WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 11, 696-719. Research Article ISSN 2277– 7105

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION CHARACTERISTICS OF FUROSEMIDE BY SOLID DISPERSION TECHNIQUE

D. Christopher Vimalson*[1], S. Anbazhagan[2], L. Gokul[1], S. Idhayadharani[1], S. Ranjith[1], J. Sabarinathan[1] and R. Surya[1]

[1]Department of Pharmaceutics, Surya School of Pharmacy, Vikravandi, TN, India.
[2]Department of Pharmaceutical Chemistry, Surya School of Pharmacy, Vikravandi, TN, India.

Article Received on
24 July 2019,
Revised on 14 August 2019,
Accepted on 04 Sep. 2019,
DOI: 10.20959/wjpr201911-15816

***Corresponding Author**
D. Christopher Vimalson
Department of Pharmaceutics, Surya School of Pharmacy, Vikravandi, TN, India.

ABSTRACT

Furosemide is practically insoluble in gastric fluid and having high permeability through stomach was selected. The present study was to improve the solubility and dissolution of Furosemide by increasing the solubility in water by solid dispersion methods like fusion and solvent evaporation method using hydrophilic polymers poly ethylene glycol 4000 and Povidone K 32. Solid dispersion techniques are predominantly promising for enhancing the oral absorption and bioavailability of the BCS Class II drugs. Compatibility studies for drug and excipients was done by FTIR. Solid dispersions of Furosemide was formulated using polar ploymers like PEG 4000 and PVP K32 either by fusion method or solvent evaporation method in four ratios like 1:1, 1:2, 1:3, 1:4. The prepared solid dispersions were characterized for Solubility, Drug Content, Flow Properties: Angle of Repose, Carr's Index and Average Particle Size, Physical Properties: Bulk density, tapped density and Hausner's ratio. Particle Morphology by using scanning electron microscopy and In Vitro drug release studies. Solid dispersions of FE prepared by fusion and solvent evaporation methods employing PEG 4000 and PVP K32 i.e. SDFE3 and SDFE7 were exhibited greater solubility and dissolution rate when compared to pure drugs. The micrometrics parameters and flowability observed to be excellent flow characteristics and fair Hasuner's index. Based on the *in vitro* drug release profiles of respective solid dispersions and their capsules it is concluded that solubility and dissolution rate of FE is increased by using the PEG 4000 and PVP K32 polymers. On

comparing with the PEG 4000 and PVP K32 prepared by fusion and solvent evaporation for Furosemide, SDFE3 is having high solubility and dissolution rate when compared with SDFE7.

KEYWORDS: Furosemide, PEG 4000, Povidone K32, Solid Dispersion.

INTRODUCTION

The oral route of administration of drug is the most widespread and well known route of delivery due to convenience, ease of administration and patient compliance. From the dosage forms drug is released and dissolves in the surrounding gastrointestinal fluid to form a solution for easy absorption.[1]

Therefore there are two areas in the pharmaceutical research field that spotlight on enhancing the oral bioavailability of active pharmaceutical agents which comprises of improving the solubility and dissolution rate of poorly water soluble drugs. Biopharmaceutics classification system (BCS) is used to correlate the *in vivo* bioavailability and *in vitro* drug dissolution that is being based on the solubility of drug and the gastro intestinal permeability which are the essential parameters for limiting the rate and extent of absorption of the drugs.[2-4]

Solid Dispersion

The terminology of solid dispersion refers to a category of solid products consisting of at least two unusual components, commonly a hydrophilic matrix and a hydrophobic drug in which the matrix could be either crystalline or amorphous. The drug can be mixed in molecular level, in amorphous particles or in crystalline particle based on their arrangement in molecular level. The advancement in management of diseases has been apparent within expansion in development of new drugs. 40% anticipated of these drugs have poor water solubility.[5]

Selection of Ideal candidates for solid dispersion

Numerous literatures were reported on the technology of solid dispersion implicated in drugs which are poorly soluble in water and are permeable extremely to the biological membranes as with these drugs dissolution is the rate hindering step to the absorption of drugs. Therefore, the theory has mentioned the rate of absorption *in vivo* will be concomitantly speeded up with an enhancement in the dissolution rate of the drug.[6] BCS class II drugs are the drugs with low solubility in aqueous media and high permeability through the membrane[7] and

therefore, solid dispersion techniques are predominantly promising for enhancing the oral absorption and bioavailability of the BCS Class II drugs.

The need for the present study is to improve the solubility and dissolution of Furosemide by increasing the solubility in water by solid dispersion methods like fusion and solvent evaporation method using hydrophilic polymers poly ethylene glycol 4000 and Povidone K 32 which entraps the drug within and thereby the solubility of the drug is increased.

MATERIALS AND METHODS

Materials

Furosemide, Polymers such as PEG 4000, PVP K32 are used. All reagents and solvent were of analytical grade and were used as received without further treatment.

Methods

Preparation of Pharmaceutical buffers[8]

pH 1.2 Simulated gastric fluid (SGF)

In 7 ml of 0.2 M hydrochloric acid 0.2 gm of sodium chloride and 3.2 gm of pepsin were dissolved final volume was made up to 1000 ml.

pH 7.4 Simulated intestinal fluid (SIF)

6.8 gm of potassium phosphate was dissolved in 50 ml of water and mixed with 190 ml of 0.2 N sodium hydroxide, 10 gm of pancreatin dissolved in 500 ml of water and resultant solution was adjusted to pH 7.5 ± 0.1 with either 0.2 N sodium hydroxide or 0.2 N hydrochloric acid and made up to 1000 ml.

Preparation of 0.2M Potassium Dihydrogen Phosphate

In 1000 ml volumetric flask, 27.22 gm of potassium dihydrogen phosphate was dissolved in distilled water and finally volume was made up to 1000 ml with distilled water.

Preparation of 0.2M Sodium Hydroxide

In 1000 ml volumetric flask, 8 gm of sodium hydroxide was dissolved in distilled water and finally volume was made up to 1000 ml with distilled water.

Calibration Curve of Furosemide[9]

Preparation of stock solution

Standard stock solution of Furosemide in simulated gastric fluid (pH 1.2)

50 mg of Furosemide was weighed accurately and dissolved in 100 ml of methanol and final volume was made up to 100 ml with 0.1N Hydrochloric acid in 100 ml volumetric flask. From this stock solution 0.05, 0.10, 0.15, 0.20 and 0.25 ml was withdrawn and final volume was made up to 50 ml by 0.1N Hydrochloric acid which gives a concentration of 10, 20, 30, 40, and 50 µg/ml.

Calibration curve of Furosemide in simulated gastric fluid (pH 1.2)

From standard stock solution, a series of dilutions were prepared using 0.1N Hydrochloric acid. The absorbance of these solutions was measured against blank of 0.1N Hydrochloric acid at 274 nm for Furosemide.

Standard stock solution of Furosemide in simulated intestinal fluid (pH 7.4)

50 mg of Furosemide was weighed and dissolved in 50 ml of methanol and the final volume was made up to 100 ml with phosphate buffer pH 7.4 in 100 ml volumetric flask. From this stock solution 0.05, 0.10, 0.15, 0.20 and 0.25 ml was withdrawn and the final volume was made up to 100 ml by phosphate buffer pH 7.4 which gives a concentration of 10, 20, 30, 40, and 50 µg/ml.

Calibration curve of Furosemide in simulated intestinal fluid (pH 7.4)

From standard stock solution, a series of dilutions were prepared using phosphate buffer pH 7.4. The absorbance of these solutions was measured against blank of phosphate buffer pH 7.4 at 274 nm for Furosemide.

Preformulation Studies

Drug–Excipient compatibility

In order to confirm no interaction happened between the drug substancesand polymers, characterization of drugs and polymers and physical mixture of respective drug: polymers were carried out by using Fourier Transform Infrared Spectroscopy (FTIR).[8]

Fourier Transform Infrared Spectroscopy (FTIR)

The test samples were dispersed in potassium bromate powder and analyzed. FTIR spectrophotometer type FTIR 8400S Shimadzu, Japan was used to obtain FTIR spectra by

diffuse reflectance. FTIR spectra were utilized to study compatibility between the drug and polymer. The positions of FTIR bands of important functional groups of drugs were identified and were cross checked with FTIR spectra of drug with excipients in 1:1ratio.[8]

Preparation of Furosemide Solid Dispersions

Fusion Method

Solid dispersion of Furosemide was prepared by using the conventional fusion method. PEG 4000 was molten by heating at 60°C. To this molten mass an accurately weighed quantity of Furosemide was mixed along continuous stirring with a glass rod till it dissolves completely. Solid dispersions of Furosemide (SDFE) were prepared at different ratios between drug and polymer. The drug: polymer ratios were as following at 1:1, 1:2, 1:3 and 1:4 w/w ratio of FE to PEG 4000. Later the molten mass was allowed to solidify at room temperature. The product obtained was kept in Desiccators for one day. The solidified mass was pulverized with the help of glass mortar and pestle andsievedin sieve number 80 to obtain a uniform particle size. Different solid dispersions of FE were coded as SDFE1, SDFE2, SDFE3 and SDFE4. The compositions are provided in the below Table No.1.[8]

Table 1: Composition of Different Solid Dispersions of Furosemide prepared by Fusion Method.

	SDFE1	**SDFE2**	**SDFE3**	**SDFE4**
Drug (mg)	80	80	80	80
PEG 4000 (mg)	80	160	240	320
Total (mg)	160	240	320	400
Ratio (Drug: Polymer)	**1:1**	**1:2**	**1:3**	**1:4**

Solvent Evaporation Method

Preparation of solid dispersion of Furosemide by solvent evaporation method involves two stages; first stage involved in the preparation of a solution consistboth the hydrophobic drug and hydrophilic polymer, whereassecond stage solvent evaporation and solid dispersion formation. To dissolve both hydrophilic polymer and drug a methanol was used. Both the drug and the polymershowed effective solubility in methanol. During the entireexperiment process drug:polymer ratio was maintained in a range of 1:1, 1:2, 1:3 and 1:4. In four different china dish 5 gm of FE was placed and dissolved in 15 ml of methanol separately and stirred for 1 hour and thirty minutes. To this four different methanol solution, PVP K32 was added. The mixtures were evaporated at 24º C ± 2ºC for one day. Later, solids obtained were dried in a vacuum oven for 20 hours at 50º C ± 5ºC, then subjected to pulverization and

sieved at sieve number 12. The granules were stored in a tightly closed container and kept in a desiccator. Different solid dispersions of FE were coded as SDFE5, SDFE6, SDFE7 and SDFE8. The detailed formulae are given in the Table No.2.[10]

Table 2: Composition of Different Solid Dispersions of Furosemide prepared by Solvent Evaporation Method.

	SDFE5	SDFE6	SDFE7	SDFE8
Drug (mg)	80	80	80	80
PVP K32 (mg)	80	160	240	320
Total (mg)	160	240	320	400
Ratio (Drug: Polymer)	**1:1**	**1:2**	**1:3**	**1:4**

Evaluation of Solid Dispersions

Percentage of Yield

The raw materials, amount of drug, either PVP K32 or PEG 4000 and other process parameters, which are going to determine and affects the percentage of yield during the preparation of solid dispersion. The yield was computed by weighing the solid dispersions loaded with drug and finding out percentage of yield against the weight of raw materials, i.e., weight of polymers and drugs used. The formula to calculate the percentage of yield is given as follow as:

$$\text{Percentage of Yield (\%)} = \frac{\text{Weight of Solid Dispersion}}{\text{Weight of polymer and drug in formulation}} \times 100$$

Drug Content

Solid dispersions equivalent to 20 mg of furosemide was weighed and transferred to a 50 ml volumetric flask, separately from SDFE1 to SDFE8. SDFEs were dissolved in 10 ml of methanol. The final volume was made up to 50ml with either pH 1.2 buffer and filtered through 0.45 µm membrane filters.5 ml of the stock solution was pipetted out and further diluted to 50 ml with pH 1.2 buffer for the solid dispersion formulations from SDFE1 to SDFE8 to give a final concentration of 20 µg/ml solution. Drug content was estimated by spectrophotometer from the absorbance obtained at 274 nm for the pH 1.2 buffers.The drug content was calculated from the absorbance obtained with the help of the calibration curve.[11]

Solubility Studies for Solid Dispersion of Furosemide

In 3 different conical flask 500 mg of SDFE was weighed and transferred. 50 ml of water, pH 1.2 SGF and pH 7.4 SIF media were added to individual conical flask and closed well. All the

three flasks were sonicated for one hour and finally filtered by using 0.45 Micron Whatman Filter Papers. The clear solutions were appropriately diluted with respective dissolution media and absorbance values were noted at 274 nm by UV spectrophotometer for SGF and SIF respectively.[12]

Micromeriticsstudies of solid dispersions

Different micrometrics parameters like tapped density, bulk density, flow property, Carr's Index and Hausner ratio were used to evaluate the solid dispersions.

Bulk Density

The bulk density for solid dispersions was assessed by dividing powder volume over the mass of the powder cm^3. 5 gm of solid dispersionswas poured in 2ml graduated cylinder. The volume taken by the powder was calculated to determine bulk density. Bulk density was calculate by equation:[13-14]

$B_d = W/ V_p$

Where B_d = Bulk density; W = Weight of the sample (g); V_p = Volume of solid dispersions (cm^3).

Tapped Density

Tapped density was estimated by dividing bulk volume over the mass of the powder cm^3. 5 gm of solid dispersions was transferred to 10 ml measuring cylinder. At the beginning, powder volume was noted at initial and measuring cylinder was tapped mechanically for 50 times, Later noted the volume after 50 taps. The tapped density of all solid dispersion formulations was computed by dividing weight of powders in gram at the end tapped volume in cm^3. Tapped density was computed by using equation: [13-14]

$T_d = W/ V_p$

Where T_d = Tapped density; W = Weight of the sample (g);

V_p = Volume of solid dispersions (cm^3)

Carr's Index

It is a dimensionless parameter, which provides similar degree as the angle of repose to predict the flow property of a granules/ powder**.** By using compressibility index and Hausner's ratio flow characteristics of powder's were studied. The compressibility index is used as alternative measures of shape and size, bulk-density, surface area and moisture

contents of material since all these properties could affect the compressibility index. The Carr's index is the ratio between differences among the tapped density and bulk density is to tapped density and the product with 100 will provide percentage of compressibility index. The Carr's index is computed using the formula as follows and the association between compressibility and flow property are shown in the following Table No.9. The averages of three readings were used to compute the compressibility index from each of the solid dispersion formulations.[13-14]

$CI = (T_d - B_d)/ T_d \times 100$

Where CI = Compressibility Index; T_d = Tapped density; B_d = Bulk density

Hausner's ratio

By using the following equation Hausner ratio was calculated for the solid dispersion.[13-14]

$HR = T_d/ B_d$

Where, HR = Hausner ratio; T_d = Tapped density; B_d = Bulk density

Angle of Repose

Angle of repose was used to estimate the flowability of powders through a fixed funnel method. A funnel with the end of the stem cut perpendicular to its axis of symmetry kept arranged over a graph paper of height which was placed on a flat horizontal surface. Solid dispersions of respective drugs were poured separately over the funnel till the tip of the conical part of the funnel reaches the end of the funnel. The height of the powder (h) and radius (r) were later measured with standard scale. The angle of repose (θ) for samples wascomputed using the following formula.

Angle of Repose $(\theta) = \tan^{-1}(h/r)$

The measurement was done in triplicate and mean of the measurement was used to compute the angle of repose for each of the formulation.[15]

Scanning Electron Microscopy (SEM)

The characteristics like morphology and surface of the prepared solid dispersions were measured by using scanning electron microscope (Joel-LV-5600, USA), at suitable magnification at room temperature. The photographs were observed for morphological characteristics and to confirm the drugs were loaded in the respective carriers.[15-16]

In vitro drug release studies

The *in vitro* release of drug profile for the formulated solid dispersions were done in USP XXIII basket type dissolution tester, TDT-08L, with an auto sampler consisting of 900 ml of pH 1.2 buffer for 3 hours. Capsules filled with solid dispersions were placed in dissolution media with constant stirring at 100 rpm and 37° ± 0.5°C temperature was maintained at bath. An aliquot of 10 ml of dissolution media were removed at an interval of every 30 minutes and fresh dissolution media was replaced immediately after sampling. The removed samples were analyzed for drug content by UV Visible spectroscopy.[15]

RESULTS AND DISCUSSION

Production Yield for Solid Dispersions of Furosemide

The values of the production yield of the 8 formulae of FE solid dispersions prior to sieve was ranged from 99.71%, 99.21%, 99.33%, 99.79%, 99.69%, 99.23%, 99.38% and 99.76% for SDFE1, SDFE2, SDFE3, SDFE4, SDFE5, SDFE6, SDFE7 and SDFE8 respectively of solid dispersions prepared with Furosemide. The results obtained were satisfactory and reproducible on repeating the preparations. The data are represented in the TableNo.3.

Table 3: Production Yields of the Prepared FE Solid Dispersions.

Formula Code	Production yield (%)	Formula Code	Production yield (%)
Prepared by Fusion Method (using PEG 4000 as polymer)		Prepared by Solvent Evaporation Method (using PVP K32 as polymer)	
SDFE1	99.71	SDFE5	99.69
SDFE2	99.21	SDFE6	99.23
SDFE3	99.33	SDFE7	99.38
SDFE4	99.79	SDFE8	99.76

Calibration Curve

Standard Curve of Furosemide

Furosemide solution showed UV λ_{max} at 274 nm and its spectra is shown in Fig. No.1, and Fig.No.2 respectively. An analytical method was developed. The developed method obeyed the Beer-Lambert's law at the concentration rangedbetween10 and 50 µg/ ml with a correlation coefficient of 0.996 and 0.999 for Furosemide in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) respectively and showed good linearity in the selected concentration range.

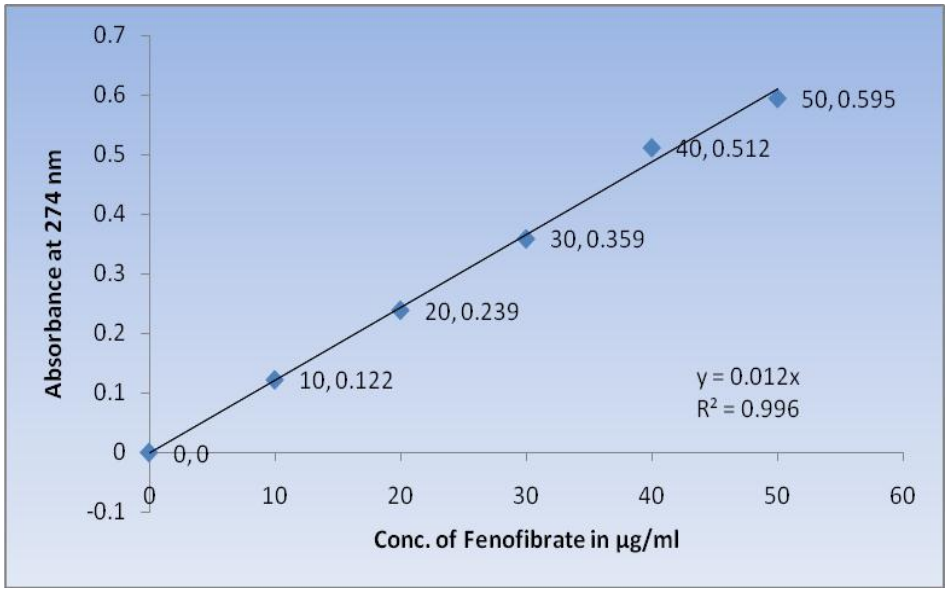

Fig. 1: Calibration Curve for Furosemidein simulated gastric fluid (pH 1.2).

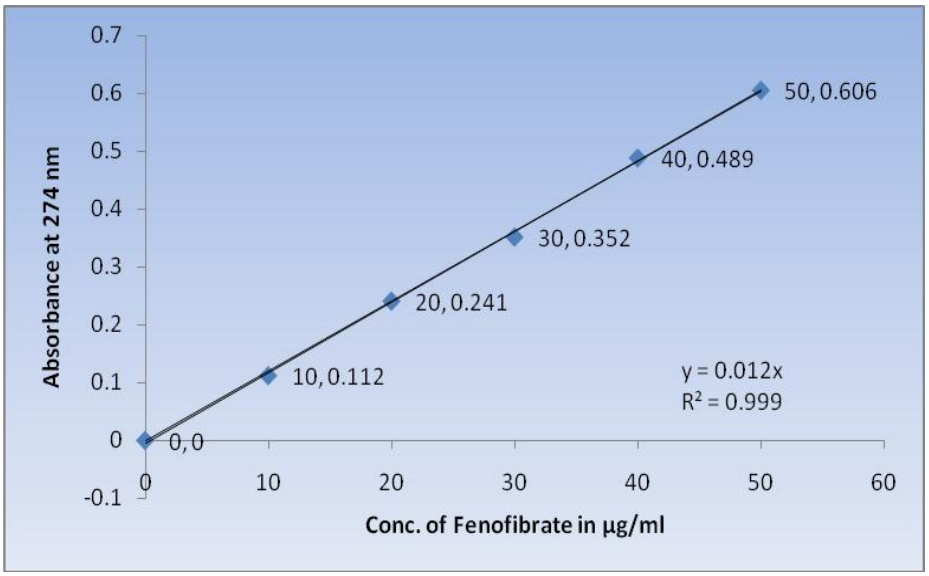

Fig. 2: Calibration Curve for Furosemidein simulated intestinal fluid (pH 7.4).

Preformulation Study [Compatibility Study]

FTIR Spectra for Pure Furosemide and its Solid Dispersion

FTIR spectrum for drug and physical mixtures of Furosemide: PVP K32 and Furosemide: PEG 4000 was determined by KBr pellet method. Both the samples were mixed with KBr pellets by applying hydrostatic press at 5 tons pressure for 5 minutes and spectra were obtained and provided in the Fig. No. 3 to Fig.No.8 shows FTIR spectra of the drug and Fig. No. 3 shows the standard drug of furosemide, Fig. No.4 shows the Spectrum for Pure Drug Furosemide, Fig. No.5: shows the Spectrum for PEG 4000 Polymer, Fig. No.6 shows the Spectrum for Povidone K32 Polymer, Fig. No.7 shows the Spectrum for Pure Drug

Furosemide and PEG 4000 Polymer and Fig. No.8 shows the Spectrum for Pure Drug Furosemide and Povidone K32 Polymer.

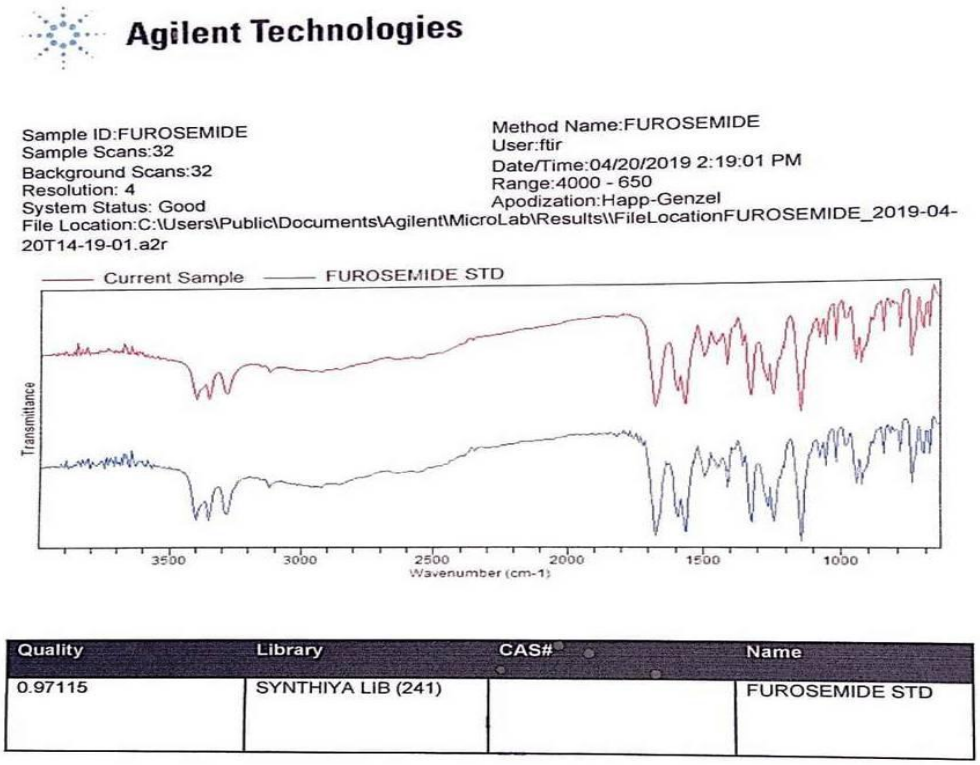

Fig. 3: FTIR Spectrum for Standard Drug Furosemide.

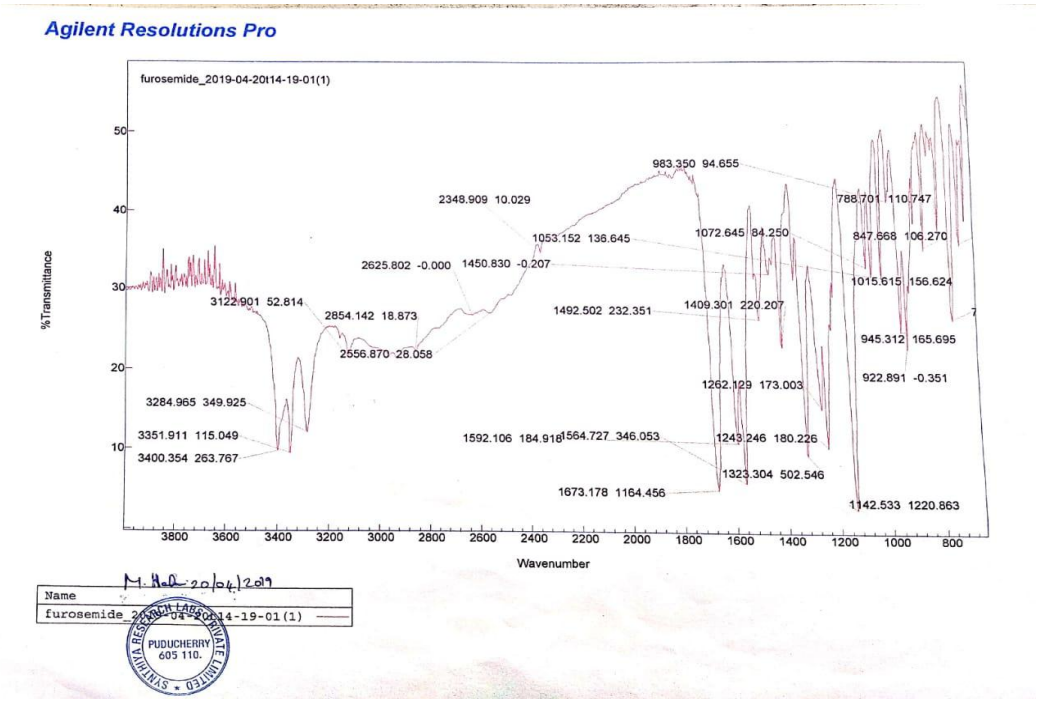

Fig. 4: FTIR Spectrum for Pure Drug Furosemide.

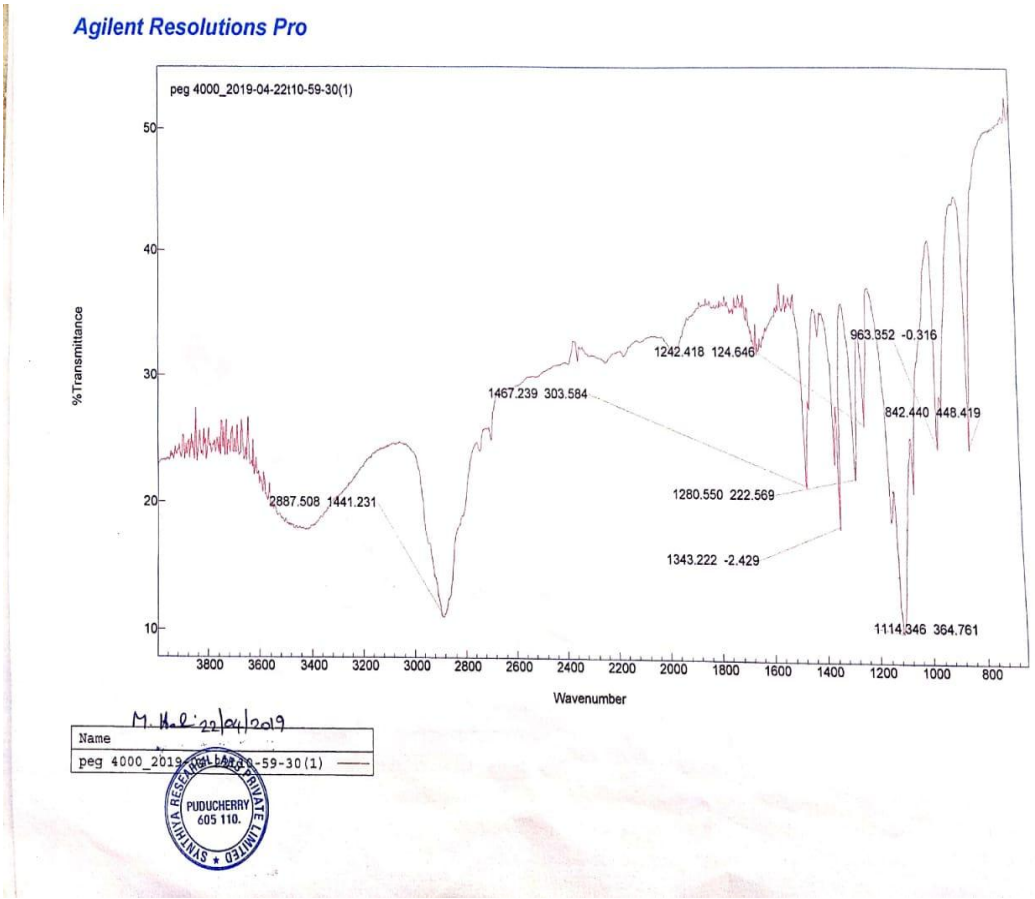

Fig. 5: FTIR Spectrum for PEG 4000 Polymer.

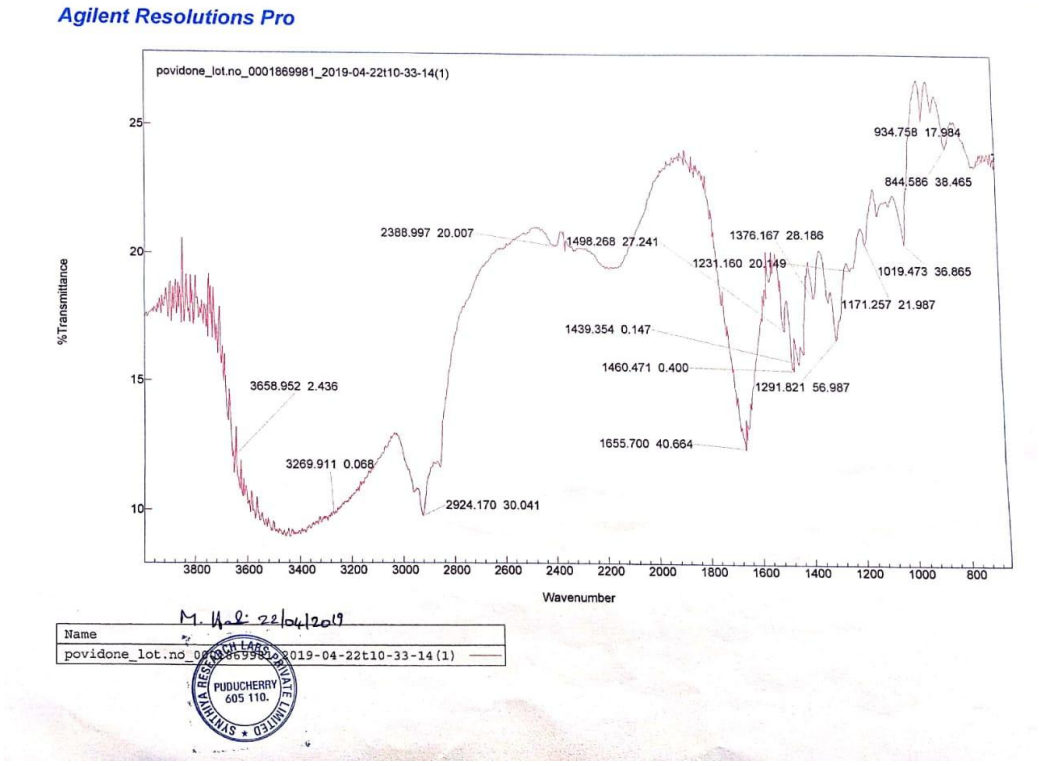

Fig. 6: FTIR Spectrum for Povidone K32 Polymer.

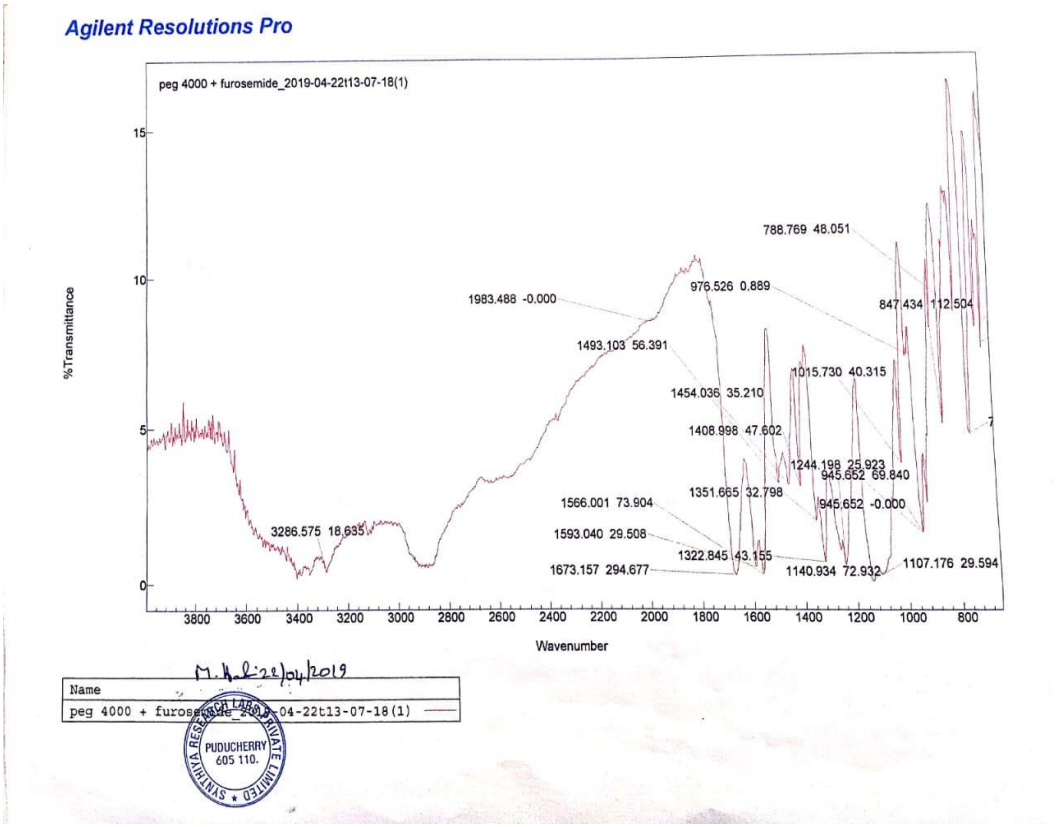

Fig. 7: FTIR Spectrum for Pure Drug Furosemide and PEG 4000 Polymer.

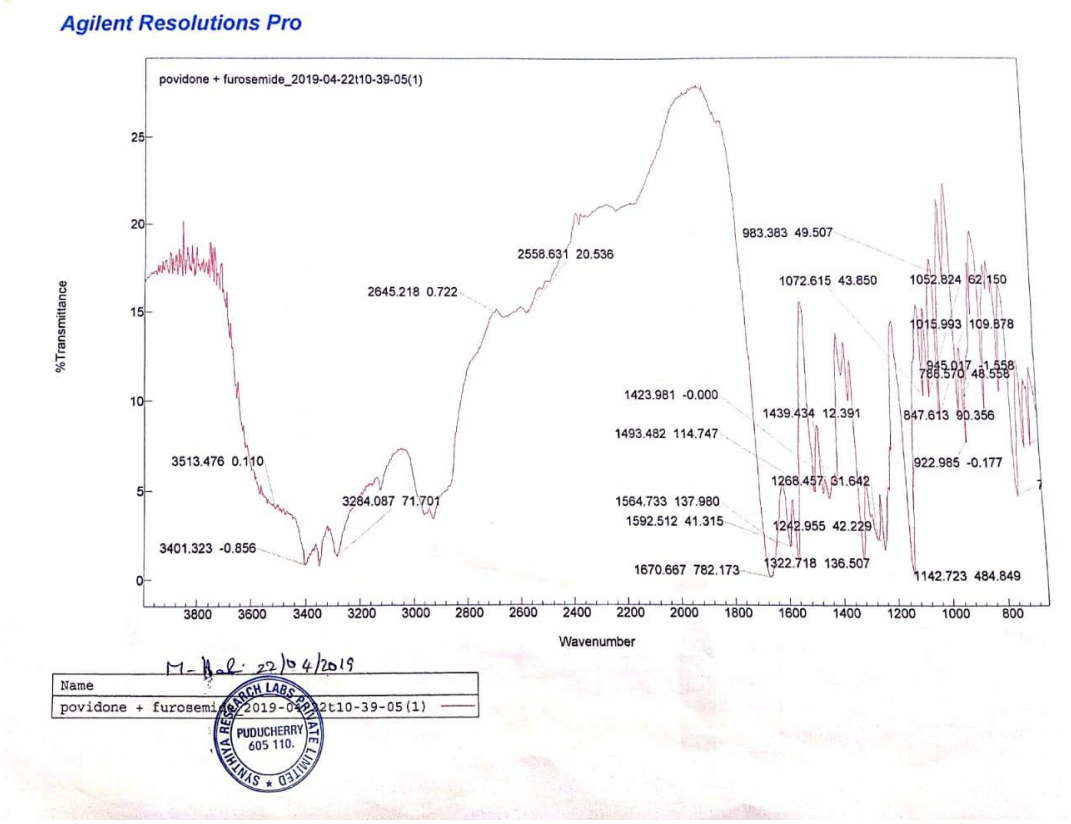

Fig. 8: FTIR Spectrum for Pure Drug Furosemide and Povidone K32 Polymer.

IR spectra of pure drug Furosemide and with carriers like PEG 4000 as well as PVPK32 and have only characteristic peaks of the compounds. These studies showed that the drug is compatible between PEG 4000 and PVP K32. From the provided spectrum (from Fig. No. 3. to 8) there were no significant alterations in the chemical integrity and functional group peaks for the pure drugs Furosemide and its physical mixture in all the IR-spectra.

Phase Solubility Studies

The results of solubility studies for the formulated solid dispersions of Furosemide in purified water, simulated gastric fluid at pH 1.2 and simulated intestinal fluid at pH 7.4 is given in Table No 4. The solubility of pure drug of Furosemide, SDFE1, SDFE2, SDFE3, SDFE4, SDFE5, SDFE6, SDFE7 and SDFE8 was found to be 1.67µg/ml, 19.22µg/ml, 36.2µg/ml, 37.82µg/ml, 21.52µg/ml, 18.62µg/ml, 36.84µg/ml, 37.56µg/ml and 21.88µg/ml in purified water respectively, whereas in SGF for pure drug of Furosemide, SDFE1, SDFE2, SDFE3, SDFE4, SDFE5, SDFE6, SDFE7 and SDFE8 was found to be 1.725µg/ml, 20.11µg/ml, 37.77µg/ml, 38.44µg/ml, 22.76µg/ml, 22.36µg/ml, 37.25µg/ml, 39.44µg/ml and 22.47µg/ml respectively while in SIF for pure drug of Furosemide, SDFE1, SDFE2, SDFE3, SDFE4, SDFE5, SDFE6, SDFE7 and SDFE8 was found to be 2.044µg/ml, 23.54µg/ml, 38.87µg/ml, 39.99µg/ml, 25.89µg/ml, 24.09µg/ml, 39.06µg/ml, 40.24µg/ml and 24.35µg/ml respectively.

Table 4: Solubility Studies of Solid Dispersions of Furosemidein Different Media.

	Amount of Drug Soluble (µg/ml)		
	Purified water	**SGF @ pH 1.2**	**SIF @ pH 7.4**
Pure Drug	1.673	1.725	2.044
SDFE1	19.22	20.11	23.54
SDFE2	36.25	37.77	38.87
SDFE3	37.82	38.44	39.99
SDFE4	21.52	22.76	25.89
SDFE5	18.62	22.36	24.09
SDFE6	36.84	37.25	39.06
SDFE7	37.56	39.44	40.24
SDFE8	21.88	22.47	24.35

The solubility studies data for pure drugs and formulated at purified water, simulated gastric medium (pH 1.2) and simulated intestinal medium (pH 7.4) was shown in the Table No.4. All the formulations, from SDFE1 to SDFE8 and pure drug have shown improved drug solubility when compared with respective pure drugs in all medium including solid dispersion. Among all the solid dispersion formulae, the formulations with optimal polymer concentrations i.e. SDFE3 (1:3), SDFE7 (1:3) have shown highest solubility in the respective medium.

Additionally, improvement in solubility of FE were affected by the polymers concentration in solid dispersions formulae. As increase in the concentration of polymers, a majorly enhanced the effect of solubility was observed to an extent only on further increase in polymer concentration there is a drop in the solubility.

Estimation of Drug content for the solid dispersions

The result of estimation of drug content in Furosemide solid dispersions is given in Table No. 5. The percentage drug content of pure drug of Furosemide, SDFE1, SDFE2, SDFE3, SDFE4, SDFE5, SDFE6, SDFE7 and SDFE8 was found to be 98.76%, 93.86%, 98.76%, 99.69%, 94.63%, 94.28%, 97.65%, 98.87% and 95.32% respectively.

Table 5: Percentage Drug content for the solid dispersions of Furosemide Prepared by PEG 4000 and PVP K32.

Formulation Code	Drug Content (%)
Pure Drug	98.76
SDFE1	93.86
SDFE2	98.76
SDFE3	99.69
SDFE4	94.63
SDFE5	94.28
SDFE6	97.65
SDFE7	98.87
SDFE8	95.32

As increase in the concentration of polymers, a majorly enhanced the effect of drug release was observed to an extent only on further increase in polymer concentration there is a drop in the drug release from the solid dispersions. In higher concentrations of selected polymers (PVP K32 and PEG 4000), there is significant increase in the amount of drug released. This could be because of the reality that PVP K32 and PEG 4000 showed increased solubility in water that resulted in improved wettability and drug particles solubility as well as indirectly improved its dissolution.

Estimation of Micrometrics Properties

Flow Properties for the Solid Dispersions of Furosemide

The angle of repose for pure drug of Furosemide was found to be 37º whereas for the solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 31º, 29º, 26º and 24º in the formulations SDFE1, SDFE2, SDFE3 and SDFE4 respectively. But for solid dispersions prepared by solvent evaporation using PVP K32 as polymer was found to be

32º, 25º, 23º and 26º in the formulation SDFE5, SDFE6, SDFE7 and SDFE8 respectively. The results of angle of repose of solid dispersions for Furosemide are given in Table No. 6.

Table 6: Flow Properties for the Solid dispersions of Furosemide Prepared by PEG 4000 and PVP K32.

	Angle of Repose (º)	Carr's Index (%)	Average Particle Size (µm)
Pure Drug	37	21.13	89.86
SDFE1	31	25.03	73.50
SDFE2	29	14.17	67.68
SDFE3	26	11.63	44.35
SDFE4	24	13.19	72.34
SDFE5	32	12.23	74.77
SDFE6	25	10.01	64.54
SDFE7	23	14.21	42.52
SDFE8	26	18.98	76.14

The Carr's Index for pure drug of Furosemide was found to 21.13% whereas for the solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 25.03%, 14.17%, 11.63% and 13.19% in the formulations SDFE1, SDFE2, SDFE3 and SDFE4respectively. But for solid dispersions prepared by solvent evaporation using PVP K32 as polymer was found to be 12.23%, 10.01%, 14.21% and 18.98% in the formulations SDFE5, SDFE6, SDFE7 and SDFE8 respectively. The results of Carr's Index of solid dispersions for Furosemide are given in Table No. 6.

The average particle size for pure drug of Furosemide was found to 89.86µm whereas for solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 73.50µm, 67.68µm, 44.35µm and 72.34µm in the formulations SDFE1, SDFE2, SDFE3 and SDFE4 respectively. For solid dispersions prepared by solvent evaporation using PVP K32 as polymer was found to be 74.77µm, 64.54µm, 42.52µm and 76.14µm in the formulations SDFE5, SDFE6, SDFE7 and SDFE8respectively. The results of average particle size of solid dispersions for Furosemide are given in Table No. 6.

Flowability of pure drugs of FE and its solid dispersions were assessed by estimation of angle of repose and Carr's index (CI). Flowability parameters of the pure FE powder and all formulated solid dispersions are listed. Table No. 6 represents the data on flowability properties in terms of angle of repose and Carr's index were much increased when compared with pure drugs powder, which might not passed through the funnel during the angle of repose. The results of angle of repose (values were between 20 and 25 for the SDFE3,

SDFE4) and carr's index shows an excellent flow property for the formulated solid dispersions.

Physical Properties for the Solid Dispersions of Furosemide

The bulk density for pure drug of Furosemide was found to be 0.54g/ml whereas for the solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 0.50g/ml, 0.46g/ml, 0.47g/ml and 0.51g/ml in the formulations SDFE1, SDFE2, SDFE3 and SDFE4 respectively. But for solid dispersions prepared by solvent evaporation using PVP K32 as polymer was found to be 0.55g/ml, 0.46g/ml, 0.51g/ml and 0.52g/ml in the formulation SDFE5, SDFE6, SDFE7 and SDFE8 respectively. The results of bulk density of Solid dispersions for Furosemide are given in Table No.7.

The tapped density for pure drug of Furosemide was found to 0.69 g/ml whereas for the solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 0.66g/ml, 0.54g/ml, 0.58g/ml and 0.54g/ml in the formulations SDFE1, SDFE2, SDFE3 and SDFE4 respectively. But for solid dispersions prepared by solvent evaporation using PVP K32 as polymer was found to be 0.58g/ml, 0.53g/ml, 0.67g/ml and 0.69g/ml in the formulations SDFE5, SDFE6, SDFE7 and SDFE8 respectively. The results of tapped density of solid dispersions for Furosemide are given in Table No. 7.

Table 7: Physical Properties for the solid dispersions of Furosemide Prepared by PEG 4000 and PVP K32.

	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio
Pure Drug	0.54	0.69	1.28
SDFE1	0.50	0.66	1.12
SDFE2	0.46	0.54	1.17
SDFE3	0.47	0.58	1.19
SDFE4	0.51	0.54	1.19
SDFE5	0.55	0.58	1.16
SDFE6	0.46	0.53	1.15
SDFE7	0.51	0.67	1.14
SDFE8	0.52	0.69	1.13

The Hausner's ratio for pure drug of Furosemide was found to 1.28 whereas for the solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 1.12, 1.17, 1.19 and 1.19 in the formulations SDFE1, SDFE2, SDFE3 and SDFE4 respectively. But for solid dispersions prepared by solvent evaporation using PVP K32 as polymer was found to be 1.16, 1.15, 1.14 and 1.13 in the formulations SDFE5, SDFE6, SDFE7 and SDFE8

respectively. The results of Hausner's ratio of solid dispersions for Furosemide are given in Table No.7.

From the results of bulk density it is inferred, which powders is loosely packed and further bulk density values were utilized for Carr's Index and Hausner's ratio calculation. The Hausner's ratio shows that the prepared solid dispersions possess very good flowability. All the prefilling parameters were within the acceptable limits. The above values of pre filling characters showed that the prepared granules are having good flow and micrometric properties.

Measurement of Particle Morphology by Scanning Electron Microscopy (SEM)

Particle Morphology of PEG 4000 and PVP K32

The polymers, PEG 4000 and PVP 32K, used in the present study were subjected the surface morphology to observe the difference between as pure polymer and after the formation as solid dispersions. The PEG 4000 was measured at 15KV and magnified upto 1300 times and captured the PEG 4000, which is shown in the Fig. No. 9, whereas for the PVP K32 values were measured at 10KV and 500 times magnified and the captured image is given in the Fig. No. 10.

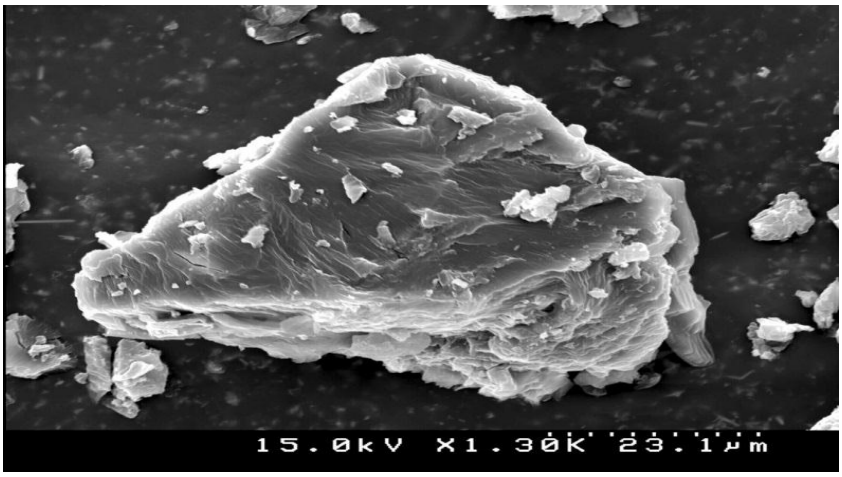

Fig. 9: SEM image of PEG 6000.

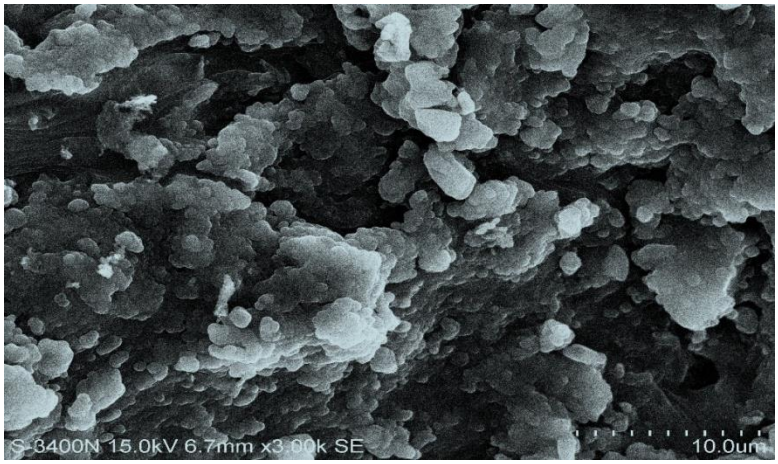

Fig. 10: SEM image of PVP K32.

Particle Morphology of Furosemide and its Solid Dispersions by SEM

The pure drug Furosemide and selected solid dispersions, SDFE2, SDFE3, SDFE6 and SDFE7, formulated in the present study were subjected the surface morphology to observe that drug particles were loaded into the polymer and the surface of the loaded particles. SEM was also done to study morphological characteristically alterations in the pure drug. All the particles, Furosemide and its solid dispersions were measured at 10KV and magnified upto 1500 times and images were captured, which is shown in the Fig. No. 11 to Fig.No. 15.

The result of SEM exhibits fine uniform particles shape of pure drug was dispersed in the polymer complexes, showing that the particles of the drug are loaded in the polymer system. The surface morphology study showed that the solid dispersions was compacted into tiny asymmetrical forms.

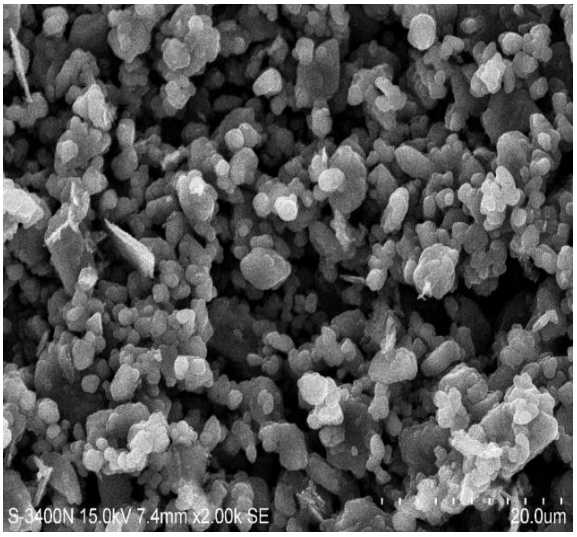

Fig. 11: SEM Image of Pure Drug Furosemide.

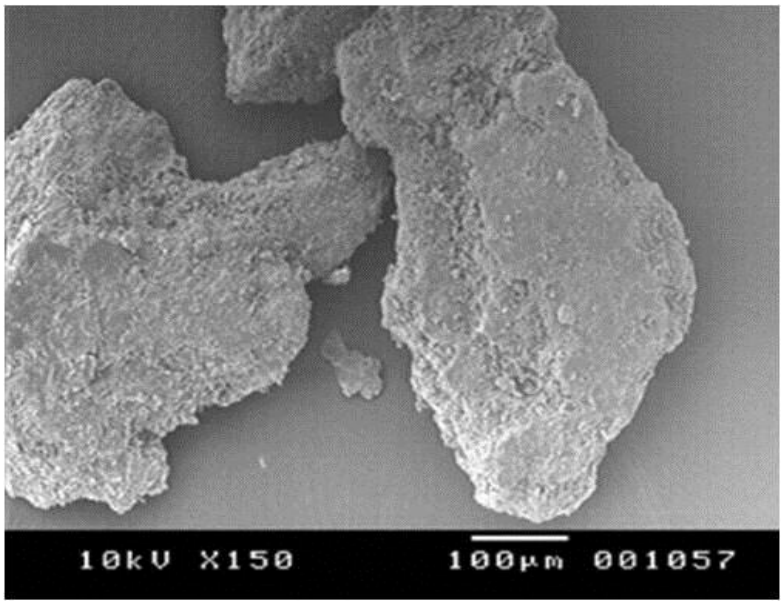

Fig. 12: SEM Image of SDFE2.

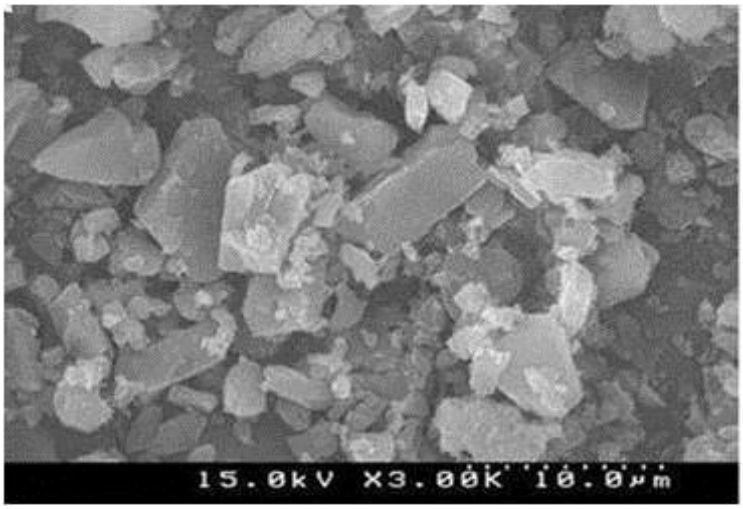

Fig. 13: SEM Image of SDFE3.

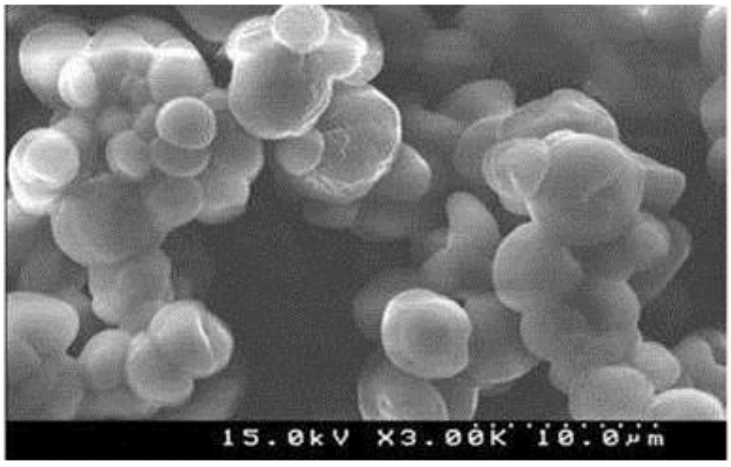

Fig. 14: SEM Image of SDFE6.

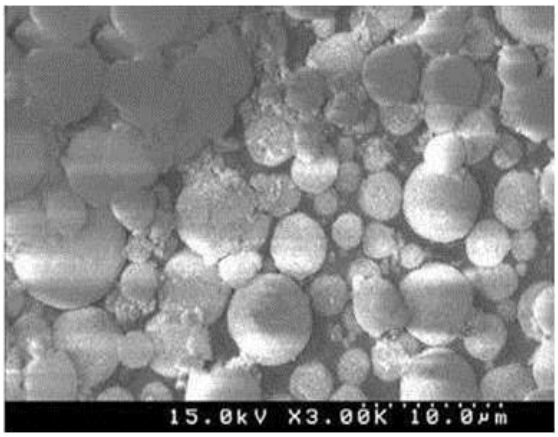

Fig. 15: SEM Image of SDFE7

***In Vitro* Dissolution Release Profile for Solid Dispersions**

***In Vitro* Dissolution Profile Study for Pure Drug Furosemide and its Solid Dispersions**

The *in vitro* dissolution profiles for pure drug of Furosemide was found to be 41.55% whereas for the solid dispersions prepared by fusion method using PEG 4000 as polymer was found to be 88.53%, 98.54%, 99.89% and 91.25% in the formulations SDFE1, SDFE2, SDFE3 and SDFE4 respectively. But for solid dispersions prepared by solvent evaporation using PVP K30 as polymer was found to be 95.25%, 98.55%, 99.24% and 95.85% in the formulationsSDFE5, SDFE6, SDFE7 and SDFE8 respectively. The results of *in vitro* dissolution profiles of solid dispersions for Furosemide are given in Fig. No. 16 and Fig. No. 17.

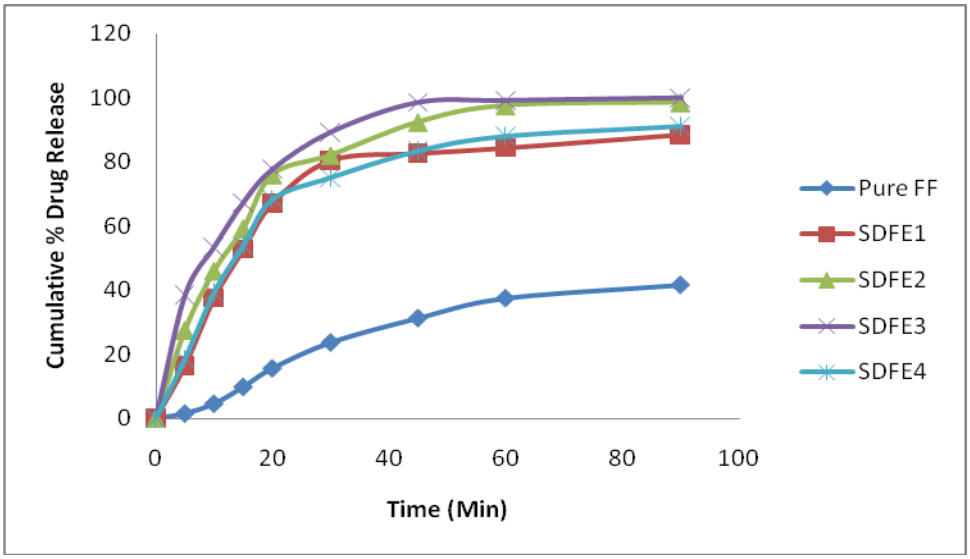

Fig. 16: Cumulative Percentage Drug Release of Furosemide Pure Drug and its Solid Dispersions prepared by Fusion method.

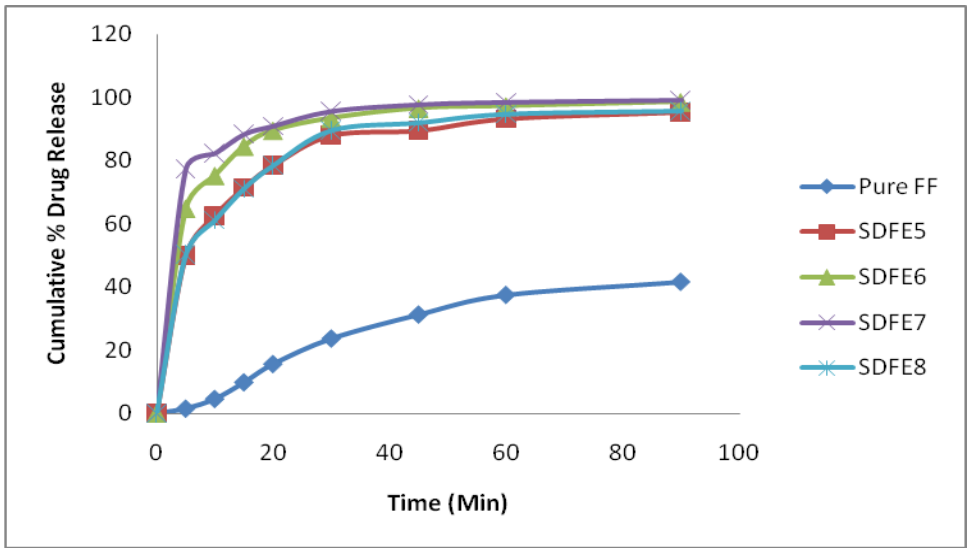

Fig. 17: Cumulative Percentage Drug Release of Furosemide Pure Drug and its Solid Dispersions prepared by Solvent evaporation method.

In vitro drug release profiles of solid dispersions of FE was prepared with various drug: polymer ratios as well as treated and pure drugs at pH 1.2 is depicted in the Fig. No. 16 and Fig. No. 17, respectively. Dissolution release rate of all solid dispersions prepared with three drugs were improved significantly when compared with the pure drugs FE, which may be due to of increased hydrophilicity of the polymers. In solid dispersions, drug release profile was improved as a result of increase in polymer concentration up to ratio of 1:1; 1:2 and 1:3 for the FE for the solid dispersion prepared by both fusion and solvent evaporation techniques. But SDFE3 andSDFE7, have shown the maximum release profile at the drug: polymer ratio of 1:2 and 1:3 respectively. Solid dispersions prepared by PVP K32 with ratios of 1:2 and 1:3 have shown an improved dissolution profile when compared with the PEG 4000 by the fusion method. The percentage of drug released at pH 7.4 is evidently higher than the amount of drug release at pH 1.2 dissolution medium. This might be because of improved solubility of the weak acids of FE may be due to higher ionization at elevated pH range.

SUMMARY AND CONCLUSION

The objective of the present study is to prepare solid dispersions of Furosemide with an aim to increase in solubility and dissolution rate by employing various polymers. Furosemide belongs to BCS class II drugs, i.e. poor solubility and dissolution rate and practically insoluble in water. Solid Dispersions were prepared by using different polymers at various concentrations by fusion and solvent evaporation methods. They were assessed for micrometric properties, flowability properties, *in vitro* drug release and stability studies.

Preformulation study was carried out for FE and polymers utilized used in the formulations and they observed to be compatible. Evaluations were performed by FTIR studies, which are interpreted and found to be no interactions between the FE with PEG 4000 and PVP K32 and found to be compatible. Solid dispersions of FE prepared by fusion and solvent evaporation methods employing PEG 4000 and PVP K32 i.e. SDFE3 and SDFE7 were exhibited greater solubility and dissolution rate when compared to pure drugs. The micrometrics parameters and flowability like angle of repose and Carr's index and bulk density, tapped density and compressibility index respectively were assessed and observed to be excellent flow characteristics and fair Hasuner's index. Evaluations of capsules were carried out and found to be within specified limits. Based on the *in vitro* drug release profiles of respective solid dispersions and their capsules it is concluded that solubility and dissolution rate of FE is increased by using the PEG 4000 and PVP K32 polymers.

On comparing with the PEG 4000 and PVP K32 prepared by fusion and solvent evaporation for Furosemide, SDFE3 is having high solubility and dissolution rate when compared with SDFE7. Hence, the solubility and dissolution rate differs from method to method and polymer to polymer used in the formulations.

REFERENCES

1. Mohini S Patil, Sheetal Z Godse, Saudagar RB. Solubility enhancement by various techniques: an overview. World journal of pharmacy and pharmaceutical sciences, 2013; 2(6): 4558-72.
2. Mogal S A, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der pharmacia letter., 2012; 4(5): 1574 – 1586.
3. Chaturvedi AK, AmitaVerma. Solubility enhancement of poorly water soluble drugs by solid dispersion.International Journal of Pharmaceutical Sciences and Research, 2011; 3(1): 26-34.
4. Gordon L Amidon, Hans Lennernas, Vinod P Shah, John R Crison. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharmaceutical Research, 1995; 12(3): 413-20.
5. Pragati Kumar. B, Subba Rao, K. V. Ramana Murthy, Ravi Kiran Sahu and B. Ramu. Solid dispersion technique: A tool for enhancing bioavailability of poorly soluble drugs. Journal of Chemical and Pharmaceutical sciences, 2011; 4(4): 170 – 179.

6. Dhirendra K, Lewis S, Udupa N and Atin K. Solid Dispersions: A Review. Pak J Pharm Sci., 2009; 22(2): 234 – 246.
7. Amidon GL, Lennernas H, Shah VP and Crison JR. Theoretical basis for a biopharmaceutical drug classification: The correlation of in avitro drug product dissolution and in vivo bioavailability. Pharm Res., 1995; 12(3): 413 – 420.
8. Khayyam Shaikh, ShaileshPatwekar, Santosh Payghan, John D'Souza. Dissolution and Stability Enhancement of Poorly Water Soluble Drug – Lovastatin by Preparing Solid Dispersions. Asian Journal of Biomedical and Pharmaceutical Sciences, 2011; 1(4): 24–31.
9. Krishna R. Gupta, Sonali S. Askarkar, Prashant R. Rathod and Sudhir G. Wadodkar. Validated spectrophotometric determination of Fenofibrate in formulation. Der Pharmacia Sinica, 2010; 1(1): 173 – 178.
10. Zawar L and Bari S. Microwave induced solid dispersion as a novel technique for enhancing dissolution rate of repaglinide. AdvPharmacol Pharm, 2013; 1: 95 – 101.
11. Brahmaiah Bonthagarala, Sreekanth Nama, Suresh Nuthakki, Katta Vamshi Kiran and Prasanth Pasumarthi. Enhancement of dissolution rate of fenofibrate by using various solid dispersion techniques. World J Pharmacy Pharmaceu Sci., 2014; 3(3): 914-932.
12. Guyot. M, Fawaz. F, Bildet. J, Bonini. F and Lagy. AM. Physiochemical characterization and dissolution of norfloxacincyclodextrin inclusion compounds and PEG solid dispersions. Int. J. Pharm., 1995; 123: 53 – 65.
13. Martin. A. Solubility and distribution phenomena, physical pharmacy and pharmaceutical sciences. Lippincott Williams and Wilkins, 6th edition, 2011.
14. Aulton. M. Dissolution and solubility in Pharmaceutics: The Science of Dosage form Design, M. E. Aulton, Ed., p. 15, Churchill Livingstone, 2nd edition, 2002.
15. Gowda. D, Gowrav. M, Gangadharappa. H and Khan. M. Preparation and evaluation of mixture of eudragit and ethylcellulosemicroparticles loaded with ranolazine for controlled release. J Young Pharm, 2011; 3(3): 189 – 196.
16. Mohamed Abbas Ibrahim and Mahmoud El-Badry. Formulation of immediate release pellets containing famotidine solid dispersions. Saudi Pharmaceutical Journal, 2014; 22: 149 – 156.