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PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION OF FUROSEMIDE

***Purohit Nimesh Bhikhabhai**

Department of Pharmaceutics, Sharda school of Pharmacy, Pethapur, Gandhinagar, Gujarat, India.

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***Correspondence for Author**
Purohit Nimesh B.
Department of Pharmaceutics, Sharda school of Pharmacy, Pethapur, Gandhinagar, Gujarat, India

ABSTRACT

The purpose of this study was to develop solid dispersion(SD) tablets of furosemide. Furosemide is poorly water soluble, anti-hypertensive and diuretic drug mainly used in hypertension and pulmonary edema.The crucial aspect in the preparation of SD of furosemide is to improve solubility of furosemide.The SD prepared by two methods using Physical mixing and Solvent evaporation method using four polymers PEG4000, PEG6000, PEG8000 and Poloxamer407 using different drug carrier ratios such as 1:1, 1:3, and 1:5. The prepared solid dispersion is characterized by solubility test, FT-IR spectroscopy, DSC study, X-ray diffraction. A successful increase in solubility of furosemide is obtained by preparing SDs. SD with Poloxamer407 with solvent evaporation method using drug carrier ratio 1:3 shows highest improvement in solubility than others. But the SD formulation is not convenient to take patient orally. So to ease of patient the tablets of SD is prepared using direct compression method. In the *In-vitro* drug release evaluation of SD tablets it also shows that the highest 97.41% drug release given by SD tablet containing Poloxamer407 with drug carrier ratio 1:3. This best formulation is compared with marketed conventional tablet of furosemide and charged for Stability study.By preparing SD of furosemide the enhancement of solubility can be achieved and solvent evaporation method is better than physical mixing can be concluded.

Keywords: Solid dispersion, Furosemide, Physical mixing, Solvent evaporation, Solubility.

INTRODUCTION

Furosemide (FRMD) is 5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoicacid, and it is a loopdiuretic mainly used in the treatment ofhypertension. The drug

has been classifiedas a class IV drug as per thebiopharmaceutical classification system (BCS)as a result of its low solubility and oralbioavailability; one of the major causes of itslow oral bioavailability is its solubility.Oral bioavailability of a drug depends on itssolubility and dissolution rate, anddissolution may be the rate determining stepfor the onset of therapeutic activity.Soefforts to increase drug dissolution of drug areoften needed.

Solid dispersion (SD) isone of such methods and it involves adispersion of one or more active ingredients inan inner carrier or matrix in solid state prepared by physical mixing and solvent evaporation method.The technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, furosemide. By increasing the solubility of drug we can minimize the problem related to low solubility like-

-High dose

-Frequent administration

-Less bioavailability

-Less therapeutic effect

The main objectives of this experiment is to,

- To improve Solubility of furosemide by using solid dispersion.
- To optimize the method of preparation of solid dispersion among physical mixing and solvent evaporation method.
- To evaluate influence of various hydrophilic carrier on enhancing the solubility of furosemide
- To formulate drug carrier complex in suitable Stable dosage form.

Materials

Furosemide was purchased from Mexocrate Enterprize, Ahmedabad, Poloxamer407 and Polyethyleneglycol, Sodium starch glycolate, Talc, Magnesium stearatewas purchased from Oxford laboratory, Mumbai. Ethanol was purchased from Chemdyes corporation, Ahmedabad.

Experimental

Solid dispersion of furosemide preparation methods

Solid dispersions of furosemide in PEG 4000, PEG 6000, PEG 8000 and poloxamer 407 were prepared with different ratio like 1:1, 1:3, 1:5. The methods used for the preparation of these

solid dispersions were physical mixtures, solvent evaporation method.

Physical mixture[1]: The physical mixtures were prepared by weighing the calculatedamount of furosemide and the carriers and then mixing them in a glass mortar by triturating.

Solvent evaporation method[2]: The required amount of furosemide and the carrierand transferred to beaker containing sufficient quantity of ethanol to dissolve. The solvent ethanol was removed by evaporation at 40ºC under vacuum. The dried product was crushed, pulverized and sieved through mesh number 80.

Table 1. Composition of furosemide and PEG 4000 solid dispersion

Sr no.	Formulation code.	Method	Solid dispersion composition	Drug:Polymer ratio
1	F1	Solvent evaporation method	Furosemide + Polyethylene glycol 4000	1:1
2	F2			1:3
3	F3			1:5
4	F1a	Physical Mixture		1:1
5	F2b			1:3
6	F3c			1:5

Table 2. Composition of furosemide and PEG 6000 solid dispersion

Sr no.	Formulation code.	Method	Solid dispersion composition	Drug:Polymer ratio
1	F4	Solvent evaporation method	Furosemide + Polyethylene glycol 6000	1:1
2	F5			1:3
3	F6			1:5
4	F4a	Physical Mixture		1:1
5	F5b			1:3
6	F6c			1:5

Table 3. Composition of furosemide and PEG-8000 Solid dispersion

Sr no.	Formulation no.	Method	Solid dispersion composition	Drug:Polymer ratio
1	F7	Solvent evaporation method	Furosemide + Polyethylene glycol 8000	1:1
2	F8			1:3
3	F9			1:5
4	F7a	Physical Mixture		1:1
5	F8b			1:3
6	F9c			1:5

Characterization of solid dispersion of furosemide

Solubility determination of Furosemide solid dispersion[3]

Excess amount of the Solid dispersion (10mg) was added to stoppered conical flask containing 20 mL of solvent media and subjected to shaking for nearly 6 hrs. Then the flasks were removed and kept aside for 24 hrs. at a constant temperature to attain equilibrium condition. Suitable aliquots were withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with a solvent and analyzed for furosemide content in UV spectroscopic by measuring the absorbance at 273 nm.

DSC study of solid dispersion[4]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug and bestsoliddispersion were recorded. DSC study was performed for furosemide and solid dispersion of furosemide

X-ray diffraction study of solid dispersion[5]

XRD patterns were recorded using, model generator Powder X-ray diffraction patterns were traced for drugs, carriers and solid dispersion. The position and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier and solid dispersion.

Preparation of solid dispersion tablet

All ingredients weighed and materials except Talc and Magnesium Stearate were passed through sieve no. 40. Prepared blend was lubricated with Talc and Magnesium Stearate which was previously passed through sieve no. 80. Tablets were compressed using on BB-tooling Compression machine. Tablet weight was maintained as per the solid dispersion polymer drug ratio. In addition to one or multiple filler binders and drug substances, generally a disintegrant, a lubricant and substance such as glidants are present in the tablet formulation.

Table 4 Formulation of solid dispersion tablet

Sr. no	Ingredients	Quantity (mg)	Use
1	Eq. wt. of furosemide solid dispersion	40	Antihypertensive, Diuretic
2	Microcrystalline cellulose	50	Filler
3	Sodium starch glycolate	20	Disintegrant
4	Talc	6	Lubricant
5	Magnesium stearate	4	Glidant

Characterization of solid dispersion Tablet

I) *In-vitro* Dissolution Study [6,7]

Dissolution medium: 900 ml of 0.1 N HCl with 1% SLS

Temperature: 37 ± 0.5°C

RPM: 50 rpm

Time: 2 hr.

Apparatus: IP Type-I (Paddle)

Aliquots: 5ml

Sampling time (min.): 15, 30, 45,60,75,90,105,120

Samples wereanalyzed for furosemide by measuring the absorbance at 273 nm. The volume withdrawn at various time intervals was immediately replaced with fresh quantity of dissolution medium.

Determination of drug content in 0.1 N HCl with 1% SLS [8]

Accurately weighed tablet powder, equivalent to 40 mg furosemide, was transferred into a 100 mL volumetric flask and amount of 0.1 N HCl with 1% SLS was added, shaken for 30 min using sonicator and diluted to the 100 mL mark with same solvent. It was then filtered to obtain sample stock solution. 1 mL of the filtrate was further diluted to 10mL with 0.1 N HCl with 1% SLS and then assayed for content of furosemide using Shimadzu UV-1800 Double beam UV/Vis spectrophotometer at 273 nm. All analyses were carried out in triplicate. From the absorbance total drug content in the batches were calculated.

III) Disintegration time [9]

The USP device to carry out disintegration was six glass tubes that are 3 inch long, open at the top, and held against 10 mesh screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37±2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

VI) Hardness

The hardness of tablet is an indication of its strength. Hardness was measured using the Monsanto hardness tester. Measure the pressure required to break diametrically placed matrix tablet, by a coiled spring.

VII) %Friability

Five tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.

% **Friability = $[(W_1-W_2)100]/W1$**

Where, W_1= Weight of tablet before test

W_2 = Weight of tablet after test

RESULTS AND DISCUSSION

Solubility test

All valuesare expressed as mean ± standard deviation, n=3

The solubility of furosemide was studied and the results are summarized in Table 5.The solubility of furosemide was found to be 0.62 to 1.20 mg/mL in different drug-polymer carrier.

Table 5 Determination solubility of furosemide solid dispersion

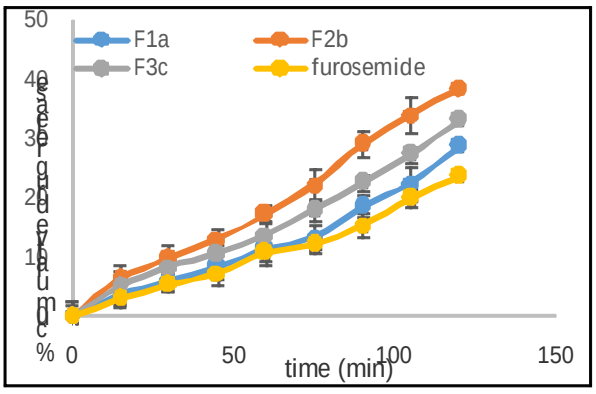
Sr. no	Formulation code.	Solubility (mg/ml)	
		Distilled water	0.1 N HCl with 1% SLS
PEG-4000			
1	F1	0.48±0.006	0.62±0.001
2	F2	0.56±0.006	0.69±0.003
3	F3	0.54±0.01	0.68±0.003

4	F1a	0.42±0.03	0.55±0.02
5	F2b	0.50±0.02	0.58±0.003
6	F3c	0.48±0.003	0.57±0.001
PEG-6000			
7	F4	0.52±0.008	0.65±0.03
8	F5	0.59±0.006	0.70±0.02
9	F6	0.68±0.01	0.69±0.01
10	F4a	0.44±0.01	0.58±0.001
11	F5b	0.51±0.03	0.60±0.002
12	F6c	0.55±0.02	0.56±0.001
PEG-8000			
13	F7	0.60±0.02	0.81±0.003
14	F8	0.77±0.01	0.82±0.02
15	F9	0.76±0.009	0.71±0.01
16	F7a	0.55±0.007	0.72±0.02
17	F8b	0.62±0.009	0.74±0.008
18	F9c	0.61±0.008	0.65±0.008
Poloxamer-407			
19	F10	0.95±0.02	0.98±0.006
20	F11	1.12±0.001	1.20±0.02
21	F12	1.03±0.002	1.18±0.03
22	F10a	0.82±0.009	0.86±0.008
23	F11b	0.97±0.007	1.05±0.01
24	F12c	0.92±0.006	0.97±0.002

The results shown that the prepared solid dispersions has better solubility than the pure furosemide drug because complexation of drug and carrier.

Characterization of Solid dispersion Tablet:

***In-vitro* dissolution study**



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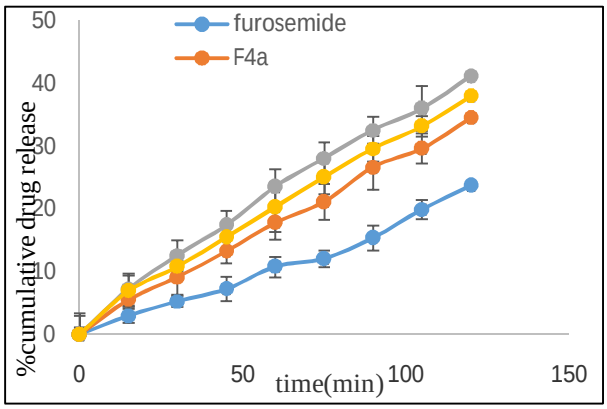

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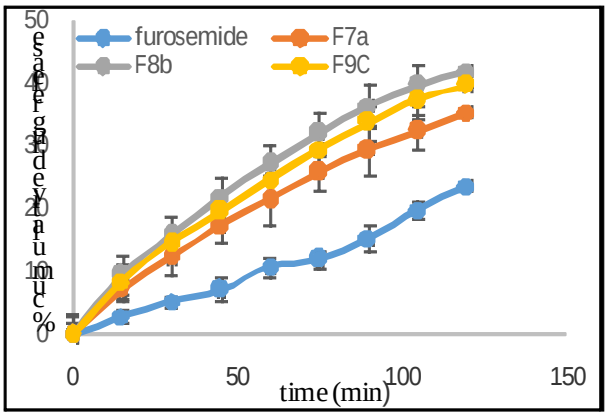

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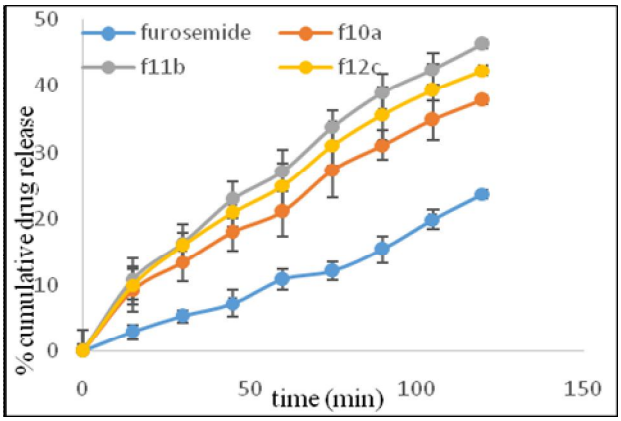

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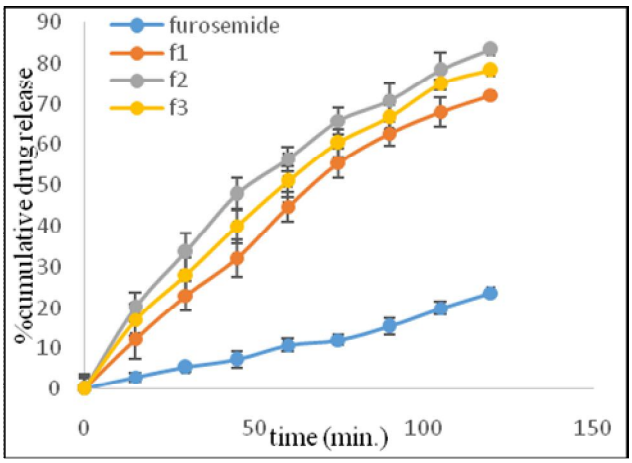

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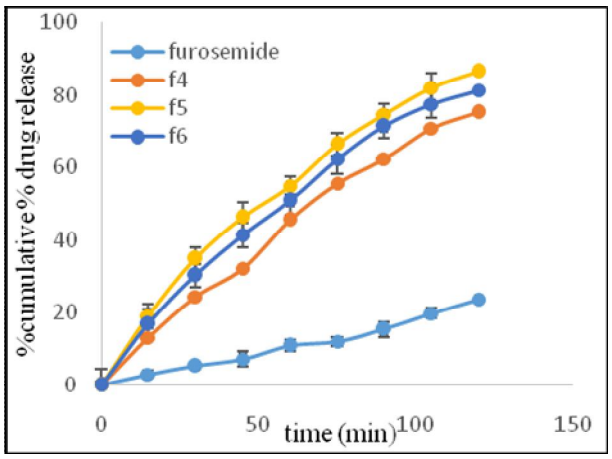

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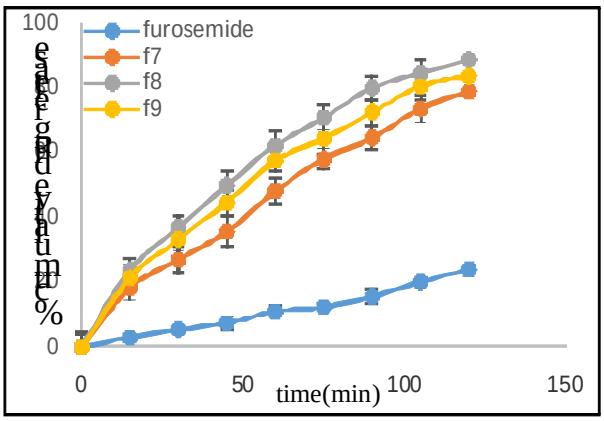

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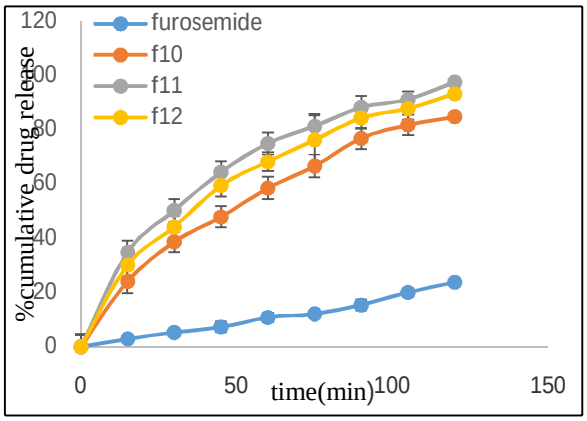

(h)

Figure 1. **Cumulative % drug release graph of Solid dispersion tablet (a) F1a, F2b, F3c , Furosemide (b) F4a, F5b, F6c, Furosemide (c) F7a, F8b, F9c, Furosemide, (d) F10a, F11b, F12c, Furosemide (e) F1, F2, F3, Furosemide (f) F4, F5, F6, Furosemide (g) F7, F8, F9, Furosemide (h) F10, F11, F12, Furosemide**

The dissolution rate profiles of pure furosemide and inclusion complexes prepared by physical method, Solvent evaporation method. It is evident that the complexes prepared by all method exhibited a faster dissolution when compared to pure drug. The percent drug release from various inclusion complexes was found by physical mixture in the range of 28.80 to 42.36% and solvent evaporation method in range of 72.10 to 97.41% within 120 minutes, whereas the pure drug exhibited only 23.75%.

Physiochemical Evaluation Parameter

Table 6. Physiochemical Evaluation Parameter

Sr. no.	Formula code	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Drug content (%)
1	F1	3.6±0.04	0.90±0.01	132±2.81	96.23±0.26
2	F2	3.8±0.02	0.86±0.04	98±2.32	98.15±0.21
3	F3	4±0.00	0.82±0.01	101±3.12	95.54±0.36
4	F4	4.2±0.02	0.85±0.03	112±2.14	94.86±0.45
5	F5	3.4±0.06	0.88±0.02	101±3.21	94.27±0.12
6	F6	3.6±0.04	0.79±0.01	133±2.12	96.98±0.23
7	F7	4±0.0	0.85±0.02	99±2.13	97.90±0.24
8	F8	4±0.0	0.88±0.02	109±3.12	97.85±0.11
9	F9	3.8±0.02	0.90±0.02	101±3.01	95.12±0.36
10	F10	3.8±0.02	0.90±0.02	112±1.01	100.25±0.21
11	F11	4±0.03	0.91±0.01	97±5.02	99.50±0.24
12	F12	3.8±0.02	0.88±0.02	100±3.01	98.52±0.11
13	F1a	3.6±0.04	0.86±0.04	123±3.78	98.21±0.15
14	F2b	4±0.0	0.86±0.04	105±2.01	97.21±0.65
15	F3c	3.8±0.02	0.79±0.01	101±3.01	102.63±0.45
16	F4a	3.8±0.02	0.78±0.02	112±1.01	99.23±0.31
17	F5b	3.8±0.02	0.74±0.03	145±1.01	100.21±0.36
18	F6c	4±0.0	0.90±0.01	158±3.11	99.95±0.21
19	F7a	4.2±0.02	0.79±0.01	112±2.025	98.45±0.11
20	F8b	4.2±0.02	0.84±0.02	124±3.058	96.23±0.14
21	F8c	3.6±0.04	0.86±0.04	116±3.01	93.23±0.15
22	F10a	3.6±0.04	0.89±0.01	110±5.10	98.23±0.35
23	F11b	3.8±0.02	0.88±0.02	115±3.25	100.12±0.26
24	F12c	4±0.0	0.84±0.06	112±5.01	99.95±0.21

All valuesare expressed as mean ± standard deviation, n=3

From the results the all the batches of formulation pass the limits of IP for the Furosemide tablets. As per IP Furosemide.Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of furosemide.

So, the all the % drug content range was in between the 90%-110%. So it pass the IP test for %drug content for tablets of furosemide.

All the batches were evaluated for various physical parameters before proceeding further. Includes the values (mean ± SD) of weight variation, hardness, friability of 20 batches prepared using different combinations of functional excipients.

Hardness of tablets was in range between 4.20±0.54 to 3.6±0.35 kg/cm^2.

Friability was in range between 0.78±0.02 to 0.91±0.02 %. Friability values were less than 1% in all cases shows good mechanical strength at the time of handling and transports.

Thus, all the physical parameters of the compressed tablets were quite within control.

Comparison of dissolution study of furosemide tablet with solid dispersion tablet(a) solvent evaporation method. (b) Physical mixture

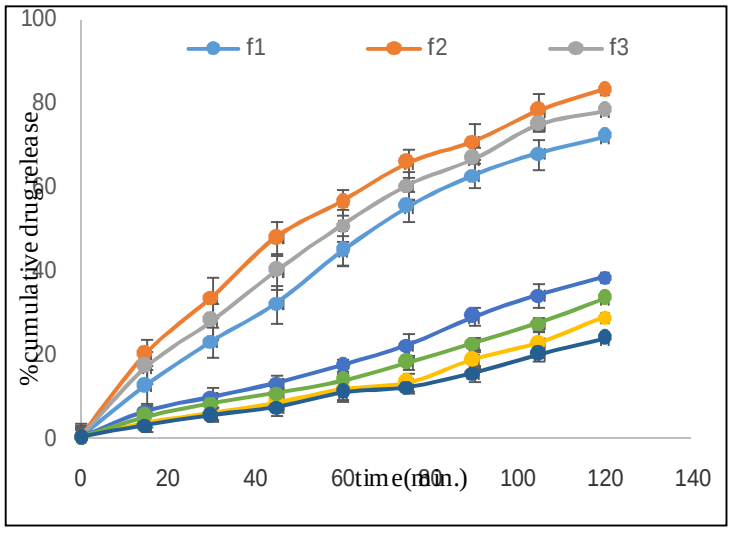

Figure 2. Comparison graph of solid dispersion tablet containing PEG-4000 as polymer

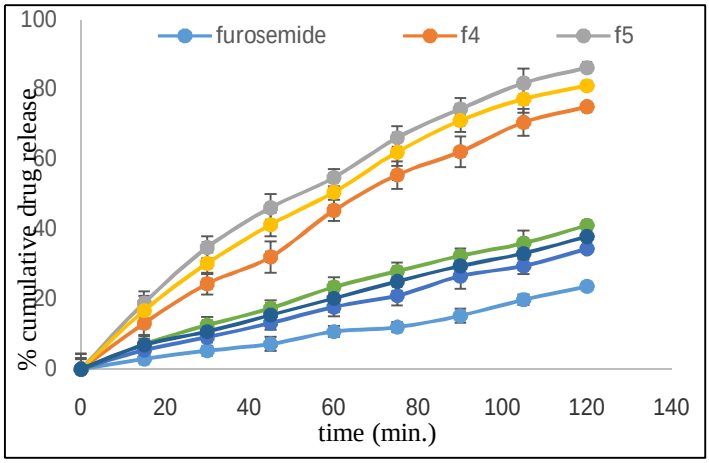

Figure 3. Comparison graph of solid dispersion tablet containing PEG-6000 as polymer

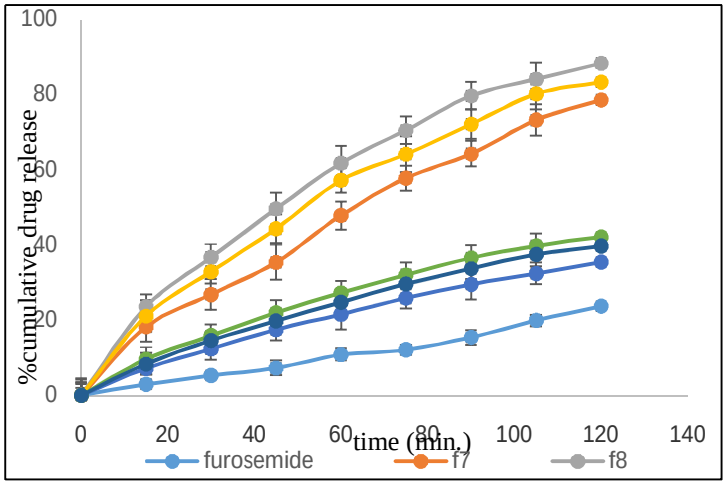

Figure 4. Comparison graph of solid dispersion tablet containing PEG-8000 as polymer

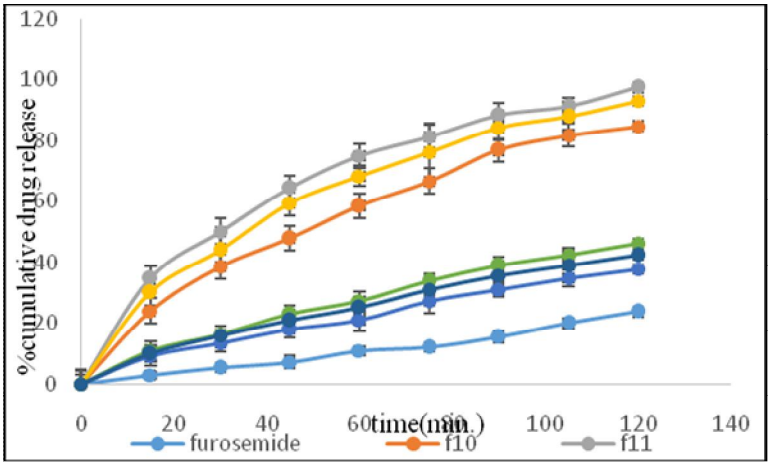

Figure 5. Comparison graph of solid dispersion tablet containing Poloxamer-407 as polymer

The percentage of drug released from the solid dispersion of furosemide with PEG 4000, PEG 6000, PEG 8000 and poloxamer 407 compared with that released from equal amounts of physical mixtures and pure furosemide. PEG 4000 and PEG 6000 showed similar dissolution patterns. The dissolution pattern indicated that the drug seemed to be getting out of the matrix rather slowly, which might be an indication of a matrix-controlled process.

It was hypothesis that increasing the proportion of carrier would result in an enhancement of the dissolution rate. This was true for all cases. The fact that physical mixtures showed a slower rate of released than the solid dispersion can be attributed to the fact that they possess a much greater particle size of the drug or that the drug was still present in its crystal form. The rather rapid release of drug during the first 45 minutes from furosemide: poloxamer 407 solid dispersion seemed to attributed to the presence of drug in a very fine state. This is mainly due to the significant reduction of the drug particles.

The mechanism by which drug dissolution enhancement occurs from solid dispersion are numerous and not yet well understood. However, factor such as reduced aggregation, increase surface area, and loss of drug crystallinity and solubilization effects associated with the carriers are considered the main ones responsible for their effect.

A marked improvement in dissolution rates of furosemide was observed with F11 prepared by solvent evaporation method. The higher dissolution rates observed with inclusion complexes prepared by solvent evaporation method may be due to better interaction of drug and polymer. So, the best formulation is selected F11 which was prepared by solvent evaporation method having poloxamer 407 as a carrier with drug: carrier ration 1:3.

X-ray diffraction spectroscopy of best formulation (F11)

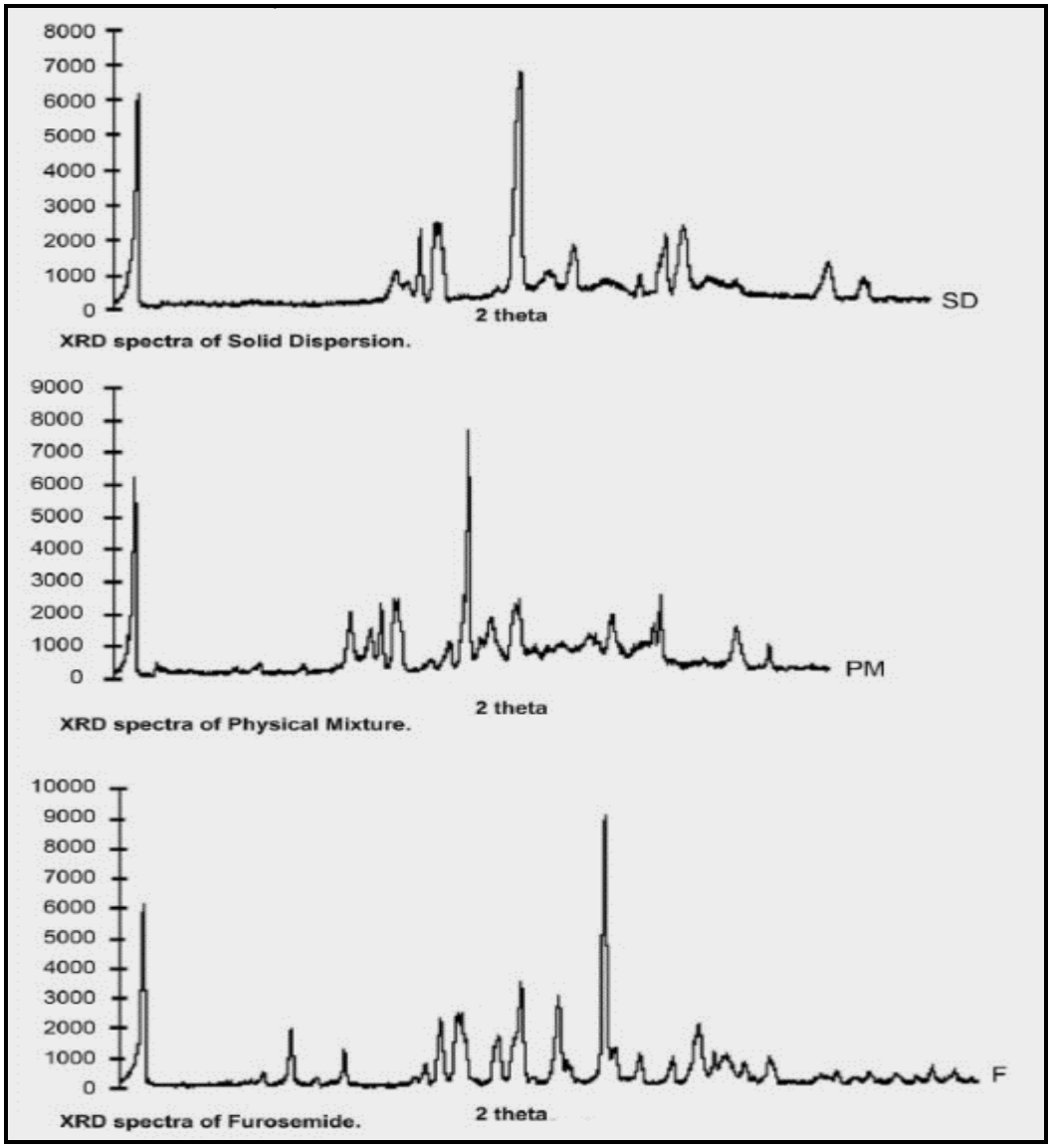

Figure 6. X-ray diffraction spectra of best formulation (F11)

The x-ray diffraction pattern of furosemide exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug, as shown in Figure 6.. It showed diffraction peaks at 2θ degree. However the x-ray diffraction patterns of the physical mixture and solid dispersion were simply a superimposition of each component with with respect to the peaks of frusemide. Moreover, the relative intensity and 2θ angle of these peaks remained practically unchanged. Thus, there was no amorphization of the drug and which still retained its original crystalline form.

DSC Spectra of best formulation (F11)

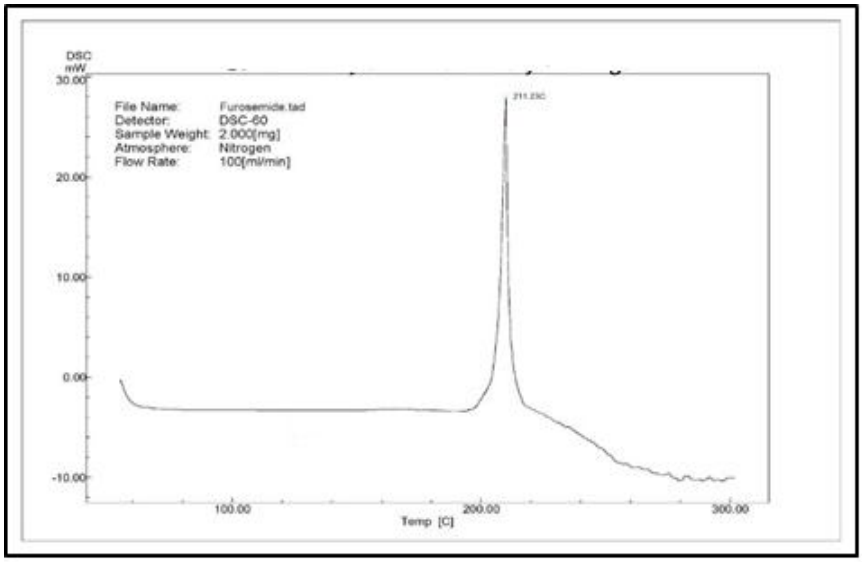

Figure 7. DSC Spectra of furosemide pure drug.

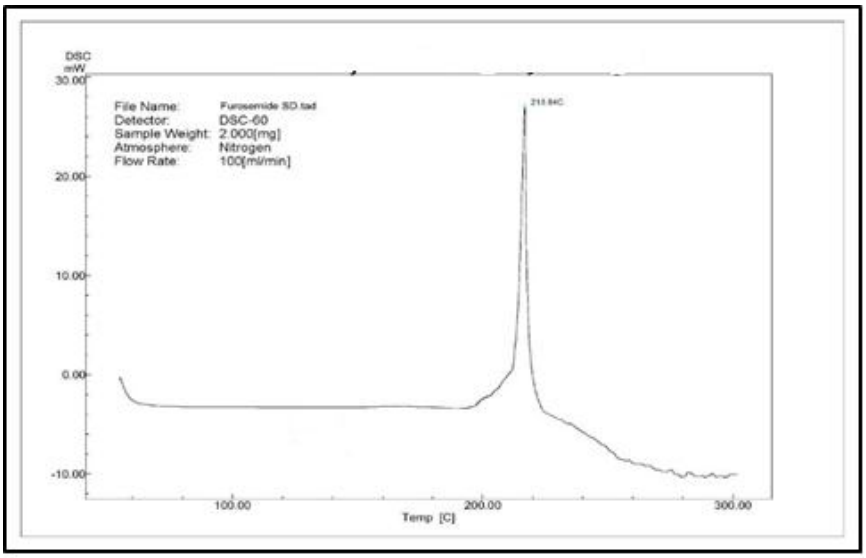

Figure 8. DSC Spectra of furosemide solid dispersion (F11)

DSC thermograms of furosemide and Solid dispersion of furosemide (F11, Poloxamer 407, 1:3), in Figure 7 and 8 respectively. DSC studies, on the basis of the melting peak of furosemide solid dispersion (213.23 ^{o}C), indicate that there was not interaction between the drug and carrier. However, the characteristic melting peak of solid dispersion slightly shifted toward a higher temperature. This may be attributed to high polymer concentration and uniform distribution of the drug in the crust of the polymer, resulting in complete miscibility of the drug in the polymer. The similarity in the DSC of the Pure drug and solid dispersion

suggests that the solvent evaporation method did not induce interaction at the molecular level.

CONCLUSION

The aim of this research work entitled “Preparation and characterization of solid dispersion of furosemide” was to formulate stable solid dispersion tablet dosage form which has improved solubility of furosemide than the pure drug.

Furosemide, is loop diuretic and antihypertensive agent used in the hypertension and pulmonary edema. Furosemide, (BCS-IV) drug having low permeability and oral bioavailability the absorption of such drug is challenging.

Initially UV Spectrum of furosemide in 0.1N HCl with 1%SLS solution and also in distilled water was carried out for determination of absorbance maxima of drug. It was found that Furosemide in both solvent gave λmax at 273nm. Using this λmax calibration curve of Furosemide was taken in 0.1 N HCl with 1%SLS as well as in distilled water.

For the identification of the drug the Physiochemical testing like melting point and solubility study carried out. The results of solubility study proven that furosemide has very low solubility in water. FT-IR spectra of drug and drug with polymer complex was taken. It was found that all the prominent functional group peaks were observed in physical mixture. This confirmed that there was no interaction between drug-excipient or incompatibility between drug and excipient.

In the present study, an attempt was given to improve solubility of furosemide by preparing solid dispersion. In the present study, the solid dispersion of furosemide was prepared using different polymers PEG4000, PEG6000, PEG8000 and Poloxamer407 using different ratio of drug and carrier 1:1, 1:3, 1:5.

The prepared solid dispersions of different drug carrier ratio were evaluated for solubility testing using shake flask method. It gives results that there was marked improved in solubility of furosemide when complexes with the polymer. Increasing the solubility of solid dispersion using carrier PEG4000, PEG6000, PEG8000 and Poloxamer 407. The maximum solubility of furosemide was observed with carrier poloxamer 407 with ratio 1:3 with solvent evaporation method. Poloxamer shows maximum solubility because it gives surface active activity with hydrophilic linkage of drugs give different crystal habit which gives solubility enhancement

The prepared solid dispersion was sieved and compressed in tablet dosage form with the use of glidant, disintegrant and adherent. The tablets are evaluated for Physical parameters such Hardness, Friability, Thickness, Diameter, Disintegration time. *In-vitro* dissolution study and Drug release study was carried out for all formulated tablets. The *In-vitro* study of tablets were compared with the pure drug dissolution study. It shows marked improvement of dissolution Profile.

As the improvement in solubility and dissolution were improved with the Polymer. As highest improvement is done with the Polymer Poloxamer 407 with the drug carrier ratio 1:3 using solvent evaporation method. It shows 97.48% drug release. In the PEG the improvement in solubility was in order of PEG8000, PEG6000 and PEG4000.
In this experiment not only the polymer optimization was done. In the method of preparation the Solvent evaporation method prepared solid dispersion tablets gave better results than the Physical mixing. As the solid dispersion prepared by solvent evaporation method gave good solubility than the physical mixing.

From the Evalution parameters the depends on solubility and %drug release the best formulation was selected that which was the formulation batch F11 Prepared by Solvent evaporation method using Poloxamer 407 as polymer and the drug carrier ratio was 1:3.

REFERENCE

1. Anupama Singh, Pramod kumar Sharma, Jay Gopal Meher, Rishabha Malviya " Evaluation of enhancement of solubility of Paracetamol by solid dispersion technique using different polymers concentration" *Asian journal of Pharmaceutical and Clinical research.***2011**, 4(!), 117-119.
2. Singh Chhater and Kumar Praveen " Solvent evaporation method for amorphous solid dispersion: Predictive tools for improve the dissolution rate for Pioglitazone Hydrochloride" *IJPCBS*, **2013**, 3(2), 350-359
3. Dr. Klara Hodi, Dr. Istvan Volko Ph. D Thesis "Development and examination of solubility measurement methods for drug solubility determination", Semmelweis University, Department of Pharmaceutical Chemistry. **2010**
4. Ladan Akbarpour Nikghalb, Gurinder Singh, Gaurav Singh and Kimia Fazaeli Kahkeshan "Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs" *Journal of Applied Pharmaceutical Science* **2012**, 2(10), 170-175

5. Teo´ filo Vasconcelos, Bruno Sarmentoand Paulo Costa "Solid dispersion as strategy to improve oral bioavailability of poor water soluble drugs" *Drug Discovery Today*, December **2007**, 12(23/24), 1068-1079
6. Indian Pharmacopoeia, The Indian Pharmacopoeia Commission Ghaziabad, Volume-2, **2007**, pp 535.
7. Ganesh Chaulang, Piyush Patel, Sharwaree Hardikar, Mukul Kelkar, Ashok Bhosale, Sagar Bhise "Formulation and Evaluation of Solid Dispersions ofFurosemide in Sodium Starch Glycolate "*Tropical Journal of Pharmaceutical Research*" **2009**, 8(!), 43-51
8. Indian Pharmacopoeia", The Indian Pharmacopoeia Commission Ghaziabad, Volume-1, **2007**, pp. 241-242.
9. Bhawana Kapoor, Ramandeep Kaur, Sukhdeep Kaur, Himani Behl, Sukhkaran Kaur " Solid dispersion: An evolutionary approach for solubility enhancement of poorly water soluble drugs" *Int J Recent Adv Pharm Res*, **2012**, 2(2), 1-16
10. Rahul M. Patil, Ajim H. Maniyar, Mangesh T. Kale, Anup M. Akarte, Dheeraj T. Baviskar " Solid dispersion: statergy to enhance solubility" *International Journal of Pharmaceutical Sciences Review and Research* May-Jun **2011**, 8(2), 66-73.
11. Dixit AK, Singh RP and Singh Stuti " Solid Dispersion - A Strategy for Improving the Solubility of Poorly Soluble Drugs " *International Journal of Research in Pharmaceutical and Biomedical Sciences* Apr-Jun **2012**, 3(2), 960-966.
12. Chau Le-Ngoc Vo, Chulhun Park, Beom-Jin Lee " Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs " *Eur. J. Pharm. Biopharm.* **2013**, 1-15
13. Tapan Kumar Giri, Kulesh Kumar, Amit Alexander, Ajazuddin, Hemant Badwaik, Dulal Krishna Tripathi " A novel and alternative approach to controlled release drug delivery system based on solid dispersion technique " *Bulletin of Faculty of Pharmacy, Cairo University*. **2012**, 50, 147–159
14. Christian Leuner, Jennifer Dressman " Improving drug solubility for oral delivery using solid dispersions"*European Journal of Pharmaceutics and Biopharmaceutics***2000**, 50, 47-60
15. Duncan Q.M. Craig " The mechanisms of drug release from solid dispersions in water-soluble polymers " *International Journal of Pharmaceutics* **2002**, 231, 131–144