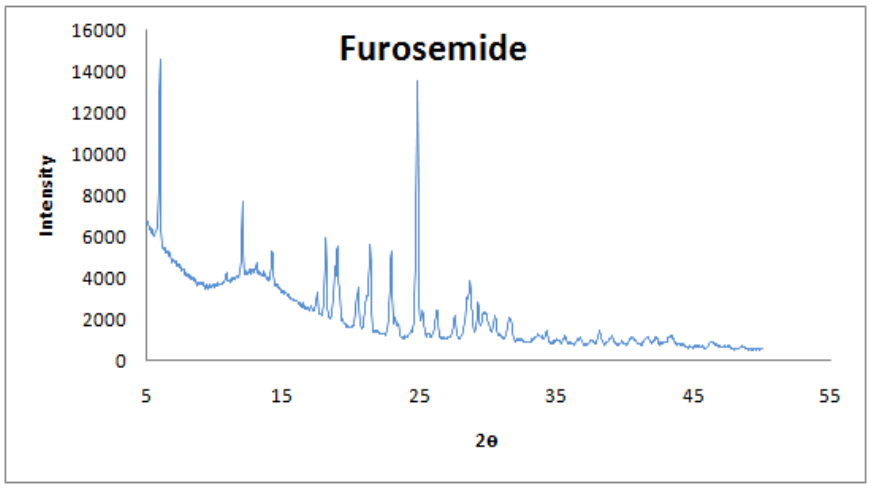


**Fig. 8: X-ray diffractogram of pure furosemide drug.**

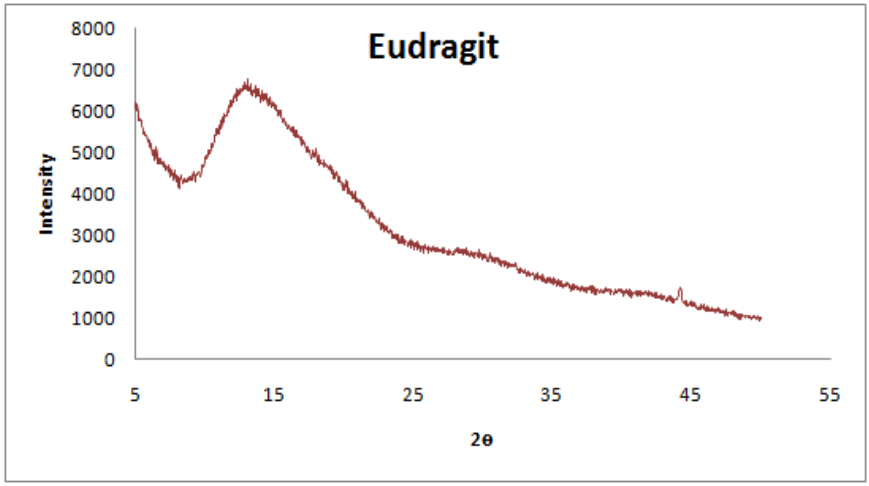


**Fig. 9: X-ray diffractogram of eudragit RSPO.**

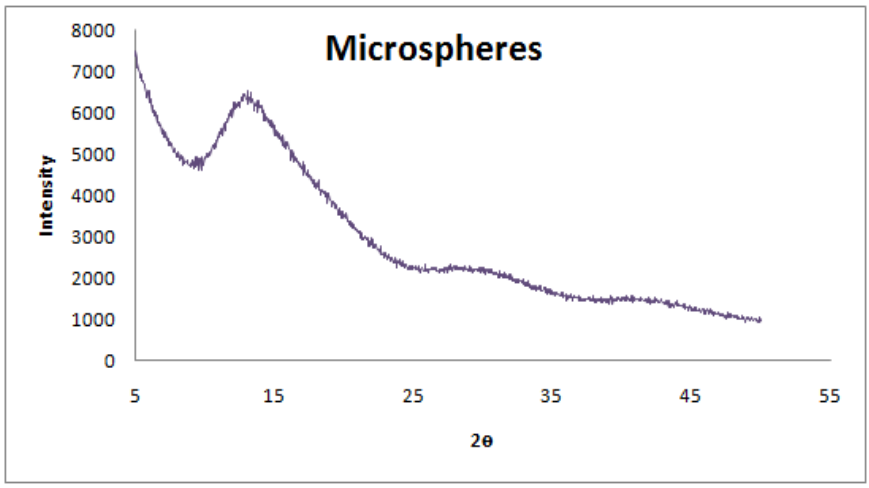


**Fig. 10: X-ray diffractogram of furosemide microspheres.**

**Differential Scanning Calorimetric Studies**

In order to obtain the DSC thermograms of the drug and formulation (microspheres), Pyris 6 DSC (Jade DSC) instrument was employed. To carry out these studies, 3.7 mg of drug and 4.1 mg of formulation of drug were weighed accurately and placed in one of the matched aluminium pan. The sample pan and the reference pan both were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10°C/min with a continuous purge of nitrogen (20 ml/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 30-350°C. DSC thermograms (melting isotherms) are shown in **figure 11** and **12.**

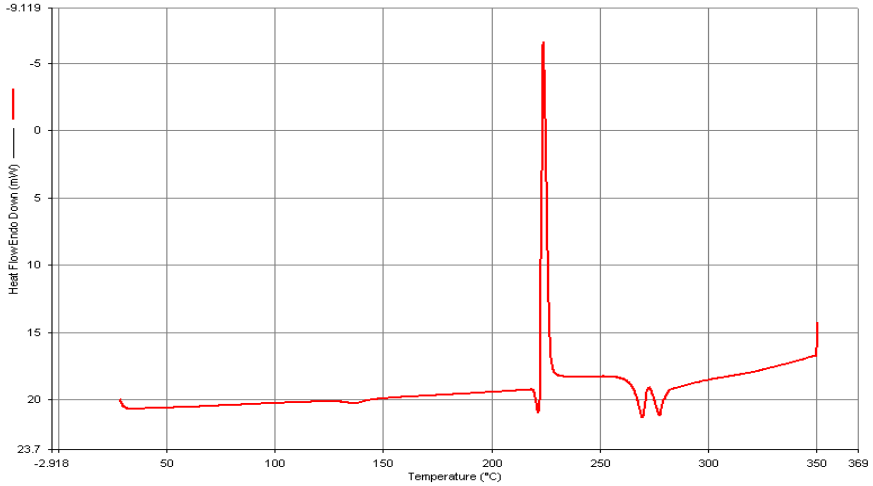


**Fig. 11: DSC thermogram of pure furosemide.**

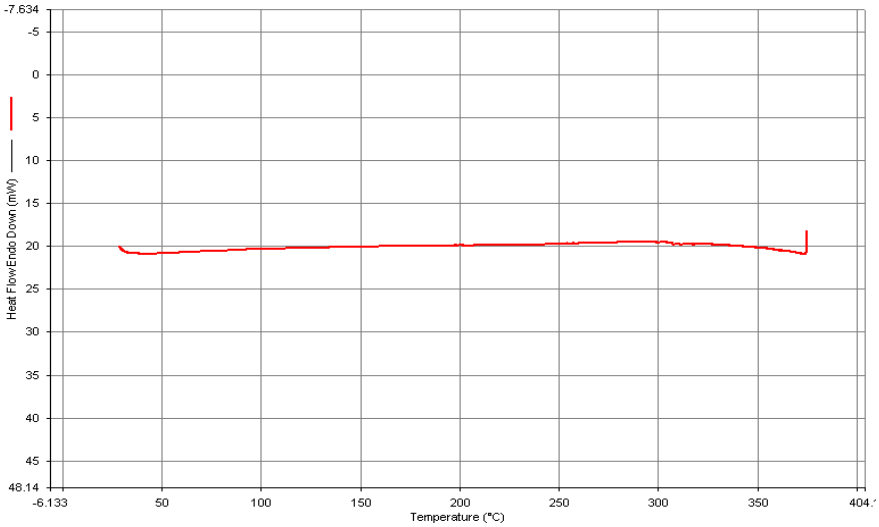


**Fig. 12: DSC thermogram of furosemide microspheres.**

**Comparison of response variables predicted and those observed for optimized batch:**

Evaluation of optimized furosemide microspheres was carried out and results are recorded in **table 9.**

**Table 9: 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% |

**In Vitro Release Profile of Furosemide Optimized Microspheres**

In vitro release from microspheres was studied by the same procedure mentioned in previous section. The percent cumulative release obtained was plotted against time. The % cumulative release data from microspheres is as per **table 10** and release profile is shown in **figure 13.**

**Table 10: 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 |

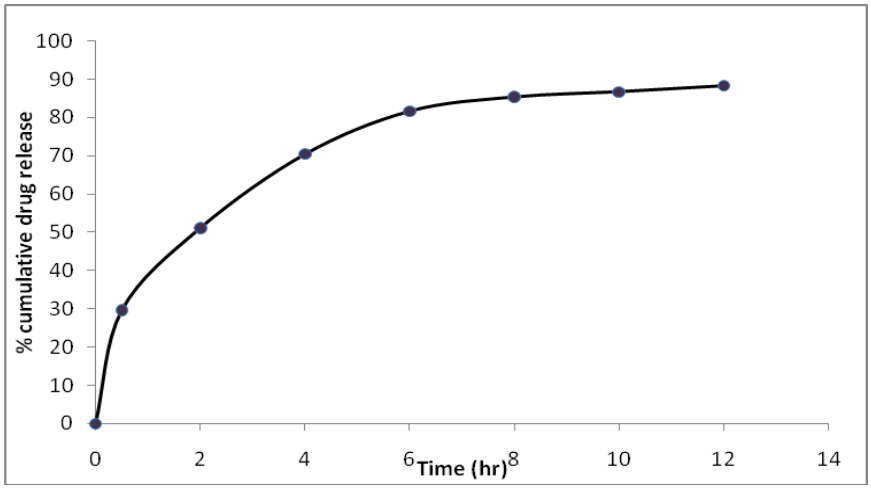


**Fig. 13: Cumulative % drug release v/s time plot of furosemide optimized microspheres**

**RESULTS**

Floating microspheres were successfully prepared using the concept of mixed solvency. Solubility studies showed that use of different solubilizers can enhance the solubility of furosemide into internal phase. Pre-optimization studies were carried out to decide process operating conditions. Design Expert software was used to generate a total of fourteen experiments. The batches were prepared and evaluated. The evaluation of batches led to generation of response variables which were used to predict optimized batch based on desired response variables. The prepared optimized batch was prepared and found to have floating efficiency of about 73% after 8 hrs. Mean size of optimized microspheres was found to be 66.97 µm and cumulative release was found to be 85.3% after 8hrs. Drug encapsulation efficiency was found out to be 96.8%

**DISCUSSION**

The concept of mixed solvency was suitably applied to microsphere formulation. The drug solubility was significantly increased in internal phase and polymer itself had acted as solubilizer in microsphere formulation. The pre optimization and optimization studies indicated that increasing polymer: drug ratio decreased the rate of dug release from formulation, led to increased microsphere size and increase in encapsulation efficiency.

Increasing the porogen amount caused decrease in microsphere size. Floating time increased proportionally with increase in porogen amount. Increasing the concentration of PVA caused decrease in size of microspheres due to reduction in surface tension caused by the presence of PVA.

The surface morphology of microspheres at 200X (**figure 7a**) and 35X (**figure 7b**) shows the presence of distinct pores on the surface of microspheres which was responsible for their buoyancy. The X-ray diffraction patters of pure drug (**figure 9**), eudragit polymer (**figure 10**) and microspheres (**figure 11**) suggest that the microspheres consisted of drug homogeneously distributed through the polymer network. D.S.C. curve of pure furosemide exhibits endothermic peak at 218°C indicative of its melting and a sharp exothermic peak at 223°C corresponding to its decomposition (**figure 12**). The microsphere formulation of furosemide resulted in a complete suppression of the drug peak (**figure 13**), suggesting homogenous distribution of the drug in the polymer.

**CONCLUSION**

The mixed solvency concept can be successfully employed where the issue of solubility hinders the development of formulation. The use of this concept can avail the use of various solvents and solvent systems which can be used for formulation development.

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