Solid self-emulsifying drug delivery system of Furosemide

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Abstract

The aim of the present investigation was to prepare and optimize solid self-emulsifying drug delivery system (S-SEDDS) of Furosemide, which is poorly water soluble drug. Solubility of furosemide was performed in different oils, surfactants, co-surfactants and co-solvents. Selection of these ingredients in liquid Self Emulsifying Formulation was done on the bases of solubility and pseudo ternary phase diagram. The selected ingredients were - Capmul MCM C8 was as oil which also has properties of co-surfactants, Tween 80 as surfactant and PEG 400 as co-solvent. Prepared liquid Self Emulsifying Formulation was converted in to solid powder with the help of PEG 6000, micro crystalline cellulose PH 102. The solid powder with liquid SEF was compressed into tablet & prepared tablets were evaluated for different pre-compression, post compression evaluation parameters. The formula for tablet was optimized by using 3^2 factorial design. The results of in-vitro drug release data of optimized batch showed drastically improved dissolution rate of Furosemide. The results of accelerated stability study of optimized batch indicated that the optimized formulation was stable.

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1. Introduction

Furosemide is a poorly soluble loop diuretic, used in the treatment of congestive heart failure and edema. [1] Furosemide is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease, including the nephrotic syndrome. [2]

Self-emulsifying formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, one or more hydrophilic solvents and co-solvents/surfactants. Self-emulsifying formulations spread readily in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. Self-emulsifying drug delivery system (SEDDS) typically produce emulsions with a droplet size between 100 and 300 nm. SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate−limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood−time profiles. [3, 4]

SEDDS are allowed to be absorbed on the various solid carriers or are formulated into the solid state using the different methods like spray drying, extrusion-spheronizer techniques. SEDDS is novel approach to improve water solubility and ultimate bioavailability of lipophilic drugs. The final formulation of SEDDS can be prepared by different methods for like Capsule filling with liquid and semisolid lipid based formulation of SEDDS, Spray cooling, spray drying, adsorpt,6]ion on solid carriers, Melt granulation, Melt extrusion/extrusion spheronization, Supercritical fluid based methods, Solid lipid nanoparticles and nanostructured lipid carriers. [5, 6,7]

2. Materials and methods

2.1. Materials

Furosemide (gifted from Sanofi Aventis Pvt Ltd., Ankleshwar), Capmul MCM-C8 (gifted from Abitec Corporation, U.S.A.), Polyethylene glycol 400, Tween 80, Methanol AR Grade, Microcrystalline cellulose PH 102, Polyethylene glycol 6000, Cross-povidone, Talc, Magnesium stearate (each from S.D. Fine-Chem. Ltd., Mumbai). All other chemicals and solvents used were of analytical reagent grade.

2.2. Solubility of Furosemide in oil, surfactant, co-surfactant & co-solvents:

Solubility of Furosemide in various oils, surfactants, co-surfactants and co-solvents was determined by adding an excess amount of drug in 3 ml of selected oils (sunflower oil, soyabean oil, olive oil, coconut oil), surfactants (Tween 80, Acrysol K140, Acrysol EL135, Span 80), co-surfactants (Captex 200, Captex 100, Capmul MCM-C8, Capmul MCM, Labrafil M 2125, Capmul PG 8, Migyol 812, Migyol 840), co-solvents (polyetylene glycol 400, ethanol, methanol). The mixture was stirred using a vortex mixer for 48 hrs. Mixture vials were kept at room temperature for 24 hr to reach equilibrium. The equilibrated samples were centrifuged at 5500-6000 rpm for 15 min. 0.1 ml of the supernatant was taken and it was diluted with suitable amount of methanol. All the samples were analyzed with HPLC at 340 nm. The concentration of Furosemide was determined. [8]

2.3 Construction of phase diagrams [9]

Pseudo-ternary phase diagrams were constructed to obtain the appropriate components and their ratio that result in large existence area of microemulsion. To optimize the concentration of oil phase, surfactant, co-surfactant and co-solvents different batches of varied concentration were prepared and titrated with distilled water until turbidity appeared. Ternary phase diagram of SEDDS were prepared by Sigma plot version 10.0 software to decide the microemulsion zone in which at any point, micro emulsion can be prepared. The ratios of surfactant and Co-solvent were selected to be (1:1, 2:1, 3:1). To construct phase diagram, for each ratio, micro emulsions were prepared by increasing the oil phase (from 10% to 90%) & simultaneously decreasing the concentration of surfactant/co-solvent (from 90% to 10%) to decide the maximum uptake of water by SEDDS up to which they remained transparent. Optimization of the

concentration of oil phase, surfactant and co-surfactant was based on maximum uptake of water by SEDDS.
Based on the results of solubility & phase diagram, the selected oil, Surfactant, co-solvent were Capmul MCM C8, Tween 80 & PEG 400 respectively.

2.4 Effect of drug on the phase diagram [10]
This study was carried out to investigate the effects of amount of Furosemide on the SEDDS. SEDDS was prepared using the optimized ratio of oil, surfactant and co-solvent. 10 mg of Furosemide was added on plain SEDDS formulation to dissolve in to SEDDS. SEDDS was infinite diluted using purified water and kept it over night at room temperature. Overnight visual inspection was carried out. If dilution was transparent, more amount of drug was added. This procedure was repeated up to dilution was turbid and found out the maximum drug loading capacity.

2.5 Evaluation of Liquid Self emulsifying Formulation of Furosemide

2.5.1 Macroscopic evaluation
Macroscopic analysis was carried out in order to observe the homogeneity of Furosemide SEDDS formulation. Any change in color and transparency or phase separation was observed in optimized formulation.

2.5.2 Determination of self-emulsification time
Self-emulsification time of optimized SEDDS formulation was determined according to USP 23, using dissolution apparatus 2. 300 mg of each formulation was added drop wise to 500ml purified water at 37°c. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually.

2.5.3 %Transmittance
Solubility of optimized SEDDS formulation with respect to dilution was checked by measuring transmittance through U.V. spectrophotometer (U.V.-90, Shimadzu). Transmittance of samples was measured at 650nm and for each sample, three replicates were performed.

2.5.4 Globule Size measurement
Size analysis of SEDDS formulation was carried out by Malvern laser light scattering mastersizer model 4700 (Malvern Instruments Ltd., Malvern, U.K.). Samples were placed in square glass cuvettes and droplet size analysis was carried out of optimized SEDDS formulation. Optimized SEDDS formulation was diluted with excess (100 times) water and globule size of the system was also determined.

2.5.5 Zeta potential measurement

Zeta potential for SEDDS was determined using Zetasizer HSA 3000 (Malvern instrument Ltd., Malvern, U.K.). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment.

2.5.6 In vitro drug release [11]

The quantitative in vitro release test was performed in 900 ml phosphate buffer (pH 5.8) using USP dissolution apparatus # 1, at 50 rpm. SEDDS formulation (Furosemide 20 mg) was placed in the basket to compare the release period with pure drug. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µ membrane filter, diluted suitably and analyzed by HPLC at 340 nm by using photo diode detector. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the beer lambert's equation (Y=10359*concentration - 4912.4).

2.5.7 Thermodynamic Stability studies

Furosemide SEDDS formulation was diluted with purified distilled water. The temperature stability of samples was checked at three different temperature ranges (2-8°C, room temperature, 40ºC) and observed for any evidences of phase separation, flocculation or precipitation.

2.5.8 Centrifugation

Furosemide SEDDS formulation was diluted with purified distilled water. Then emulsion was centrifuged at 1000 rpm for 15 minute and observed for any change in homogeneity of emulsion.

2.6. Formulation of Preliminary trial batches of Furosemide self-emulsifying tablet

Melt PEG 6000 it in to porcelain dish at 60ºC and add Liquid SEDDS in to the melt of PEG 6000. Mix it properly and add adsorbent in to the mixture of PEG 6000 and Liq. SEDDS. Where PEG 6000 is absent in formulation, mix liquid SEDDS directly with the adsorbent. After complete mixing, add diluents and other ingredients in to the mixture. Now add Magnesium stearate and talc in double cone blender for 10 minutes at 18 RPM. The prepared trial batches (F001 – F007) were evaluated for pre-compression parameters like angle of repose, hausner's ratio, Carr's index, Tapped density, bulk density. The prepared blend was compressed using tablet machine & evaluated for post compression parameters like hardness, friability, average weight, thickness and disintegrating time & in-vitro drug release.

2.8 Optimization of self-emulsifying tablets of Furosemide by using 3^2 full factorial designs [14]

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The amount of PEG 6000 (X_1) and concentration of Cross Povidone (X_2) were selected as independent variables.

2.9 Formulation of Furosemide self-emulsifying tablet

Factorial batches from FS1 to FS9 were prepared by varying the concentration of Poly ethylene glycol 6000 (50, 75, 100 mg) and disintegrating agent Cross povidone (2%, 4%, 6%).

2.10 Evaluation of Furosemide self-emulsifying tablet

2.10.1 Pre compression parameters

An accurately weighed amount of powder blend (15 g) was evaluated for different parameters of flow property like angle of repose, hausner's ratio, Carr's index, Tapped density, bulk density.

2.10.2 Post Compression parameters

Post compression parameters like hardness, friability, average weight, thickness and disintegrating time of tablets were evaluated by applying specific procedures.

2.10.3 In vitro drug release

In vitro drug release was determined for FS1 to FS9 batches. Concentration of Furosemide was determined by HPLC method. Dissolution study was carried in phosphate buffer (pH 5.8) for 1 hr as per USP 23.

2.11 Accelerated Stability Studies

Optimized batch was treated for one month accelerate stability study.

3. Result & Discussion

3.1 Solubility determination of Furosemide in oil, surfactant, co-surfactant and co-solvent

Furosemide showed the highest solubility in olive oil as compared to the other oils. So olive oil was selected as oil ingredient for the self-emulsifying system, shown in Figure 1. Similarly, the drug showed the highest solubility in Tween 80. So, it was selected as surfactant as shown in Figure 2. Capmul MCM C8 showed the highest solubility of drug and was selected as ingredient for the self-emulsifying system, shown in Figure 3. PEG 400 showed the highest solubility of drug as compared to the other co-solvents. So PEG 400 was selected as co-solvent for the self-emulsifying system, shown in figure 4. Capmul MCM C8 has properties of both of Oil as well as Co-surfactant. So, the comparison was carried out to select oil between olive oil and Capmul MCM C8.

3.2 Construction of phase diagrams

Different ratios were considered for optimization of concentration of Oil, Surfactants, Co-surfactants and Co-solvents. Highest self-emulsification region was obtained in Tween 80: PEG 400 (1:1 ratio). Selection of Tween 80: PEG 400 (1:1) ratio was better because amount of surfactants was also reduced in Self emulsifying formulation, shown in figure 5. During the preparation of ternary phase diagram, Olive oil was showing the problem of haziness within 1 hr storage of the emulsion. Capmul MCM C8 has properties of both of Oil as well as Co-surfactant. It doesn't show any problem of haziness during the storage. So, Capmul MCM C8 was taken as oil as well as co-surfactant and Olive oil was omitted from the final formulation.

3.3 Effect of drug on the phase diagram

Transparency of emulsion was checked visually. 125 mg of Furosemide could be safely incorporated in to optimized formulation without affecting other properties of SEDDS, results are shown in table 1.

3.4 Evaluation of Self emulsifying Formulation (SEF) of Furosemide

3.4.1 Macroscopic Evaluation

Formulation appeared uniform in color and transparency as well as there is no phase separation observed during normal storage (37 ±2°C) condition under preservation for the 2 months, shown in figure 6(A).

3.4.2 %Transmittance [8]

It was concluded that formulation was clear and transparent. It was not affected even with dilution, shown in table 2.

3.4.3 Globule size measurement [11]

Globule size was found to be 45.22 nm and it is in nano size range, shown in figure 7.

3.4.4 Zeta potential measurement [11]

Zeta potential was found to be -38.50mV, So formulation was prepared from the nonionic which show relatively neutral charge it means it will not affected by body membrane charge during absorption, shown in figure 8.

3.4.5 In vitro drug release [12]

In vitro drug release testing was carried out between Furosemide drug powder, Liquid SEF. Results of in vitro testing are given in table 3. Dissolution study was carried out for one hour as per USP 23. Comparison of drug release profile is given in fig.9. Powder drug Furosemide (20 mg) was slowly dissolved in dissolution media as compared to liquid SEF. Liquid SEF formulation showed excellent drug release profile as compared powder drug. Liquid SEF formulation gave favorable results compare to powder drug

and enhances our confidence for the further study on self-emulsifying tablet of furosemide.

3.4.6 Thermodynamic Stability studies [13]

Temperature stability was carried out at three different temperatures i.e. 2ºC to 8ºC, room temperature & 40°C. Precipitation, flocculation and phase separation was not observed in any case of temperature.

3.4.7 Centrifugation

Centrifugation study was carried out by subjecting the samples at 1000 rpm in centrifuge. Centrifugation study of liquid SEF showed no phase separation after 1 months.

3.5 Preliminary trial batches of furosemide self-emulsifying tablet

From the results of pre formulation study of trial batches F1 to F7, it was concluded that batch F7 has good pre-compression & post compression characteristics compared to other batches. The drug release of the F7 was also compared with that of pure drug & Liquid SEEDS, shown in Table 5. From over all evaluation study of self-emulsifying tablet, it was concluded that F7 batch containing PEG 6000, which was used for the solidification of liquid SEF was successful as compared to other batches & direction to enhance the solubility and bioavailability of Furosemide was correct.

3.6. Optimization of self-emulsifying tablets of Furosemide by using 3^2 full factorial designs

Full factorial design layout is shown in table 6. Formula for factorial batches (FS1 to FS9) is shown in table 7.

3.6.1. Pre-compression & Post compression parameters

It was observed that flow property of powder blend was enhanced by incorporation of PEG 6000 but in comparison to all nine batches, FS3 batch was found good. From the evaluation of post compression parameters it was concluded that appropriate hardness and friability could not be achieved in FS4 to FS9 batches. FS3 batch had less friability and hardness as compared to other batches.

3.6.2. In vitro drug release

Results of drug release profiles of factorial batches are given in table 8. Batches those contained highest percentage of disintegrating agent and lowest amount of PEG 6000 polymer were showing highest drug release. When PEG 6000 was cooled to a room temperature, bigger particles were formed. These bigger particles were producing difficulties in mixing as well as create interference for drug to come outside from the particles during the dissolution. Due to this reason last three batches FS7 to FS9 which contain high amount of PEG 6000 were showing less release in 1 hr. While the batches those contains less amount of PEG 6000 and high percentage of Cross povidone, FS1

to FS3, were showing complete release in 1 hr and this was better as compared to other batches, as shown in figure 11.
From the study of above evaluation parameters, it was observed that batch FS3 was good batch as compared to other batches. 50 mg of PEG 6000 and 6% of Cross povidone was present in FS1 batch.

3.7. Accelerated Stability Studies

Self-emulsifying tablets of Furosemide of batch FS3 was treated for accelerated stability study. Results of stability testing for temperature study are given in table 9. The results indicate formulation is stable and not affect significantly during this phase.

4. Conclusion

Furosemide is poorly water soluble drug. It shows high inter-intra subject variation. A Self emulsifying tablet formulation of Furosemide was formulated using Capmul MCM C8 as oil and co-surfactant, Tween 80 as surfactant, and PEG 400 as a co-solvent. Optimization of these ingredients in liquid Self Emulsifying Formulation (SEF) was done on the bases of solubility and pseudo ternary phase diagram. Prepared liquid SEF was treated for stability study and simultaneously liquid SEF was converted in to solid powder with the help of PEG 6000, micro crystalline cellulose PH 102. The solid powder with liquid SEF was compressed into tablet & prepared tablets were evaluated for different evaluation parameters. The formula for tablet was optimized by using 3^2 factorial design. From the results of pre-compression, post compression & in-vitro drug release data, batch F010 was selected as an optimized batch. The optimized batch F010 was treated for stability study for 1 month. The evaluation data indicates F010 batch was stable. The results from this study demonstrate the utility of SEDDS to enhance solubility and dissolution of poorly water soluble compounds like Furosemide which may result in improved therapeutic performance.

5. References

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Tables

Table 1 Effect of Drug on the Transparency of Emulsion

Amount of Furosemide	Visual inspection [Tween 80/PEG 400 (1:1)]
10 mg	Transparent
20 mg	Transparent
30 mg	Transparent
40 mg	Transparent
50 mg	Transparent
60 mg	Transparent
75mg	Transparent
100mg	Transparent
125mg	Transparent
150mg	Turbid

Table 2. % Transmittance of Liquid SEF Upon Dilution With Water

Batch	Transmittance (%) ± S.D (n=3)	
	50 times dilution with water	100 times dilution with water
Liquid SEF	99.42 ± 0.009	99.67 ± 0.009

Table 3 In vitro Drug Release From Liquid SEF and Powder of Furosemide

Time (min)	Powder of Furosemide	Liquid SEF
	% CDR	% CDR
0	0	0
10	5.70	31.89
20	15.3	59.32
30	27.2	94.16
40	39.7	100.2
50	52.1	100.1
60	62.8	100.2

Table 4 Formulation Table of Trial Batches F1 to F7

Trial	F1	F2	F3	F4	F5	F6	F7
Ingredients	Quantity per each tablet (mg)						
Liquid SEDDS	250	250	250	145	145	145	145
MCC (Avicel PH 102)	115	150	240	200	208	208	399
Poly ethylene glycol 6000	-	-	-	-	-	-	200
Maltodextrin	-	-	-	367	-	-	-
Dicalcium phosphate	-	-	-	-	367	-	-
Spray dried lactose	-	-	-	-	-	367	-
Cross povidone	15(3%)	18(3%)	28(4%)	32(4%)	32(4%)	32(4%)	32(4%)
Sodium starch glycolate	-	-	-	24(3%)	24(3%)	24(3%)	-
Silicon dioxide	105	164	161	16	-	-	-
Talc (1%)	5	6	7	-	8	8	8
Magnesium Stearate (2%)	10	12	14	16	16	16	16
Tablet Weight	500	600	700	800	800	800	800

Table 5 In-vitro Release of Trial Batch F7, Liquid SEF and Powder Drug

Time (min.)	Powder of Furosemide	Liq. SEF	F007
	% CDR	% CDR	% CDR
0	0	0	0
10	5.70	31.89	15.39
20	15.3	59.32	27.31
30	27.2	94.16	43.17
40	39.7	100.2	60.85
50	52.1	100.1	72.11
60	62.8	100.2	86.11

Table 6 Optimization of Formulation by 3^2 Factorial Design

3^2 Full Factorial Design Layout		
Batch No.	Independent variables	
	X_1	X_2
FS1	-1	-1
FS2	-1	0
FS3	-1	1
FS4	0	-1
FS5	0	0
FS6	0	1
FS7	1	-1
FS8	1	0
FS9	1	1
Concentration of Independent variable		
Level	Amount of PEG 6000	Concentration of Cross Povidone
-1	50 mg	2%
0	75 mg	4%
1	100 mg	6%

Table 7 Formulation Table of Factorial Batches

Formula of Factorial batches									
Trial	**FS1**	**FS2**	**FS3**	**FS4**	**FS5**	**FS6**	**FS7**	**FS8**	**FS9**
Ingredients	**All the weights are in mg**								
Drug + Liq. SEF	145	145	145	145	145	145	145	145	145
PEG 6000	50	50	50	75	75	75	100	100	100
Avicel PH 102	510	495	480	485	470	455	460	445	430
Cross Povidone	15 (2%)	30 (4%)	45 (6%)	15 (2%)	30 (4%)	45 (6%)	15 (2%)	30 (4%)	45 (6%)
Magnesium stearate (3%)	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Talc (1%)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total (mg)	**750**	**750**	**750**	**750**	**750**	**750**	**750**	**750**	**750**

Table 8 In-Vitro Release Study of Factorial Batches

In-vitro release study of Factorial batches									
Phosphate buffer (5.8), 900ml, USP - II (Paddle) Apparatus, 50 RPM									
Time (hrs.)	**%CDR**								
	FS1	**FS2**	**FS3**	**FS4**	**FS5**	**FS6**	**FS7**	**FS8**	**FS9**
0	0	0	0	0	0	0	0	0	0
10	21.5	23.9	25.3	20.8	22.1	23.7	17.8	19.7	18.4
20	37.6	41.1	47.1	39.5	37.7	40.3	33.4	37.8	40.1
30	55.8	59.0	76.0	53.1	51.9	55.2	57.3	57.1	53.9
40	69.6	74.9	87.5	67.3	72.3	77.2	73.8	70.8	69.7
50	83.1	90.3	101.3	82.0	86.8	89.6	82.6	80.1	84.6
60	95.7	97.3	101.2	91.3	92.7	96.6	90.4	89.8	91.4

Table 9 In-vitro release study of stability batch

In-vitro release study of stability batch		
Time (min)	**Phosphate buffer (5.8), 900ml, USP - II (Paddle) Apparatus, 50 RPM**	
	% CDR	
	Initial	**After 1 month**
0	0	0
10	23.3	22.76
20	45.1	43.31
30	73.89	72.98
40	84.63	87.54
50	99.11	98.72
60	100.4	99.47
Similarity Factor F2 = 91.68		

Figures:

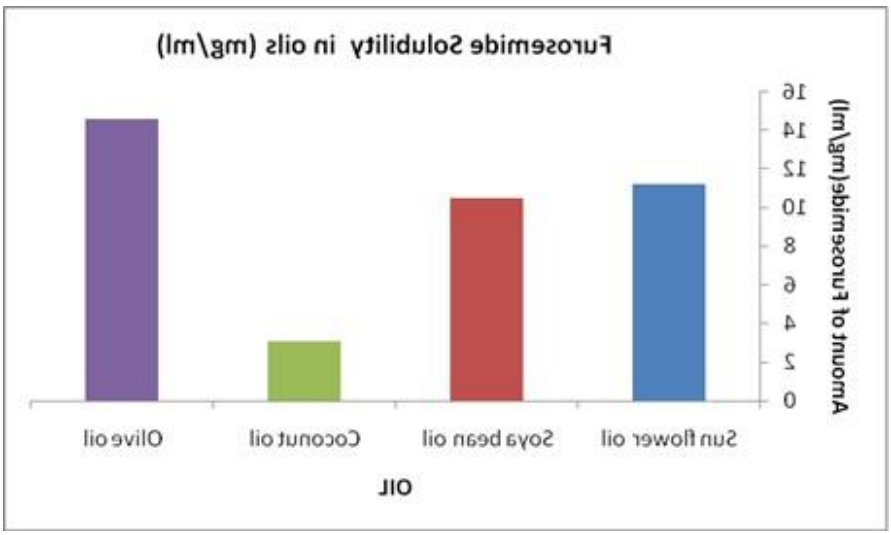


Figure 1 Solubility of Furosemide in Oils

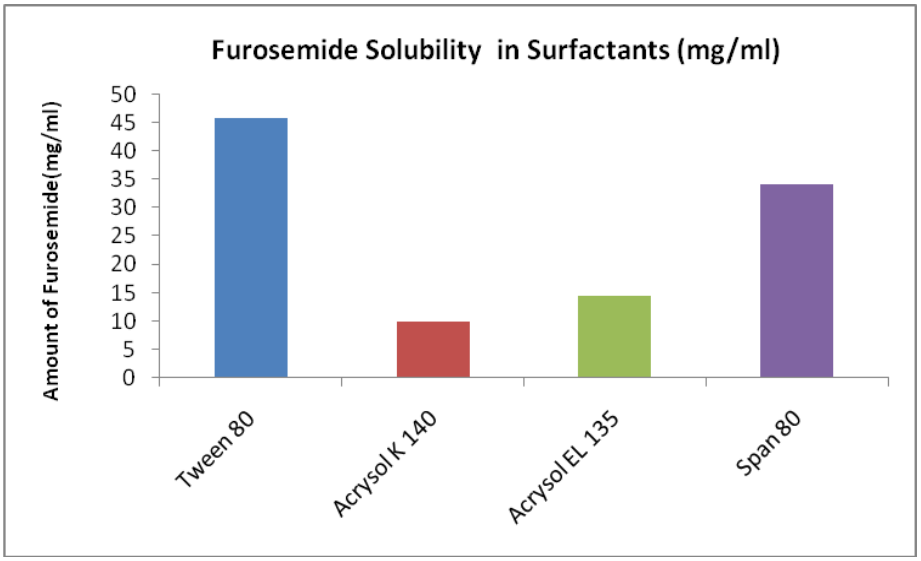


Figure 2 Solubility of Furosemide in surfactants

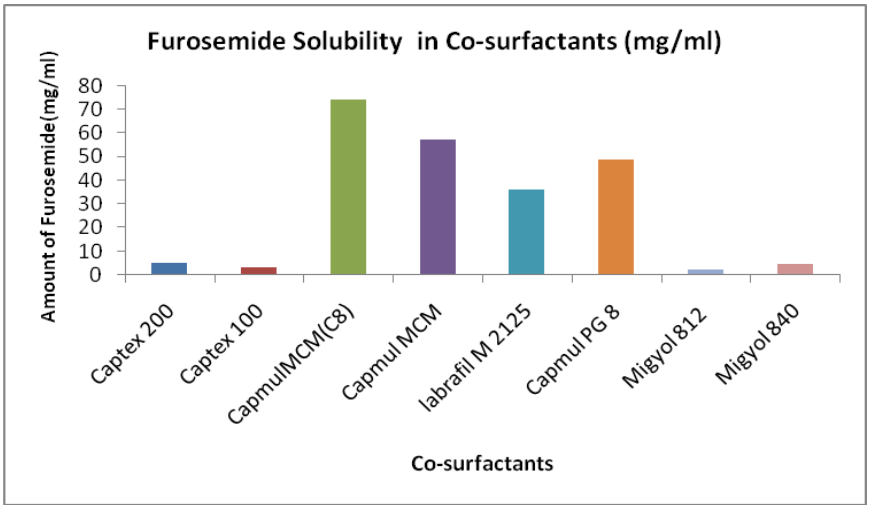


Figure 3 Solubility of Furosemide in co-surfactants

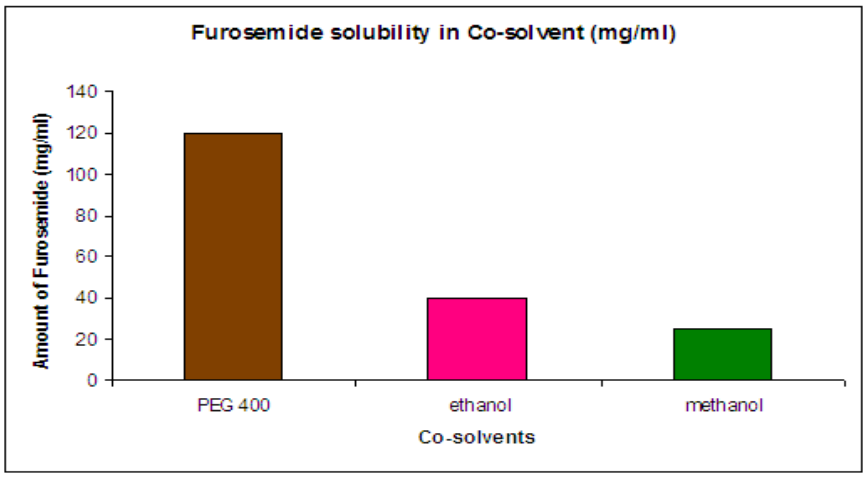
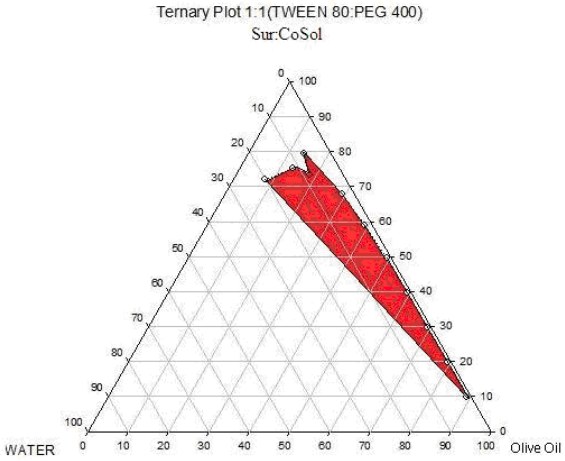
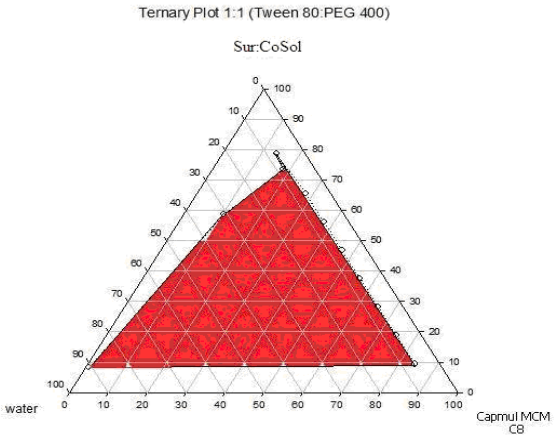


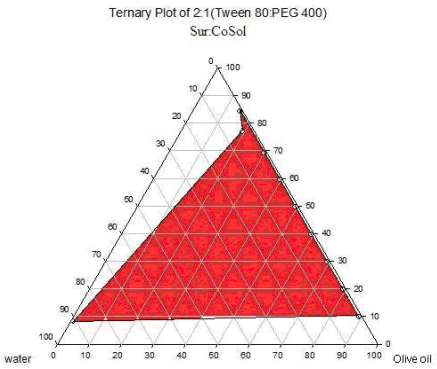
Figure 4 Solubility of Furosemide in co-solvents



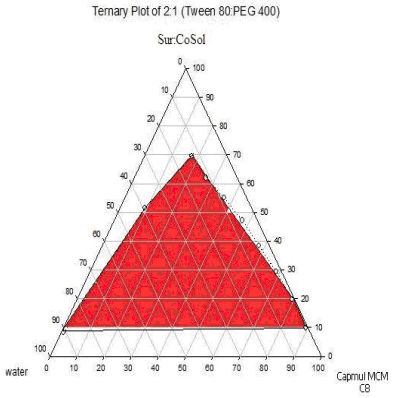
Tween 80:PEG 400 (1:1i.e. 9 part)
Oil (Olive oil) (1 part)Oil



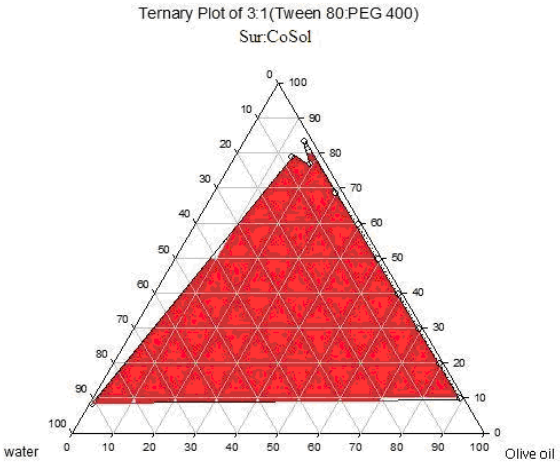
Tween 80:PEG 400 (1:1 i.e. 9 parts)
(Capmul MCM C8) (1 part)



Tween 80: PEG 400 (2:1 i.e. 9 part)
Oil (Olive oil) (1 part)

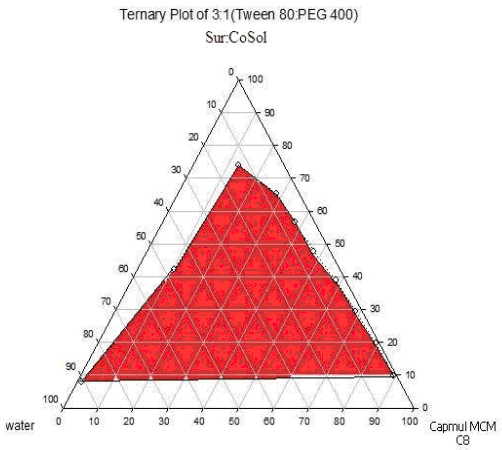


Tween 80: PEG 400(2:1 i.e. 9 parts)
Oil (Capmul MCM C8) (1 part)



Tween 80: PEG 400 (3:1 i.e. 9 part)

Oil (Olive oil) (1 part)



Tween 80: PEG 400 (3:1 i.e. 9 parts)

Oil (Capmul MCM C8) (1 part)

Figure 5 Construction of phase diagrams

(A) **(B)**

Figure 6 Emulsion after dilution A) Transparent B) Turbid

Results

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm): 45.22	**Peak 1:**	45.22	98.2	9.020
PdI: 0.198	**Peak 2:**	4537	1.8	856.9
Intercept: 0.921	**Peak 3:**	0.000	0.0	0.000

Result quality : Good

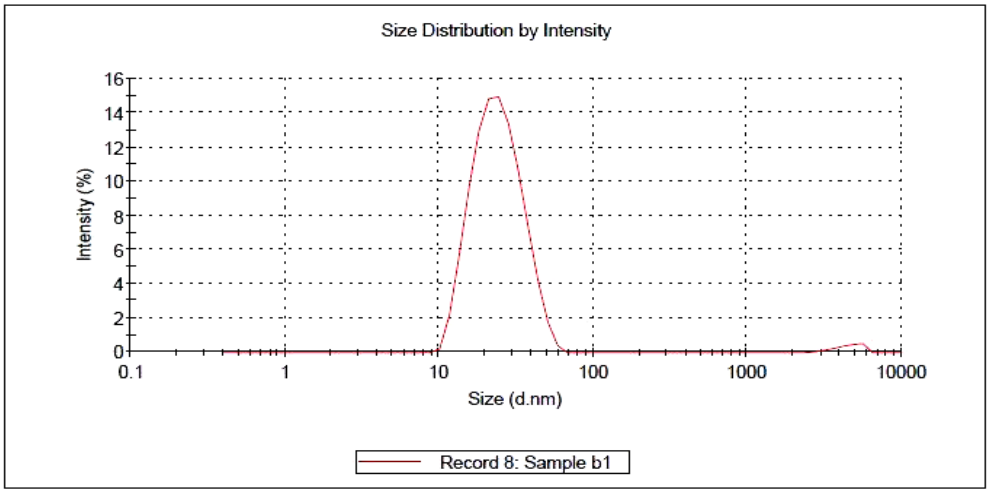


Figure 7 Particle size measurement

Results

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -38.50	**Peak 1:**	-38.50	97.7	7.28
Zeta Deviation (mV): 8.16	**Peak 2:**	19.0	2.3	3.47
Conductivity (mS/cm): 0.0821	**Peak 3:**	0.00	0.0	0.00

Result quality : Good

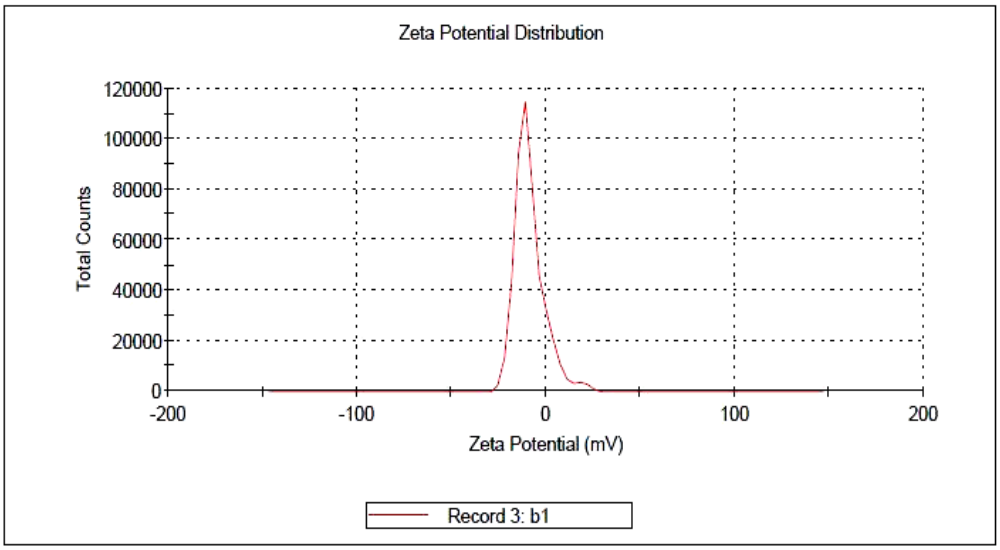


Figure 8 Zeta potential measurement

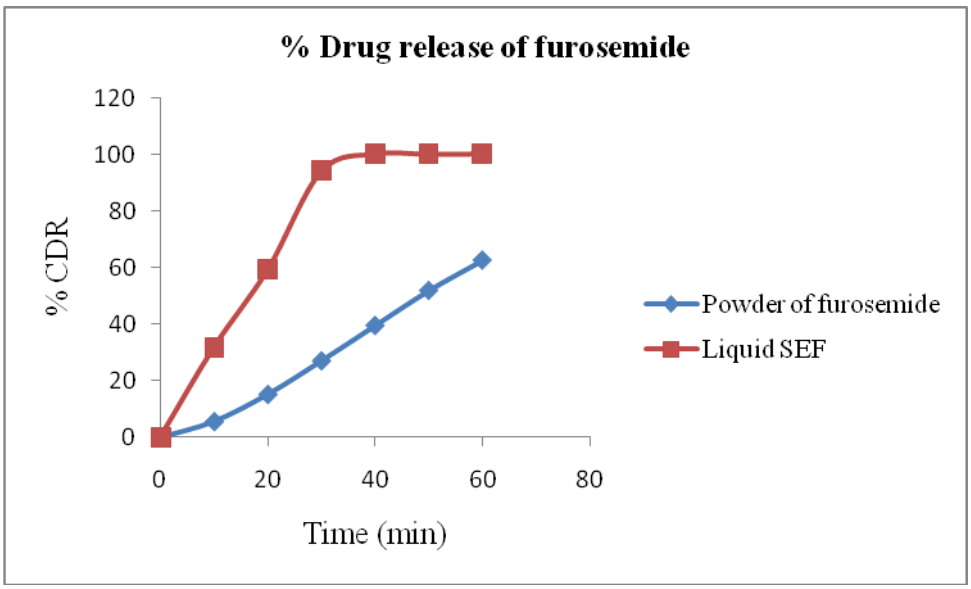


Figure 9 Comparison drug release profile of Furosemide powder, liquid self-emulsion

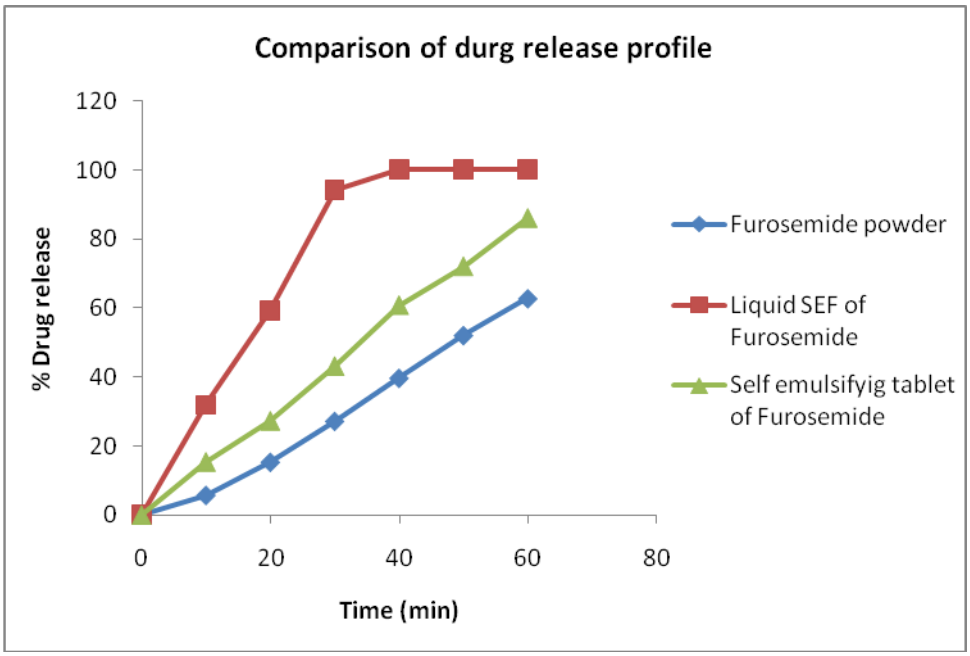


Figure 10 Comparison drug release profile of Furosemide powder, liquid self-emulsifying of Furosemide and F7

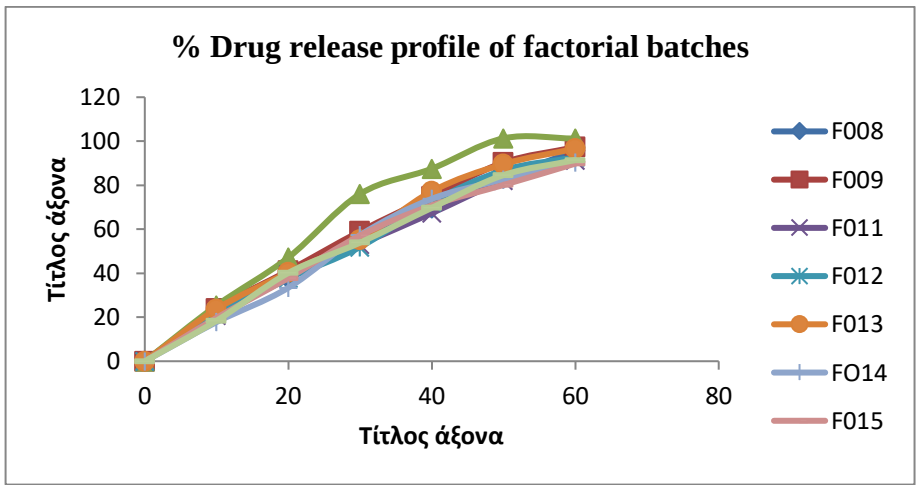


Figure 11 %Drug release profile of factorial batches