Study of Dissolution Enhancement of Furosemide by Solid Dispersion Technique Using Different Polymer

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Abstract: The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. The objective of this study is to determine the dissolution enhancement quality of various polymers to Furosemide. Furosemide was selected as the model drug because it is therapeutically extremely important, having very low aqueous solubility and dissolution rate, but they are well permeable through membranes of the gastro-intestinal tract. Solid dispersions of Furosemide were also prepared by fusion method and solvent evaporation method. In this study, the effectiveness of the two methods for furosemide was investigated and compared while the effect of polymer on the dissolution kinetics of the drug was also observed. Poloxamer (two grades of Poloxamer; poloxamer 188 and poloxamer 407 were used in this study), PEG and HPMC were expected to raise the dissolution rate of the poorly water-soluble furosemide and given its good permeation through GI membrane, to increase their oral bioavailability. To enhance the dissolution and efficacy of furosemide, Poloxamer188, PEG6000, and HPMC 6cps were used in different quantities. This work examined the influence of polymers such as Poloxamer 188 & 407, PEG6000 and HPMC 6cps in different amounts on release profile of furosemide. Through the dissolution studies, the *in vitro* release profile of the drug formulations was evaluated. An improved *in vitro* dissolution was obtained in all the systems.

Keywords: Dissolution Enhancement, Excipients, Solid Dosage Form, Furosemide.

1. INTRODUCTION

The oral route of drug administration is the most common and preferred method of drug delivery due to convenience and ease of ingestion [1]. Approximately 40% of newly discovered chemicals are poorly water soluble. BCS class IV drugs (*e.g.*, amphotericin B, furosemide, acetazolamide, ritonavir, paclitaxel) are the drugs having low solubility and permeability according to the classification system given by Amidon *et. al.* in 1995. These drugs are formulated such that they are made more permeable and more soluble with help of different formulation techniques. Due to being simple and economical, solid dispersion is a vastly used technique [2]. Furosemide (FRMD) is 5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid, and it is a potent high ceiling (loop) diuretics, mainly used in the treatment of hypertension. The drug has been classified as a class IV drug, according to the biopharmaceutical classification system (BCS), as a result of its low solubility [3, 4]. The technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine. Solid Dispersion technology has been successfully used for improving the solubility of the drugs and hence bioavailability e.g., tenoxicam [5], tacrolimus [6], indomethacin [7], ibuprofen [8], nilvadipine [9].

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most

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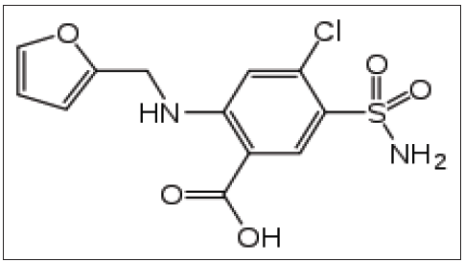
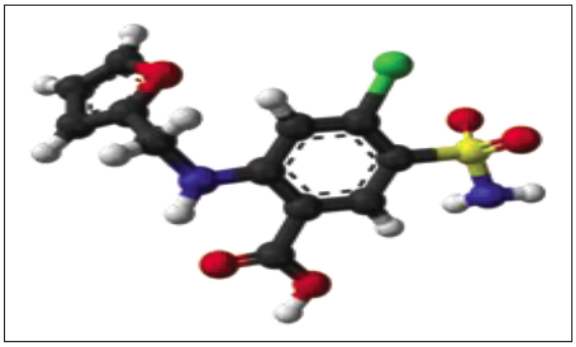
challenging aspects of drug development. Salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs [10]. This method, which was later termed as solid dispersion, involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures; *Sekiguchi and Obi* [11] suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg *et al*. [12] demonstrated that the entire drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high. Furosemide (INN) is a loop diuretic used in the treatment of congestive heart failure and edema. Furosemide is a white to off-white, odorless, crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids [3, 13]. Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 µg/mL are 91% to 99% bound in healthy individuals. The unbound fraction averages 2.3 to 4.1% at therapeutic concentrations [14].



Scheme 1: Structure of Furosemide.



Scheme 2: Structure of Furosemide (3D).

2. MATERIALS AND METHODS

2.1. Materials

Furosemide was a generous gift sample from Incepta Pharmaceuticals Limited, Dhaka, Bangladesh. The other materials such as PEG 6000 (LobaChemie, India), HPMC 6cps (Samsung, Korea) and Poloxamer 407 (BASF) were obtained from qualified sources.

2.2. Media Preparation

Initially, phosphate buffer (pH 5.8) was used as dissolution media. At first, 4 grams of NaOH was dissolved into 500 ml of distilled water by vigorous stirring to prepare a 0.2 M NaOH solution. Then 27.22 grams of dibasic potassium phosphate was dissolved into 1000 ml of distilled water by vigorous stirring to prepare a phosphate buffer solution. After that, 300 ml of phosphate buffer solution was mixed with 16 ml of 0.2M NaOH solution and diluted up to 1200 ml with distilled water to by vigorous stirring to prepare a phosphate buffer of pH 5.8, which was measured using a pH meter (HANNA Instruments, Romania) [15].

2.3. Methods

2.3.1. Preparation of Solid Dispersion by Solvent Method

The solvent process either comprises of dissolving a sparingly water-soluble drug and a water-soluble polymer, *i.e.* the carrier, in an organic solvent that is capable of dissolving both and removing the solvent by evaporation, it comprises of dissolving the drug in an organic solvent, dispersing the solution in the carrier and removing the solvent by evaporation to provide the desired solid dispersion.

2.3.2. Formulation of Furosemide Solid Dispersion with Different Polymer

Furosemide was taken in vials and methanol was added in each one of them until furosemide was completely dissolved in the solvent. Then polymer was added in the solution and sonicated for 5 min by sonicator (Hwashin Technology Co., Seoul, Korea.). All solutions were dried by hot air. When the solutions were evaporated completely, they were stored in a desiccator. The formulations were then withdrawn from vials, crushed in mortar and pestle, passed through 36-micron sieves (Endecotts Limited, England). Then the formulations were transferred back in the vials and stored in desiccators.

Table 1: Formulation of Furosemide Solid Dispersion by Changing Amounts of HPMC (6cps) with Poloxamer

Formulation of furosemide solid dispersion by changing amounts of furosemide and poloxamer 188			
Formulation	**SD1**	**SD2**	**SD3**
Furosemide	300 mg	500 mg	700 mg
Poloxamer 188	700 mg	500 mg	300 mg
Methanol	3.5 ml	4 ml	4 ml
Formulation of furosemide solid dispersion by changing amounts of HPMC(6cps) with PEG 6000			
Formulation	**SD4**	**SD5**	**SD6**
Furosemide	700 mg	700 mg	700 mg
PEG 6000	300 mg	300 mg	0
HPMC(6cps)	0	1000 mg	1000 mg
Methanol	1.5 ml	1.5 ml	2 ml
Formulation of furosemide solid dispersion by changing amounts of HPMC(6cps) with poloxamer 407			
Formulation	**SD13**	**SD14**	**SD15**
Furosemide	700 mg	700 mg	700 mg
Poloxamer 407	300 mg	300 mg	0
HPMC(6cps)	0	1000 mg	1000 mg
Methanol	1.5 ml	1.5 ml	2 ml

2.3.3. Preparation of Solid Dispersion by Fusion Method

The melting or fusion method involves the preparation of physical mixture of a drug and a water-soluble carrier, and heating it directly until it melts. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

The drug was taken in a vial along with polymer(s) and heated directly in paraffin bath within 80-90ºC while stirring. When the mixture turned into liquid, it was solidified directly in an ice bath. The final solid mass was crushed, pulverized and sieved.

2.4. *In-Vitro* Dissolution Study of Furosemide from Solid Dispersion

In-vitro dissolution study was performed in a paddle type Dissolution Apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA). A fixed amount of solid dispersion, containing 20 mg equivalent furosemide from each batch, was calculated for dissolution

Table 2: Formulation of Furosemide Solid Dispersion by Changing Amounts of Furosemide with PEG 6000 and Poloxamer 188

Formulation of furosemide solid dispersion by changing amounts of furosemide and poloxamer 188			
Formulation	**SD7**	**SD8**	**SD9**
Furosemide	300 mg	500 mg	700 mg
Poloxamer 188	700 mg	500 mg	300 mg
Formulation of furosemide solid dispersion by changing amounts of furosemide and PEG 6000			
Formulation	**SD10**	**SD11**	**SD12**
Furosemide	300 mg	500 mg	700 mg
PEG 6000	700 mg	500 mg	300 mg

purpose. Phosphate buffer (pH 5.8) was used as the dissolution media. 900 ml of phosphate buffer (pH 5.8) was used as the dissolution medium in each dissolution basket at a temperature of 37° c and a paddle speed of 75 rpm. The fixed amount of solid dispersion from each batch was weighed and transferred in each dissolution basket.

The dissolution was carried out for 1 hour and a 10 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 30, 40, 50 & 60 minutes. Each and every time 10 ml dissolution sample was compensated by another fresh 10 ml phosphate buffer (pH 5.8). Dissolution samples were withdrawn with the help of disposable syringe filters and were kept in a test tube. The dissolution samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV-mini-1240, SHIMADZU CORP., Kyoto, Japan). The dissolution study for each batch was performed in duplicate.

3. RESULTS AND DISCUSSION

The present study was aimed to observe release pattern of the drug from the solid dispersion by using different excipients such as poloxamer188, Polyethylene Glycol 6000 (PEG 6000) and different polymers such as HPMC (6cps). The variables affecting drug dissolution were dispersion property, hydrophilic polymer loading and physicochemical property of the drug molecule. Secondary curve was obtained from the dissolution rate of the different formulation. Consequently, release kinetics was determined from the various kinetic equations. In the dissolution study, it was expected that the polymers could improve the *in vitro* release of active drug from the prepared solid dispersions.

3.1. *In-Vitro* Release Study of Furosemide from Different Solid Dispersions

In-vitro dissolution study was performed in a paddle type Dissolution Apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA). A fixed amount of solid dispersion containing 20mg equivalent furosemide from each batch was calculated for dissolution purpose. Phosphate buffer (pH 5.8) was used as the dissolution media. 900 ml of phosphate buffer (pH 5.8) was used as dissolution medium in each dissolution basket at a temperature of 37° c and a paddle speed of 75 rpm. The fixed amount of solid dispersion from each batch was weighed and transferred into each dissolution basket.

The dissolution was carried out for 1 hour and a 10 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 30, 40, 50 & 60 minutes. Each and every time the 10 ml dissolution sample was compensated by another fresh 10 ml of phosphate buffer (pH 5.8).

Dissolution samples were withdrawn with the help of disposable syringe filters and were kept in a test tube. The dissolution samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV-mini-1240, SHIMADZU CORP., Kyoto, Japan). The dissolution study for each batch was performed in duplicate. The dissolution profiles of furosemide SDs that were prepared by using various polymers and corresponding pure drugs are shown in the following figures.

3.1.1. In-Vitro Release of Furosemide Using Poloxamer 188 Prepared by Solvent Evaporation Method

In the dissolution study where poloxamer 188 is used in solvent evaporation method, enhanced drug release is observed as compared to the pure drug (shown in Figure **1**). Here, three formulations are used to study the dissolution profile. Each formulation contains 300 mg, 500 mg and 700 mg of furosemide along with 700 mg, 500 mg and 300 mg of poloxamer 188 which are indicated by SD1, SD2 and SD3, respectively. The dissolution profile of formulation increases gradually with the % release values of 69.99%, 76.95% and 68.53 % for SD1, SD2, and SD3, respectively, after 1 hour. The % release value for pure furosemide is found approximately 50.13%. So, the best result is observed with solid dispersion SD2 (76.95 %) by % release of furosemide *in vitro* test. SD2 formulation contains 500 mg of furosemide and 500 mg of poloxamer 188.

3.1.2. In-Vitro Release of Furosemide Using PEG6000 & HPMC (6cps) Prepared by Solvent Evaporation Method

In the dissolution study where PEG6000 & HPMC (6cps) is used in solvent evaporation method, enhanced drug release is observed as compared to the pure drug (shown in Figure **3**). Here, three formulations are used to study the dissolution profile. Each formulation contains 700 mg of furosemide, 300 mg, 500 mg and 0 mg of PEG6000 along with 0 mg, 1000 mg and 1000 mg of HPMC (6cps) which were indicated by SD4, SD5 and SD6, respectively. The dissolution profile of formulations increases gradually with the % release values of 82.14%, 98.77% and 99.0 % for SD4, SD5 and SD6, respectively, after 1 hour. The %

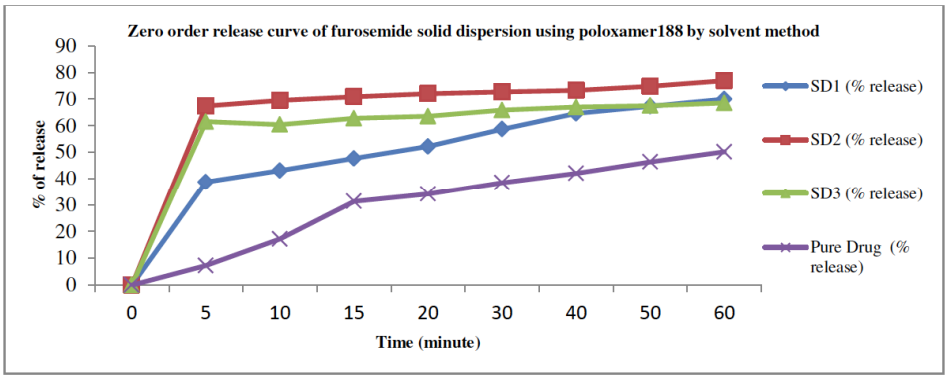


Figure 1: Effect of poloxamer188 on dissolution profile of furosemide solid dispersion by solvent evaporation method.

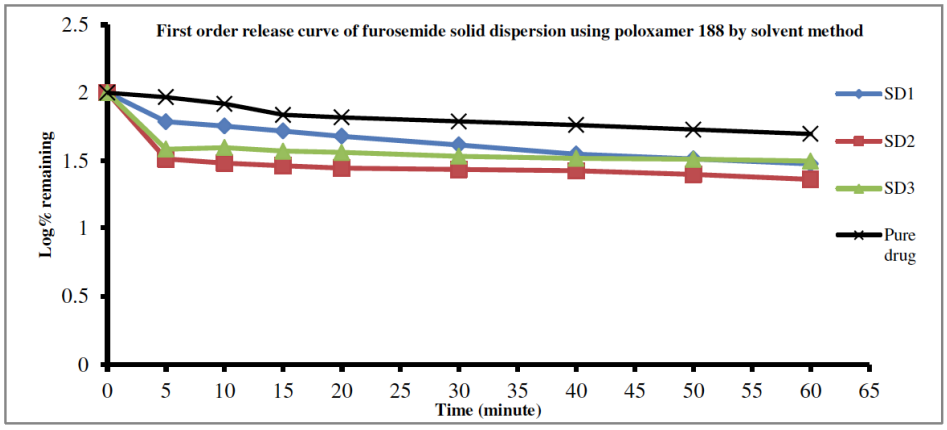


Figure 2: Effect of poloxamer188 on dissolution profile of furosemide solid dispersion by solvent evaporation method.

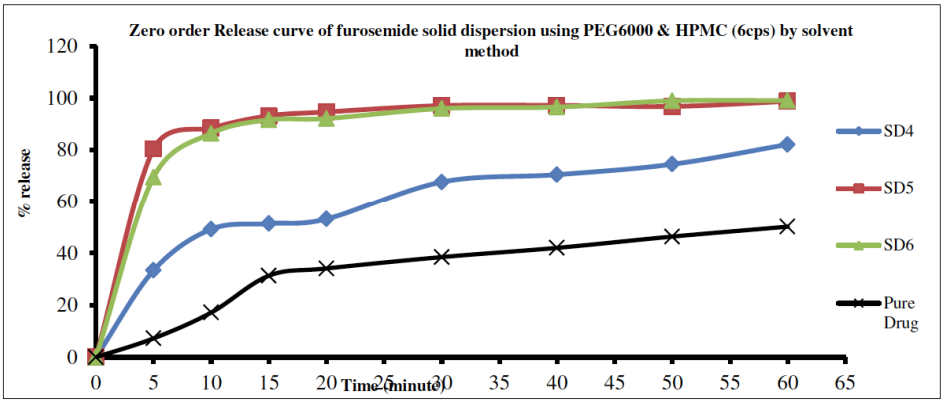


Figure 3: Effect of PEG6000 & HPMC (6cps) on dissolution profile of furosemide solid dispersion by solvent evaporation method.

release value for pure furosemide is found to be approximately 50.13%. So, the best result is observed with solid dispersion SD6 (99 %) by % release of furosemide *in vitro* test. SD6 formulation contains 700 mg of furosemide and 1000 mg of HPMC (6cps).

3.1.3. In-Vitro Release of Furosemide Using Poloxamer 188 Prepared by Fusion Method

In the dissolution study where poloxamer 188 is used in solvent evaporation method, enhanced drug release is observed as compared to the pure drug (shown in Figure **5**). Here, three formulations are used to study the dissolution profile. Each formulation contains 300, 500, 700 mg of furosemide and 700, 500, 300 mg of poloxemer188 which were indicated by SD7, SD8 and SD9 respectively. The dissolution profile of formulations increases gradually with the % release values of 97.79 %, 86.67% and 97.03 % for SD7, SD8 and SD9, respectively after 1 hour. The % release value for pure furosemide is found to be approximately

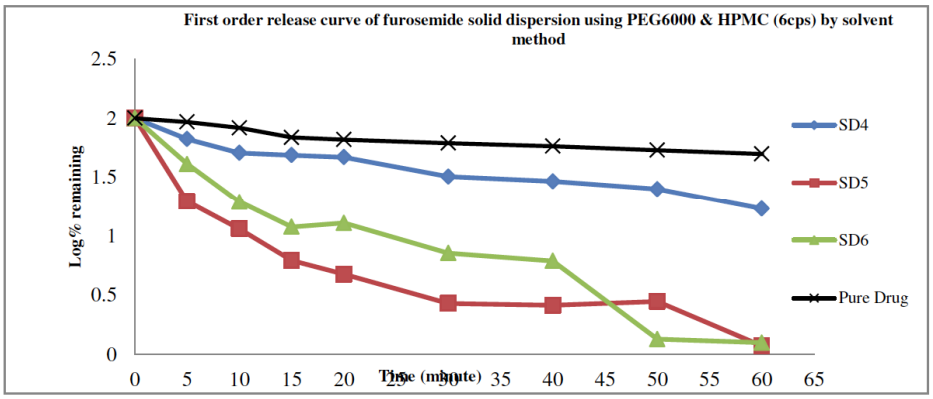


Figure 4: Effect of PEG6000 & HPMC (6cps) on dissolution profile of furosemide solid dispersion by solvent evaporation method.

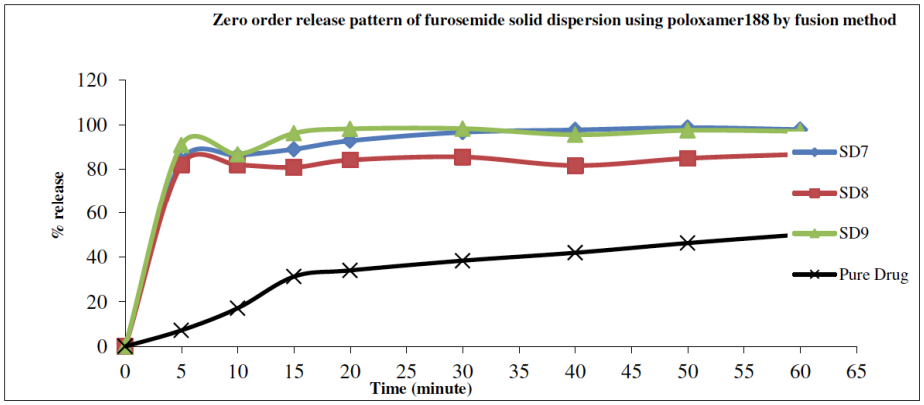


Figure 5: Effect of poloxamer 188 on dissolution profile of furosemide solid dispersion by fusion method.

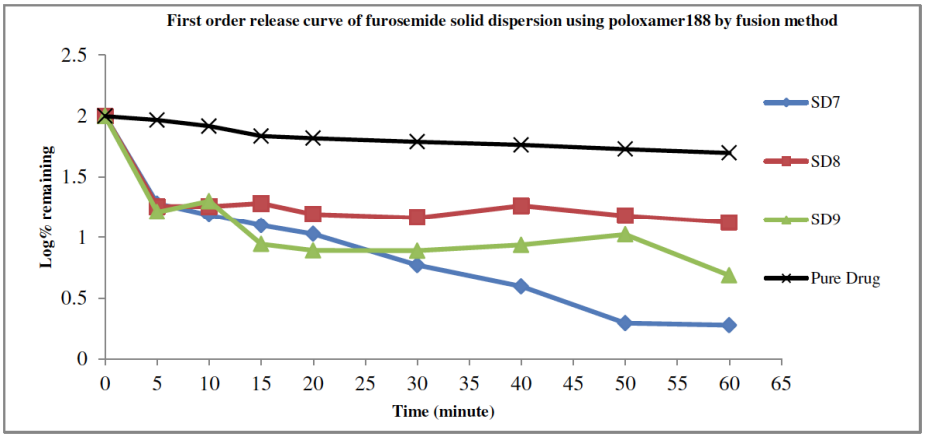


Figure 6: Effect of poloxamer188 on dissolution profile of furosemide solid dispersion by fusion method.

50.13%. So, the best result is observed with solid dispersion SD7 (97.79 %) by % of release of furosemide *in vitro* test. SD7 formulation contains 300 mg of furosemide and 700 mg of poloxamer 188.

3.1.4. In-Vitro Release of Furosemide Using PEG6000 Prepared by Fusion Method

In the dissolution study where PEG6000 is used in solvent evaporation method, enhanced drug release is observed as compared to the pure drug (shown in Figure **7**). Here, three formulations were used to study the dissolution profile. Each formulation contains 300, 500, 700 mg of furosemide and 700, 500, 300 mg of PEG 6000 which were indicated by SD10, SD11 and SD12, respectively. The dissolution profile of formulations increases gradually with the % release values of 77.37 %, 70.85 % and 83.05 % for SD10, SD11 and SD12, respectively, after 1 hour. The %

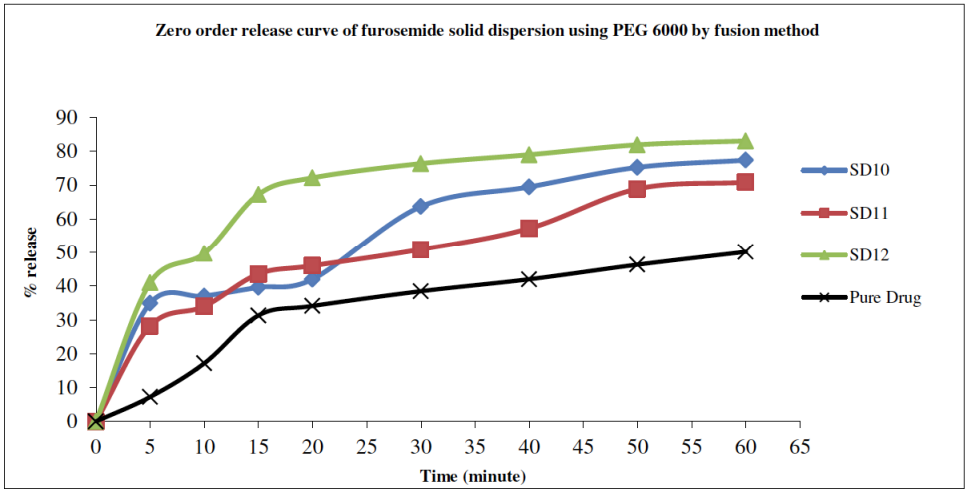


Figure 7: Effect of PEG6000 on dissolution profile of furosemide solid dispersion by fusion method.

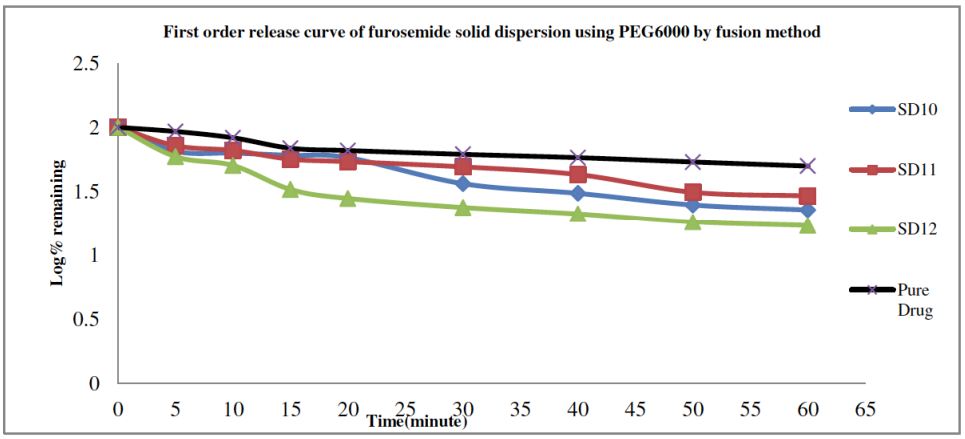


Figure 8: Effect of PEG6000 on dissolution profile of furosemide solid dispersion by fusion method.

release value for pure furosemide is found to be approximately 50.13%. So, the best result is observed with solid dispersion SD12 (83.05 %) by % release of furosemide *in vitro* test. SD12 formulation contains 700 mg of furosemide and 300 mg of PEG6000.

3.1.5. Comparative Dissolution Study for Fusion and Solvent Evaporation Method of Furosemide Solid Dispersion Using Poloxamer 188

In the dissolution study where poloxamer 188 is used, enhanced drug release is observed for both fusion (SD7) and solvent evaporation method (SD1) as

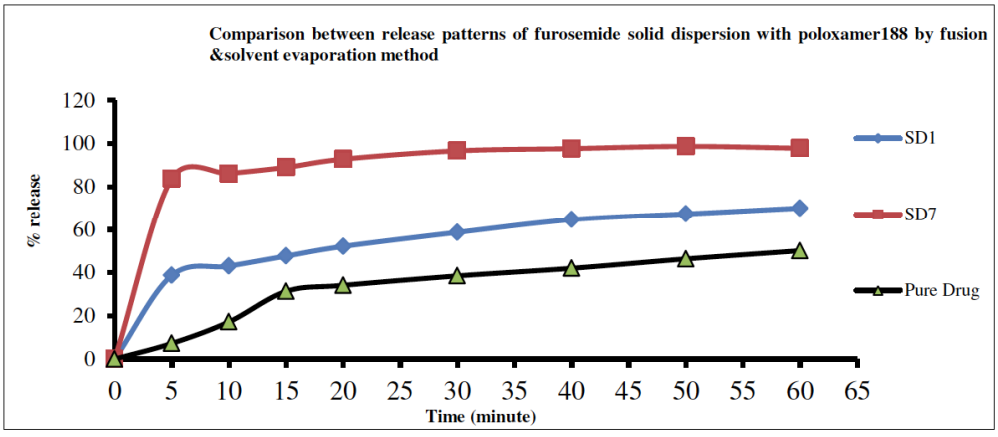


Figure 9: Effect of fusion and solvent evaporation method on dissolution profile of furosemide solid dispersion by using poloxamer 188.

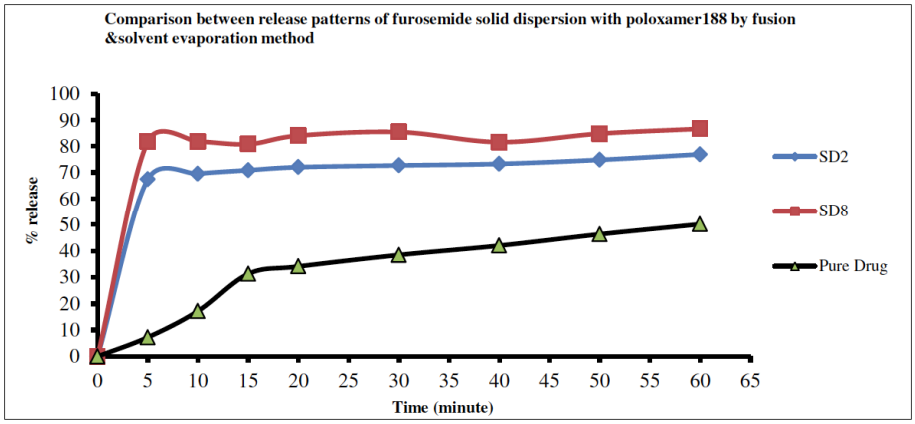


Figure 10: Effect of fusion and solvent evaporation method on dissolution profile of furosemide solid dispersion by using poloxamer 188.

compared to the pure drug (shown in Figure **9**). Each formulation contains 300mg of furosemide and 700mg of poloxamer 188. Enhanced release is observed for fusion method than that of solvent evaporation method with % release values of 67.99 % and 97.79 % for SD1and SD7; respectively, after 1 hour.

In the dissolution study where poloxamer 188 is used, enhanced drug release is observed for both fusion (SD8) and solvent evaporation method (SD2) as compared to the pure drug (shown in Figure **10**). Each formulation contains 500mg of furosemide and 500mg of poloxamer 188. Enhanced release is observed for fusion method than that of solvent evaporation method with % release values of 76.95 % and 86.67 % for SD1and SD, respectively, after 1 hour.

In the dissolution study where poloxamer 188 is used, enhanced drug release is observed for both fusion (SD9) and solvent evaporation method (SD3) as compared to the pure drug (shown in Figure **11**). Each formulation contains 500mg of furosemide and 500mg of poloxamer 188. Enhanced release is observed for fusion method than that of solvent evaporation method with % release values of 68.53 % and 97.03 % for SD3and SD9 respectively after 1 hour.

3.1.6. Comparative Dissolution Study for Fusion Method of Furosemide Solid Dispersion Using Poloxamer 188 and PEG6000 Respectively

In the dissolution study where fusion method is used, enhanced drug release is observed for both poloxamer188 (SD8) and PEG6000 (SD11) as compared to the pure drug (shown in Figure **12**). Each formulation contains 500mg of furosemide and 500mg of polymer. Enhanced release was observed for poloxamer188 than that of PEG 6000 with % release values of 86.67 % and 70.85 % for SD 8 and SD11, respectively, after 1 hour.

3.1.7. In-Vitro Release of Furosemide Using Poloxamer 407 & HPMC (6cps) Prepared by Fusion Method

In the dissolution study where poloxamer407 & HPMC (6cps) are used in solvent evaporation method,

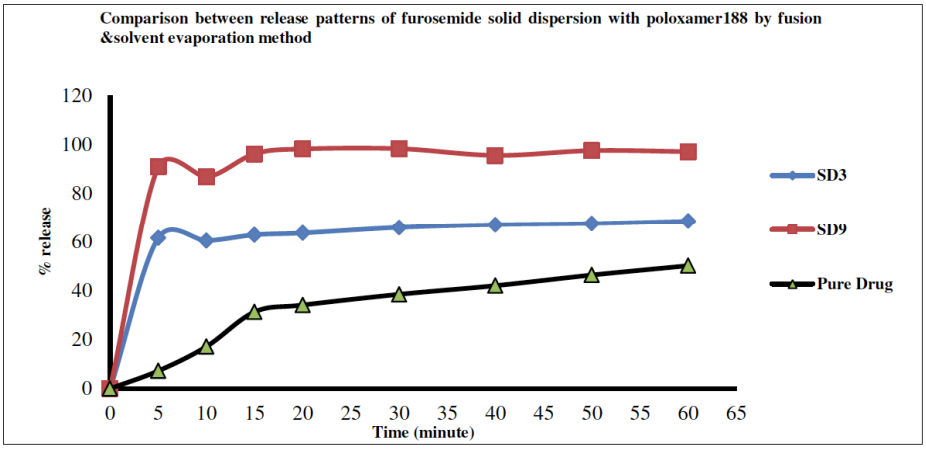


Figure 11: Effect of fusion and solvent evaporation method on dissolution profile of furosemide solid dispersion by using poloxamer 188.

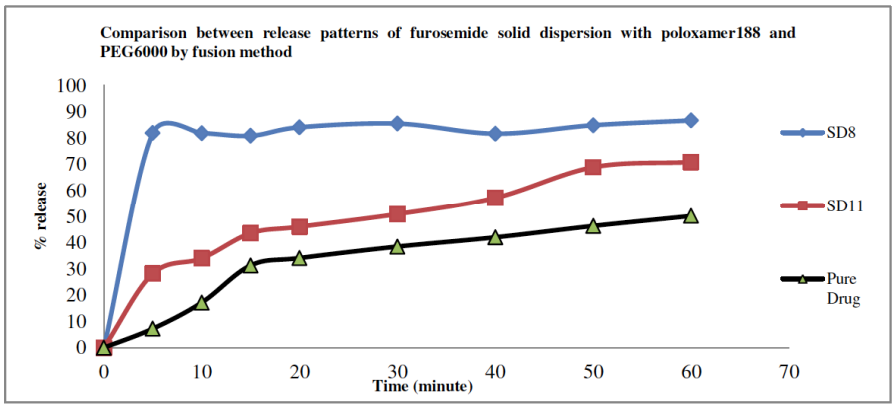


Figure 12: Effect of poloxamer 188 and PEG6000 on dissolution profile of furosemide solid dispersion by using fusion method.

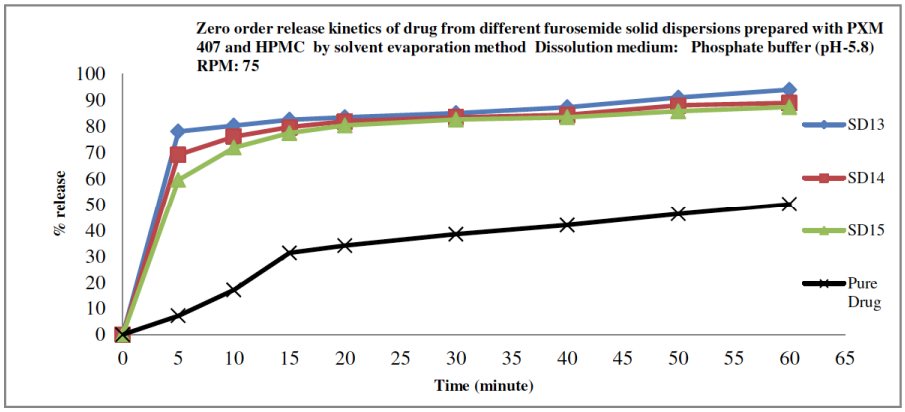


Figure 13: Effect of poloxamer 407 & HPMC (6cps) on dissolution profile of furosemide solid dispersion by solvent evaporation method.

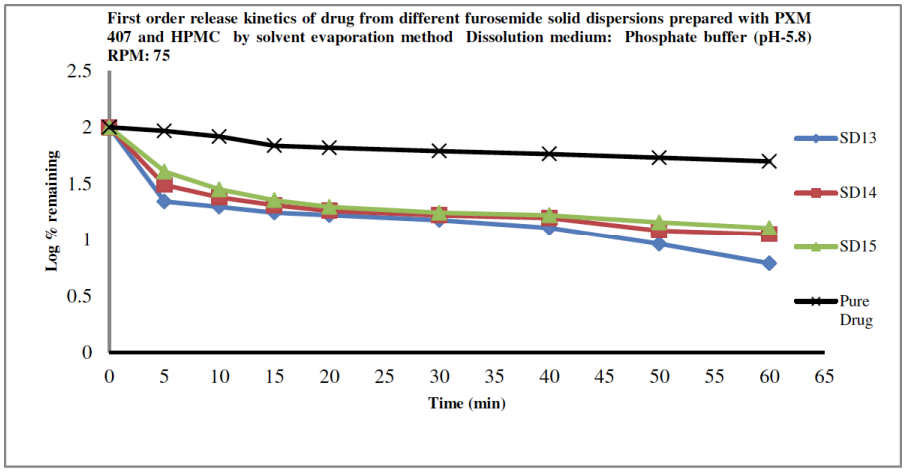


Figure 14: Effect of poloxamer & HPMC (6cps) on dissolution profile of furosemide solid dispersion by solvent evaporation method.

enhanced drug release is observed as compared to the pure drug (shown in Figure **13**). Here, three formulations are used to study the dissolution profile. Each formulation contains 700 mg of furosemide and 300 mg, 300 mg and 0 mg of poloxamer 407 along with 0 mg, 1000 mg and 1000 mg of HPMC (6cps) which were indicated by SD13, SD14 and SD15, respectively. The dissolution profile of formulations increases gradually with the % release values of 93.86%, 88.81% and 87.21 % for SD13, SD14 and SD15, respectively, after 1 hour. The % release value for pure furosemide is found to be approximately 50.13%. So, the best result is observed with solid dispersion SD13 (93.86 %) by % release of furosemide *in vitro* test. SD13

formulation contains 700 mg of furosemide and 300 mg of HPMC (6cps).

4. DISCUSSION

From the dissolution study, it is evident that for the furosemide solid dispersion with poloxamer, dissolution rates increase significantly more by fusion method as compared to the solvent evaporation method (Figures **9**, **10** & **11**). For 1:1 formulation of polymer with drug by fusion method, poloxamer increases dissolution rate of furosemide more than PEG (Figure **12**). When HPMC is used in combination with either poloxamer or PEG, the dissolution rates decrease slightly for poloxamer & increase slightly for PEG but with HPMC along, the highest increase in dissolution rate was obtained in case of solvent evaporation method (Figures **3** & **13**). However, in general, dissolution rate was increased more or less significantly for all the formulations. So, in conclusions, we observed that Poloxamer and PEG combination of HPMC with PEG and that of HPMC with poloxamers all increased dissolution rate of furosemide observed significantly.

5. CONCLUSION

The increasing dissolution property of furosemide by poloxamer & HPMC will be of big advantage in clinical setups. Both fusion and solvent evaporation method increase the dissolution rate of furosemide significantly.

Among polymers, Poloxamer and HPMC show the best dissolution rates.If further research can be done, significant advances can be made in the field of furosemide solid dispersion.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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