

## FORMULATION AND EVALUATION OF FLOATING TABLETS OF FUROSEMIDE



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### ABSTRACT

Floating tablet of Furosemide (F) were prepared by direct compression technique. Furosemide was chosen as model drug because it is slightly soluble in water and poorly absorb from lower intestine. PEG-6000 is used as complexing agent for increasing solubility of Furosemide in water. Hydroxypropylmethylcellulose, sodium bicarbonate and carbapole were used as Matrixing agent gas generating agent and floating enhancers respectively. The tablets were evaluated for *in-vitro* buoyancy and dissolution studies Tablets were evaluated for physical characteristic viz. hardness, floating capacity, thickness, swelling index, and weight variation. Further, tablets were evaluated for in vitro release characteristic for 8 hrs. The data of *in-vitro* dissolution study shows that the zero order plots were found to be fairly linear as indicated by their high regression value ( $R^2=0.9772$  to  $0.9911$ ). To confirm the exact mechanism of drug release from different formulation, the data was fitted to Korsmeyer Peppas equation. Regression values were from 0.9862 to 0.9963 which indicates linearity.

**Keywords:** Furosemide, Floating tablet, PEG 6000, HPMC

## INTRODUCTION AND MATERIALS & METHODS

### INTRODUCTION

Furosemide (FUR) is poorly water-soluble drug and its bioavailability is very low from its crystalline form. For poorly water-soluble, low permeable the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. The FUR exhibits highly erratic and very low dissolution profile in gastric and intestinal fluids. This is possibly due to its very high hydrophobic character. The rate of absorption and/or the extent of bioavailability for such insoluble hydrophobic drug are controlled by the rate of dissolution in the gastrointestinal fluids. Hence, number of attempts were made to increase the rate of dissolution of such poorly water soluble hydrophobic drugs, to increase their effectiveness and simultaneously reduce their doses and hence the toxic effects.

Solid dispersions traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. Many substances can be employed as carriers to prepare solid dispersions. Among the popular carriers used in the formation of solid dispersions is polyethylene glycol, polyvinylpyrrolidone, HPMC, Poloxamer, Span, Tween, Eudragit RS, Eudragit RS etc. These polymers are often employed as a vehicle due to its low toxicity, low melting point, rapid solidification rate, high aqueous solubility, & availability in various molecular weights, economic cost and physiological tolerance.

Furosemide is absorbed mostly in the stomach and upper small intestine possibly due to its weak acidic properties (pKa 3.9) and is characterized by a short half life of 1.3 to 2 hr. The bioavailability of FUR after oral administration is about 60% and dose quite variable (20–60mg) owing to the presence of an absorption window in the upper intestinal tract. Diuresis and natriuresis of FUR depends upon its active tubular secretion because. FUR acts directly on renal tubule. Rapid exposure of FUR to its site of action elicits high peak natriuretic and diuretic effects. The desirable therapy is to maintain a continuous diuresis to improve therapeutic benefit, which requires slow release of FUR from the formulation close to the absorption window.

In this study furosemide was selected as a model drug, whose absorption is limited to the upper part of the GIT. Therefore, prolongation of residence time of a dosage form in the stomach or the upper small intestine, close to the absorption window, would be effective in enhancing the absorption compared with that of a nonfloating dosage form and at the same time decrease the side effects. Furosemide (FR), a potent loop diuretic drug, widely used in patients with oedema of various origins. FR is absorbed mostly in the stomach and upper small intestine possibly due to its weak acidic properties (pKa 3.9) and is characterized by a short half life of  $1.3 \pm 0.8$  h. The bioavailability of FR after oral administration is about 60% and is quite variable (20–60%) owing to the presence of an absorption window in the upper intestinal tract. It acts by inhibiting the Na-K-2Cl symporter in the thick ascending loop of Henle. It also has inhibitory activity on carbonic anhydrase. Diuresis and natriuresis of FR depends upon its active tubular secretion because FR acts directly on renal tubule. Rapid exposure of FR to its site of action elicits high peak natriuretic and diuretic effects. As a consequence, there is a rapid and massive activation of compensatory responses, including activation of the sympathetic nervous system and the renin angiotensin–aldosterone system. This results in development of resistance to the effect of FR due to sodium and water retention in nephron.

The desirable therapy is to maintain a continuous diuresis to improve therapeutic benefit, which requires slow release of FR from the formulation close to the absorption window.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

## **MATERIALS AND METHODS**

Furosemide (FR) was obtained from AMRI India Pvt. Ltd., Waluj, Aurangabad. HPMC K4M, HPMC K100M gift sample from colorcon asia pvt. Ltd., Goa, India, Carbopol was supplied by Loba Chemie, Mumbai, India. Sodium bicarbonate, Citric acid, were supplied by S.D.Fine chemicals Ltd. Mumbai. Microcrystalline cellulose was gifted by Alkem Pharmaceuticals Ltd., Mumbai. All other reagents and solvents used were of analytical grade.

### **Preparation of Solid Dispersion**

#### **Preparation of solid dispersion by physical mixture:**

Physical mixtures of Furosemide with PEG-6000 in different weight ratios (1:1, 1:2, 1:4, 1:6) were prepared by thoroughly mixing appropriate amounts of Furosemide and PEG-6000 in a mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through a 100 # sieve and stored in a dessicator.

#### **Preparation of solid dispersion by melting method:**

Solid dispersions of Furosemide with PEG-6000 in different weight ratios were prepared by melting method. PEG-6000 was melted at 60°C and Furosemide was added to the melted carrier and stirred continuously to form a homogenous mixture. The resulting homogenous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in desiccators for 24 h. Subsequently, the dispersion was ground in a mortar and sieved through 100 # and stored in a dessicator.

#### **Formulation of Floating Tablet of Furosemide:**

Various ratios of solid dispersions of furosemide with PEG-6000 were evaluated for its dissolution rate in 1.2 pH buffer and out of them the best ratio was selected for preparation of floating tablet of furosemide. Tablets were prepared by direct compression method by using HPMC K4M, HPMC K15M and Carbopol as polymers.

Quantity of HPMC K4M, HPMC K15M and Carbopol for each formulation was calculated which is as shown in table I. Accurate quantity of drug and polymers were weighed according to formula shown in table I and mixed well in a mortar and pestle. Sodium bicarbonate, citric acid was added as a gas generating agent and HPMC and Carbopol as a swelling and matrix forming agent, then compressed on a ten-station rotary tablet machine using 12 mm round-shaped, flat punches to obtain tablets.

### **Evaluation parameters of solid dispersion and floating tablets:**

#### **Characterization of Solid Dispersion of Furosemide with PEG-6000**

#### **Analysis of drug content in solid dispersions:**

The amount of furosemide in physical mixture and solid dispersion was determined using UV/VIS spectroscopy. Accurately weighed physical mixture and solid dispersion equivalent to 40 mg of furosemide was transferred to a 100 ml volumetric flask and diluted upto 100 ml with 0.1 N NaOH and sonicated for 30 min for complete solubilization of drug. From this stock 1 ml of solution was withdrawn and diluted upto 100 ml with 0.1 N NaOH and absorbance was noted at 274 nm.

### **DSC, PXRD and FTIR analysis**

Evaluations of Furosemide with PEG-6000 performed by DSC, PXRD and FTIR spectroscopy.

### **In-vitro dissolution study of prepared Solid Dispersion in 1.2 pH buffer**

Dissolution studies of pure furosemide and all other prepared solid dispersion (SD) and physical mixture (PM) in the ratio 1:1, 1:2, 1:4, 1:6 were performed using USP XXIII apparatus type 2 (paddle) for 2 hr. Samples of pure furosemide, PM and SD equivalent to 40 mg of the drug were added to the dissolution medium (pH 1.2), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, fixed amount of samples were withdrawn and analyzed at 274 nm using UV spectrophotometer.

### **Evaluation of furosemide floating tablets**

#### **Physical evaluation, drug content and floating properties**

The formulated floating tablets of furosemide were evaluated for average weight, hardness, thickness, friability, floating lag time and drug content.

#### **Floating Evaluation**

The formulated furosemide floating tablets were evaluated for floating lag time, total floating time, and swelling index.

**In-vitro Drug release:** In-vitro drug release studies of the prepared floating tablets were conducted for a period of 12 hrs using USP XXIII type II apparatus at  $37 \pm 0.5^\circ\text{C}$  and at 50 rpm speed at pH 1.2. After withdrawing, the samples were analyzed by a UV spectrophotometer at 274 nm using dissolution medium in reference cell. The total amount of drug release was calculated.

## **RESULT AND DISCUSSION:**

### **Analysis of drug content in physical mixture and solid dispersion:**

The drug content in physical mixtures and solid dispersions are shown in table II.

### **Differential Scanning Colorimetry (DSC) Analysis:**

DSC spectra of solid dispersion of FUR with PEG-6000 prepared in 1:6 ratio exhibited a sharp endothermic peak at  $63.17^\circ\text{C}$  and complete absence of any peak at  $220^\circ\text{C}$  which indicates that FUR is getting complexed and present as an amorphous form.

### **Powder X-ray Diffraction (PXRD) Analysis**

1:6 PM showed presence of characteristic diffraction peaks of both FUR and PEG-6000 indicating that FUR was present as a crystalline material in the physical mixture.

1:6 SD showed presence of most of the diffraction peaks due to PEG-6000 while peaks corresponding to FUR were absent which indicate that FUR was present in the amorphous state in the solid dispersion

### **Infrared (IR) Spectroscopic Analysis:**

The spectra of 1:6 PM is the addition spectra of FUR and PEG-6000 which contains characteristic peaks due to both drug and PEG-6000, where as in case of FTIR spectra of 1:6 SD most of characteristic peaks due to PEG-6000 were present but the characteristic peaks due to FUR were absent which indicates the complexation/interaction of FUR molecule with the polymer matrix.

### **In-vitro dissolution study of prepared Solid Dispersion in 1.2 pH buffer**

Dissolution studies of pure Furosemide and all other prepared systems were carried out in 1.2 pH buffer media for 2 hr. The data obtained from the dissolution study is shown in table III and Fig. IV.

Prepared floating tablets of furosemide were evaluated for various parameters such as thickness, hardness, friability, weight variation, drug content etc. The results are shown in table IV.

### Evaluation of floating properties

Prepared floating tablets of furosemide were evaluated for its floating behaviour such as floating lag time, total floating time and swelling index. The results are shown in table V.

### In-vitro dissolution study of furosemide floating tablet

In-vitro drug release studies of the prepared floating tablets were conducted for a period of 12 hrs using USP XXIII type II apparatus at  $37 \pm 0.5^\circ\text{C}$ . Results are shown in table VI and fig. V.

### CONCLUSION:

Initially physical mixtures and solid dispersions of furosemide with PEG-6000 was prepared in 1:1, 1:2, 1:4, 1:6 ratios to improve its aqueous solubility. FTIR, DSC, and X-ray diffraction spectroscopy were used to characterize the samples of solid dispersions and physical mixture. The results of its in-vitro dissolution study shows that solid dispersion of 1:6 ratio dissolves 99.41% drug as compared to plain furosemide which dissolves only 28.43% within 2 hr. The solubility enhancement by PEG-6000 may be due to its surface tension lowering effect of polymer on the dissolution medium and enhancing effect on the wettability and dispersibility of the drug in the dissolution media.

The tablets were prepared by using various polymers such as HPMC K4M, HPMC K15M and Carbopol. Formulations were evaluated for floating behaviour, which showed floating lag time in the range of 126-223 sec, and total floating time in the range of 20-24 hr. *In-vitro* drug release study was performed in simulated gastric fluid (1.2 pH), which shows that all formulations follow zero order drug release pattern and non-fickian as a drug release mechanism. The optimized batches (F3 and F7) shows drug release in a controlled manner for 12 hr.

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## TABLES AND FIGURES:

**Table I: Composition of Floating Tablet of Furosemide**

Ingredients In mg	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Solid Dispersion (1:6 ratio) equivalent to 40 mg of Furosemide	280	280	280	280	280	280	280	280
HPMC K4 M	70	--	93	--	105	--	140	--
HPMC K15 M	--	70	--	93	--	105	--	140
Carbopol 934	70	70	47	47	105	105	70	70
Sodium bicarbonate	45	45	45	45	65	65	65	65
Citric acid	30	30	30	30	40	40	40	40
Avicel PH 102	50	50	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight	550	550	550	550	650	650	650	650

HPMC – Hydroxypropyl methyl cellulose

**Table II: Drug content in physical mixture and solid dispersion of final ratio 1:6**

Sr. No.	Physical mixture/ Solid dispersion ratio	Drug content (%)
1	1:6 PM	99.1 ± 0.41
2	1:6 SD	99.3 ± 0.45

All values are mean ± SD, (n = 3)

**Table III: In-vitro dissolution of solid dispersion and physical mixture**

Time (min)	% Cumulative drug dissolved		
	Furosemide	1:6 SD	1:6 PM
0	0	0	0
5	7.45±0.015	58.41±0.015	13.03±0.013
15	13.31±0.011	79.25±0.024	19.03±0.025
30	18.23±0.031	84.34±0.031	24.79±0.015
60	23.12±0.021	92.32±0.015	29.03±0.012
120	28.43±0.010	99.41±0.023	34.21±0.032

### Evaluation of Floating Tablet

**Table IV: Evaluation of tablet parameters**

Formulation Code	Thickness (mm)	Hardness (Kg/cm <sup>2</sup> )	Friability (%)	Weight variation (mg)	Drug content (%)
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F1	4.5±0.011	4.3±0.4	0.34±0.07	552.4±1.3	99.86±0.15
F2	4.4±0.014	4.5±0.3	0.41±0.01	551.8±1.8	99.45±0.08
F3	4.5±0.013	4.1±0.6	0.38±0.05	554.3±0.8	99.96±0.18
F4	4.5±0.012	4.3±0.4	0.36±0.02	551.1±1.4	100.01±0.04
F5	5.5±0.015	4.8±0.1	0.45±0.06	653.1±1.2	98.90±1.05
F6	5.6±0.012	5.1±0.3	0.51±0.03	656.3±0.2	100.02±0.01
F7	5.6±0.014	4.2±0.4	0.49±0.03	654.7±0.5	99.94±0.92
F8	5.5±0.016	4.9±0.5	0.53±0.02	652.5±1.4	99.97±0.84

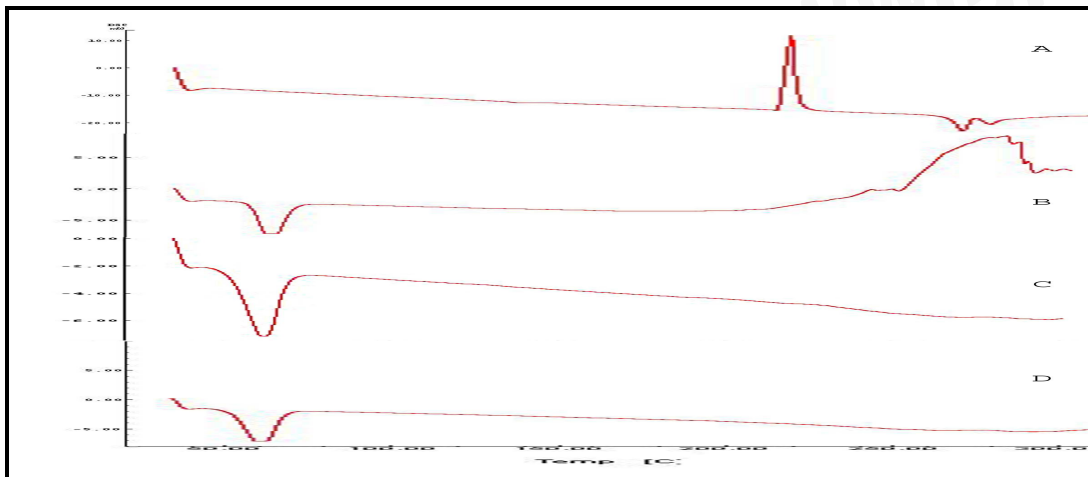
All values are mean ± SD (n=3).

**Table V: Evaluation of floating properties**

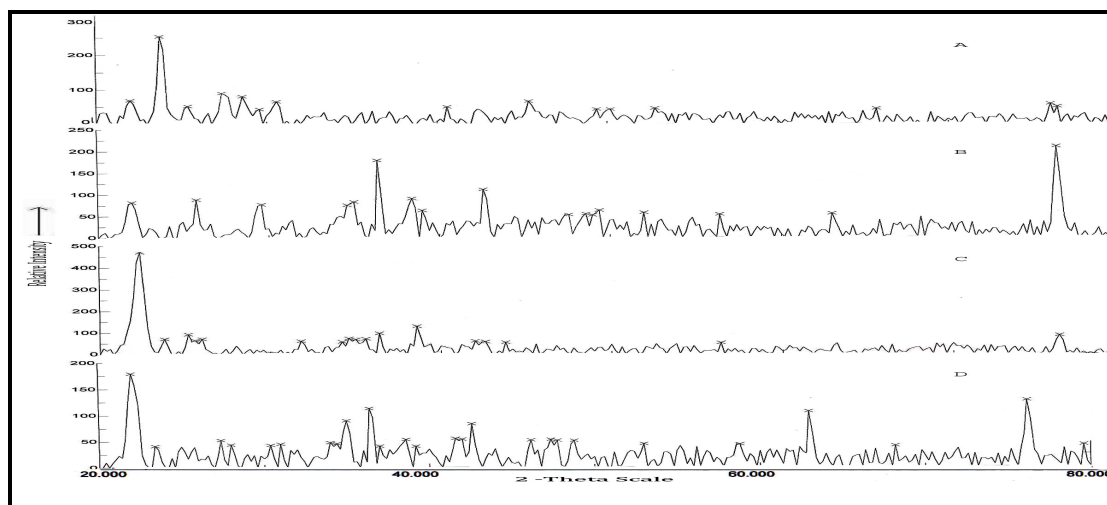
Formulation Code	Floating Lag Time (sec)	Total Floating Time (hr.)	Swelling Index (%)
F1	126	22	220.86
F2	182	24	218.00
F3	163	21	200.82
F4	158	20	239.73
F5	221	24	256.29
F6	223	21	324.06
F7	207	24	297.68
F8	230	22	264.30

**Table VI: In-vitro dissolution study of furosemide floating tablet.**

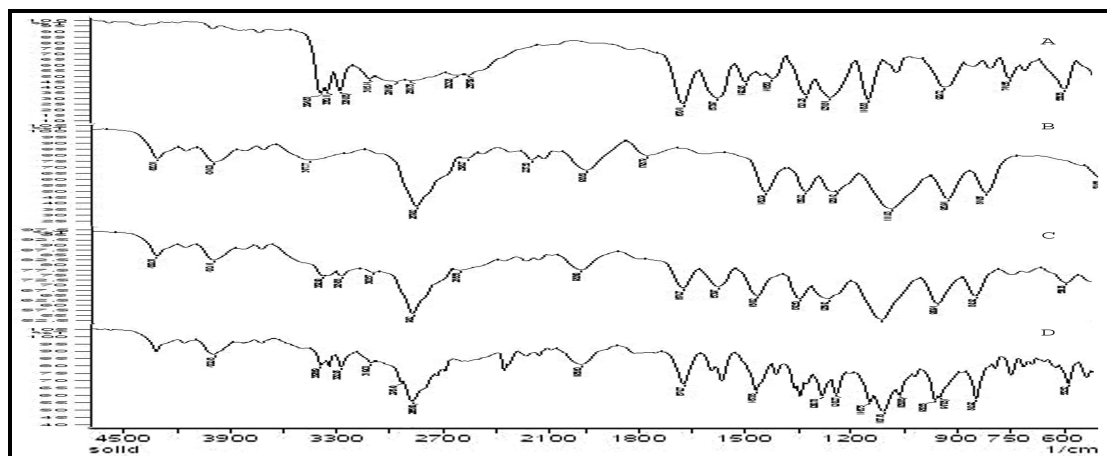
Time (min)	% Cumulative drug release (mean ± SD)	
	Batch F3	Batch F7
0	0	0
30	9.38±0.87	8.84±0.14
60	13.46±0.25	13.30±1.49
120	20.69±0.76	20.44±1.59
240	33.93±1.32	33.47±2.55
360	54.87±0.13	59.62±1.02
480	77.67±1.35	75.43±2.95
600	93.84±1.03	89.34±1.40
720	98.86±1.13	97.37±1.95



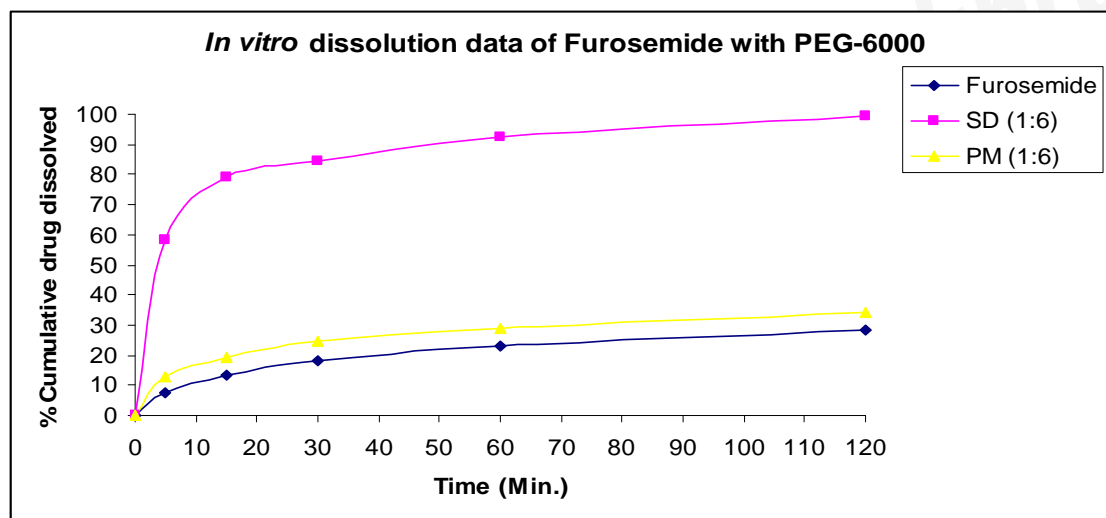
**Fig. I:** DSC Spectra of Furosemide (A), PEG-6000 (B), 1:6 Solid Dispersion (C), 1:6 Physical Mixture (D).



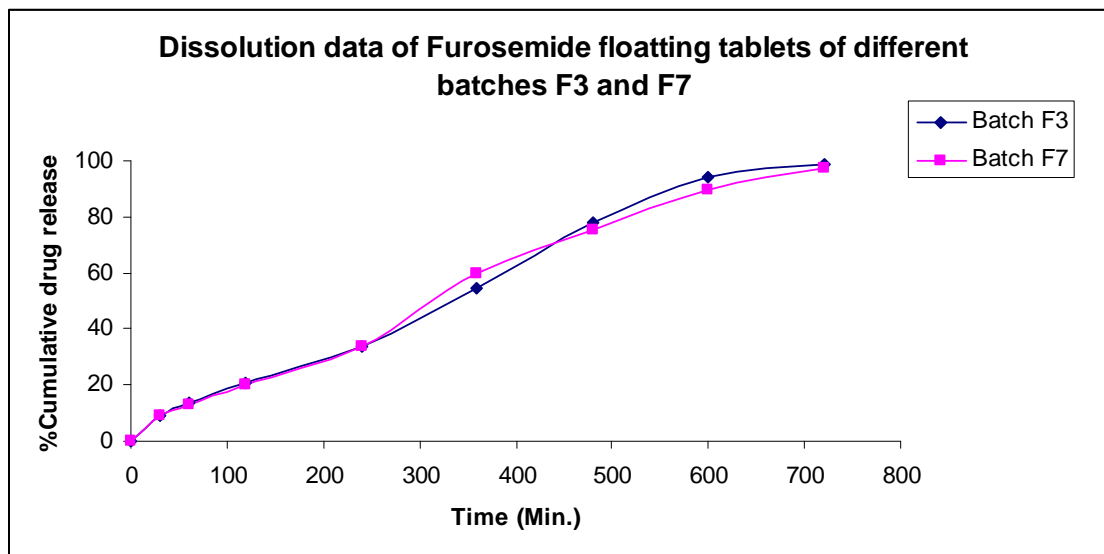
**Fig. II:** Powder X-ray Diffraction Spectra of Furosemide (A), PEG-6000 (B), 1:6 Solid Dispersion (C), 1:6 Physical Mixture (D).



**Fig. III:** FTIR Spectra of Furosemide (A), PEG-6000 (B), 1:6 Solid Dispersion (C), 1:6 Physical Mixture (D)



**Fig. IV:** In-vitro dissolution of solid dispersion and physical mixture



**Fig. V: In-vitro dissolution of furosemide floating tablets of different batches**

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