

PERFORMANCE OF POLOXAMER 188 AND POLOXAMER 407 AS HYDROPHILIC CARRIER ON THE BINARY MIXTURES OF MESALAZINE

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ABSTRACT

A solid dispersion (SD) approach has been performed to enhance the dissolution rate of insoluble drugs by improving their aqueous solubility. An insoluble drug, Mesalazine was chosen as a model drug, non-steroidal anti-inflammatory drug. In the present investigation, an attempt were made to improve the solubility and dissolution rate of a poorly soluble drug, Mesalazine by solid dispersion method using Poloxamer 188 and Poloxamer 407 as carriers. Solid dispersion of Mesalazine was prepared by Fusion Method (FM), Solvent Evaporation Method (SEM), and Kneading Method (KM). In vitro release profiles of all Solid dispersions were comparatively evaluated and also studied against pure Mesalazine. Faster dissolution was exhibited by PDS3, Solid dispersion containing 1:3 ratio of drug: Poloxamer 407 by Solvent evaporation method. The prepared Solid dispersions were subjected for Drug Content, Infrared (I.R.) Spectroscopic Studies and Differential Scanning Calorimetry (DSC). FT-IR spectra revealed no chemical incompatibility between drug and Carrier. Drug - polymer interaction were investigated using differential scanning calorimetry (DSC). In addition to dissolution studies, XRD results revealed that Mesalazine was converted to its amorphous state. The dissolution rate of the prepared solid dispersion systems were determined in Hydrochloric Acid Buffer pH 2.0 All the formulation showed marked improvement in the solubility and dissolution rate of drug which may be due to hydrophilic polymers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. The dissolution rate was enhanced in the following order SEM > FM > KM. The enhancement of dissolution rate may be due to increase in wettability, dispersibility as well as particle size reduction of the drug.

Keywords: Poloxamer 188, Poloxamer 407, Mesalazine, Solid Dispersion.

INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration¹⁻⁵.

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Poorly water-soluble drugs present many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability. The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development⁶. Together with the permeability, the solubility behaviour and the dissolution rate of a drug is a key determinant of its oral bioavailability and is one of the most important concerning aspects of the pharmaceutical industries⁶⁻⁸. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SDs) is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the

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bioavailability of poorly soluble drugs⁸. Solid dispersions have been widely reported as an effective method for enhancing the dissolution rate and bioavailability of poorly water soluble drugs⁹. The dissolution rate is directly proportional to solubility of drug¹⁰. The term 'solid dispersion' refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the fusion, solvent evaporation and melt solvent methods³. The release mechanism of drug from a variety of solid dispersions depends on the physical properties of carriers as well as drug substances and preparation methods⁹. Solid dispersions have been used for a long time to solve many problems related to poor water solubility, low bioavailability and stability of many drugs¹⁰⁻¹¹. Many procedures can be used to prepare solid dispersions such as fusion, solvent evaporation and solvent-fusion methods¹². Other relevant methods can be used to prepare solid dispersions such as spray drying¹³, freeze-drying¹⁴ and microwaves¹⁵. Despite the great potential of solid dispersions for enhancing drug dissolution, the methods traditionally used have some problems such as physical instabilities of some drugs and difficulty in completely removing liquid solvent¹⁶⁻¹⁷.

Poloxamer block copolymers have been exploited in pharmaceutical formulations for solubilization of poorly water-soluble drugs. Poloxamers consist of an ethylene oxide hydrophilic core and polypropylene oxide hydrophobic core blocks arranged in a tri block structure¹⁸⁻²⁰. Owing to their low melting point, they are suitable for the melt technique in solid dispersions. Their ability to self-aggregate, thereby forming micelles and liquid crystalline phases and greater hydrophilicity is another advantage for the solubilization of poorly water-soluble drugs. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of the micelle or conjugated to the micelle-forming polymer. These amphiphilic co-polymers are available in different grades as poloxamer 188 and poloxamer 407¹⁸⁻²⁰. Poloxamer 407 was used to enhance the dissolution rate of several drugs such as atenolol²¹, piroxicam²² and ibuprofen²³⁻²⁴.

The aim of the present investigation was to enhance the solubility, dissolution rate of Mesalazine with solid dispersion technique using Poloxamer 188 and Poloxamer 407 as a hydrophilic carrier. Solid dispersion systems of the drug with Poloxamer 188 Poloxamer 407 were prepared in different ratios by Fusion Method (FM), Kneading Method (KM) and Solvent Evaporation Techniques (SEM). The physicochemical properties of the prepared solid dispersion were evaluated using different methods.

Materials and Methods:

Mesalazine was supplied by Startek Pvt., Ltd, Hyderabad. Poloxamer 188, Poloxamer-407 (Pluronic F-98) was obtained as gift sample from Dr. Reddy's Laboratories, Hyderabad. All other reagents were of analytical grade.

Preparation of Mesalazine Solid Dispersions (SDs) using different techniques:

Different drug: polymer ratios were used for preparing Mesalazine solid dispersions in Poloxamer 188 and Poloxamer-407 matrix, via Fusion method (FM), Solvent Evaporation Method (SEM) and Kneading Method (KM).

Kneading Method (KM):

In this method, Mesalazine and PXM 188 or 407 were weighed according to these drug and carrier ratios (1:1, 1:2 and 1:3) and were triturated using a small volume of Ethanol: Water (80:20) to give a thick paste, which was kneaded for 30 minutes and then dried at 40° C in an oven. PDK1881 to PDK1883 corresponds to preparations containing PXM 188 and PDK4 to PDK6 correspond to preparations containing PXM 407. The dried mass was then pulverized, passed through mesh no. 30, stored in a vacuum desiccator (48 hrs) and passed through sieve no. 60 before packaging in an airtight container.

Solvent Evaporation Method (SEM):

In this method, Mesalazine and PXM 188 or 407 were weighed according to these drug and carrier ratios (1:1, 1:2 and 1:3) and dissolved in a common solvent, after complete dissolution of drug and carrier in Ethanol: Water (80:20), the solvent is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. PDS1 to PDS3 corresponds to preparations containing PXM 188 and PDS4 to PDS6 correspond to preparations containing PXM 407. The dried mass was then pulverized, passed through mesh no. 30, stored in a vacuum desiccator (48 hrs) and passed through sieve no. 60 before packaging in an airtight container.

Fusion Method (FM):

In this method, Mesalazine and PXM 188 or 407 were weighed according to these drug and carrier ratios (1:1, 1:2 and 1:3) and dissolved in a Poloxamer, after complete dissolution of drug and in carrier, cooled to solidify by keeping on Ice bath. The film is further dried to constant weight. PDF1881 to PD1883 corresponds to preparations containing PXM 188 and PDF4 to PDF6 correspond to preparations containing PXM 407. The dried mass was then pulverized, passed through mesh no. 30, stored in a vacuum desiccator (48 hrs) and passed through sieve no. 60 before packaging in an airtight container.

Characterization of Mesalazine - Carrier Mixture:

Solubility Study:

For determination of solubility of Mesalazine alone and SDs, excess amounts of samples were added to 20.0 mL distilled water, sonicated for 1 h (J. P. Selectasa., Spain) and shaken in a shaker water bath with the temperature maintained at 37 °C for 48 h (SBS Instrument, Germany). The suspension was filtered (0.45 µm micro-filter), suitably diluted and analyzed spectrophotometrically at 210 nm for Mesalazine content.

Scanning Electron Microscopy (SEM)

The morphological characteristics of prepared solid dispersion particles were observed by scanning electron microscopy. The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs were taken with a JSM-1600 scanning electron microscope (Jeol, Tokyo, Japan).

Differential Scanning Calorimetry (DSC)

Calorimetric studies of the drug and the prepared solid dispersion systems were performed using a DSC-60 (Shimadzu, Kyoto, Japan). The 4–5 mg samples were placed in hermetically sealed aluminum pans. A 10°C/ min scanning rate was used

over the 25–200°C temperature range. Indium was used as the temperature and enthalpy standard.

Powder X-ray diffractometry (PXD)

Powder X-ray diffraction patterns of the drug-Carriers solid dispersions were compared to the individual components that were generated using a wide-angle Rigaku Ultima IV X-ray diffractometer (Rigaku Corporation, Tokyo, Japan). The instrument was operated on the 2θ scale. The angular range was 10° to 50° (2θ) and counts were accumulated for 1 sec at each step.

In-vitro Dissolution Study:

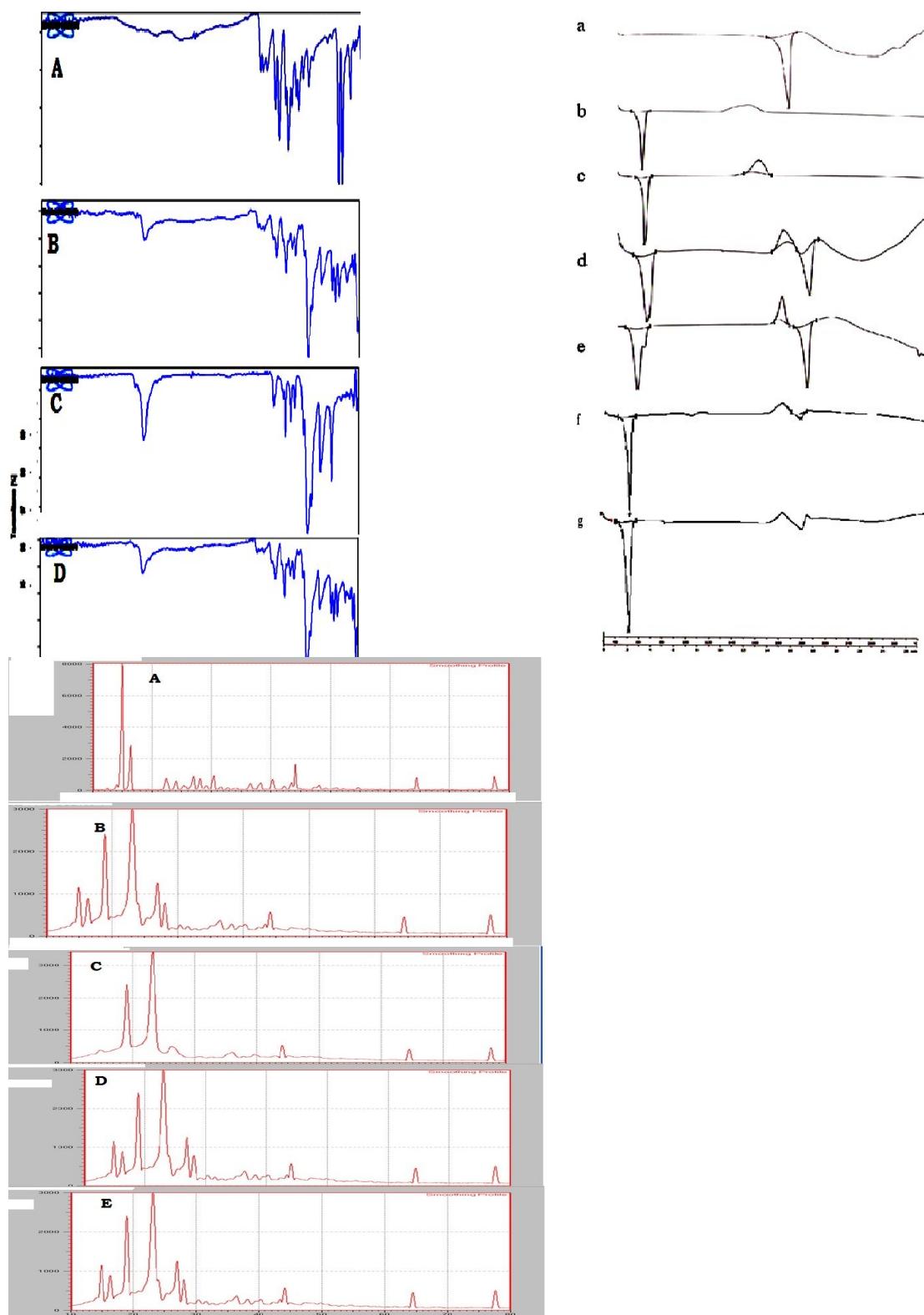
The dissolution of Mesalazine from different samples was carried out in 900 mL Hydrochloric Acid buffer pH 2.0 maintained at 37±0.5°C under 50 rpm stirring rate (Electro Lab TDT – 08L). 100 milligrams of the drug or its equivalent in SD was dispersed on the surface of the dissolution medium. Five mL were withdrawn at appropriate time intervals, and filtered. The % cumulative amount of drug released with time was determined spectrophotometrically at 210 nm. Triplicate runs were carried out and the amount of drug dissolved was calculated.

Statistical Analysis:

All data were expressed as mean standard deviations (± SD). Statistical analysis was performed using student t-test at 0.01 level of significance.

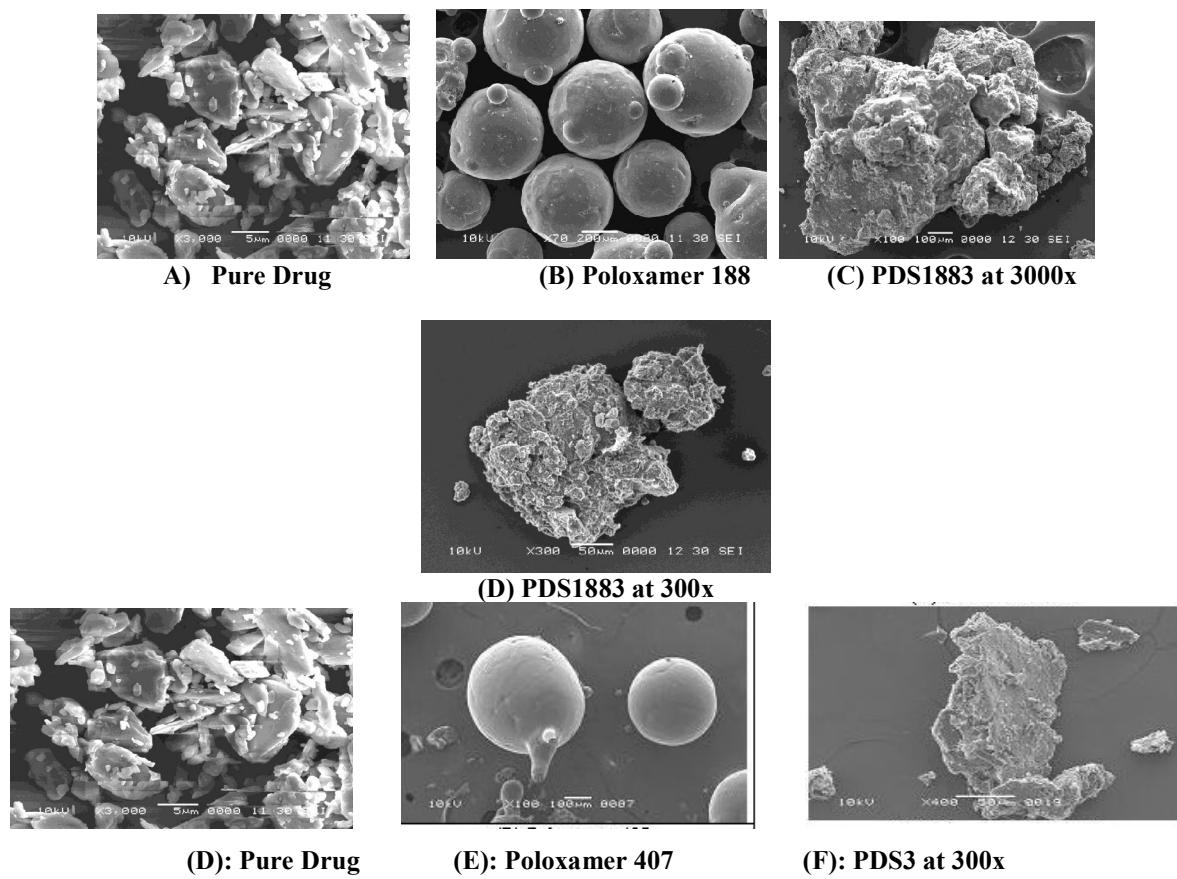
Table-1: Solubility, Drug Content and *In-Vitro* Release Studies of Mesalazine and its solid dispersion in Hydrochloric Buffer pH 2.0.

S.no	Formulation Code	Solubility (±S.D), n=3	Drug Content (% w/w) (± SD, n =4)	In-vitro Release in Hydrochloric Acid pH 2.0	
		HCL pH 2.0	HCL pH 2.0	T _{50%} (min) (± SD) n=4	T _{80%} (min) (± SD) n=4
1	Pure Drug	1.34 ± 0.032	---	4 ± 0.01	20 ± 0.04
2	PDK1881	1.36 ± 0.56	95.56(0.47)	27 ± 0.02	76 ± 0.12
3	PDK1882	1.44 ± 0.71	96.72(1.46)	22 ± 0.30	61 ± 0.51
4	PDK1883	1.56 ± 0.88	98.43(1.87)	18 ± 0.91	53 ± 0.11
5	PDS1881	1.86 ± 0.53	96.69(1.11)	20 ± 0.22	35 ± 0.51
6	PDS1882	1.93 ± 0.45	98.72(1.44)	16 ± 0.21	25 ± 0.61
7	PDS1883	2.21 ± 0.71	98.16(1.39)	12 ± 0.71	20 ± 0.71
8	PDF1881	1.54 ± 0.21	95.29(3.48)	24 ± 0.41	50 ± 0.21
9	PDF1882	1.64 ± 0.11	96.84(2.49)	20 ± 0.31	48 ± 0.18
10	PDF1883	1.82 ± 0.41	97.50(2.90)	16 ± 0.11	30 ± 0.22
11	PDK1	1.54 ± 0.91	96.90(0.99)	20 ± 0.41	33 ± 0.41
12	PDK2	1.58 ± 0.81	95.14(2.24)	15 ± 0.19	29 ± 0.91
13	PDK3	1.61 ± 0.41	95.44(1.12)	12 ± 0.51	19 ± 0.11
14	PDS1	3.44 ± 0.01	96.07(1.71)	13 ± 0.17	27 ± 0.39
15	PDS2	3.66±0.05	98.66(1.56)	10 ± 0.15	20 ± 0.51
16	PDS3	3.87±0.09	99.62(1.56)	6 ± 0.61	10 ± 0.21
17	PDF1	1.29±0.43	95.35(1.27)	15 ± 0.19	30 ± 0.11
18	PDF2	1.49±0.54	97.45(1.74)	12 ± 0.13	24 ± 0.51
19	PDF3	2.35±0.75	98.65(1.99)	8 ± 0.12	15 ± 0.91



Figures -1 & 2: FTIR & DSC graphs of (A) Pure Drug; (B) Poloxamer -188; (C) Poloxamer – 407; (D) Drug-Poloxamer -188; (E) Drug – Poloxamer- 407.

Figure -3: A: Drug- Mesalazine, B: Poloxamer 188, C: Poloxamer 407, D: Poloxamer+188(Fusion Method), E: Poloxamer+407(Fusion Method), F: Poloxamer+188(Solvent Evaporation Method), G: Poloxamer+407(Solvent Evaporation Method).



Figures - 4: SEM photographs of Drug, Poloxamers and Solid Dispersions.

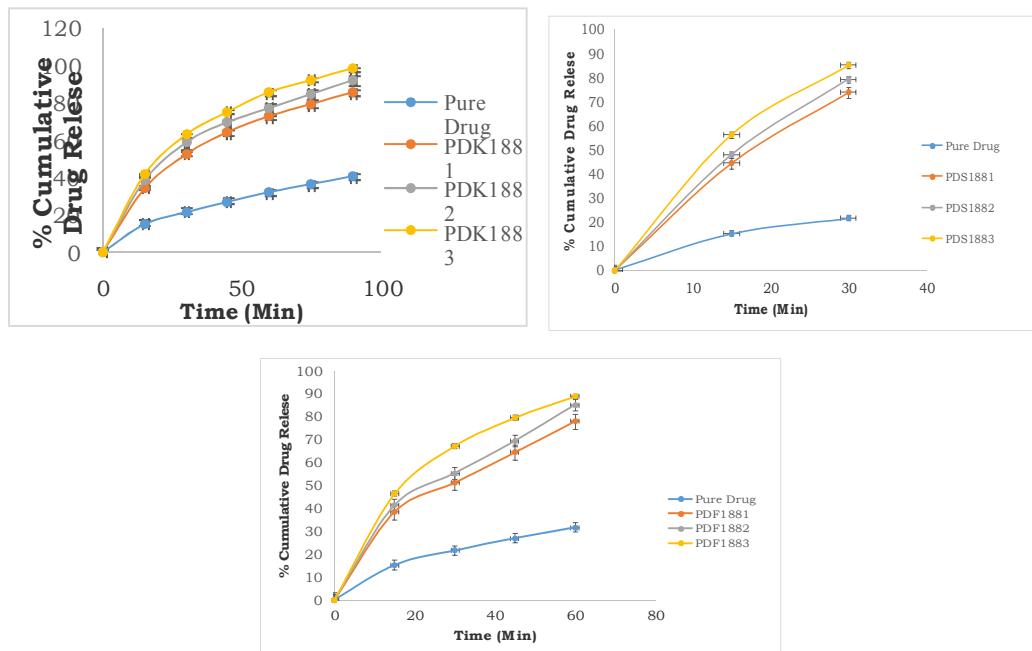


Fig-5, 6 & 7: *In-Vitro* Drug Release Profile of Mesalazine using Poloxamer 188 in Hydrochloric Acid Buffer pH 2.0 by Kneading Method, Solvent Evaporation Method & Fusion Method.

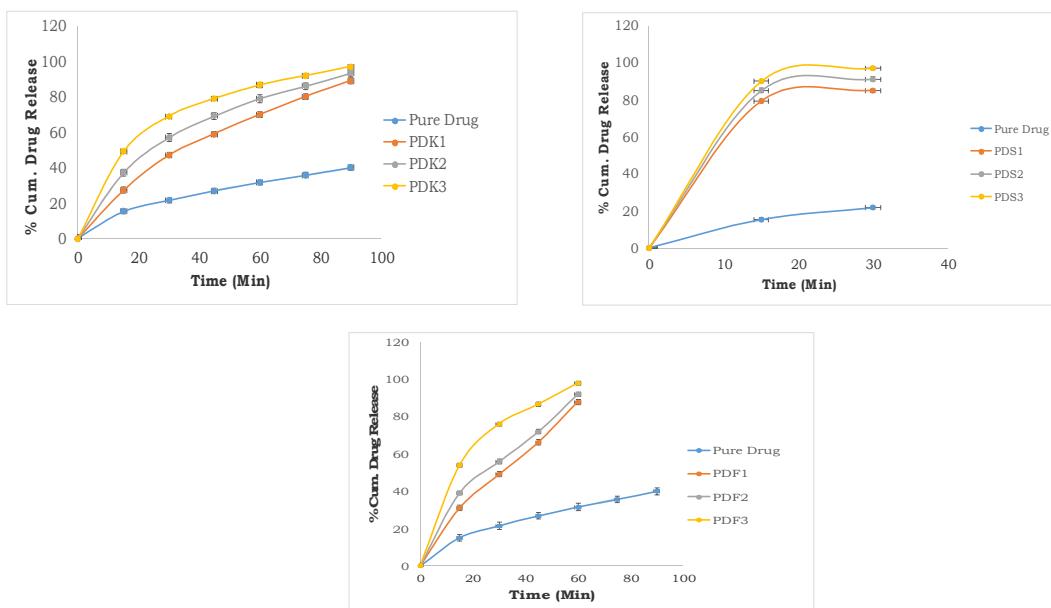


Fig 8, 9 & 10: *In-Vitro* Drug Release Profile of Mesalazine using Poloxamer 407 in Hydrochloric Acid Buffer pH 2.0 by Kneading Method, Solvent Evaporation Method & Fusion Method

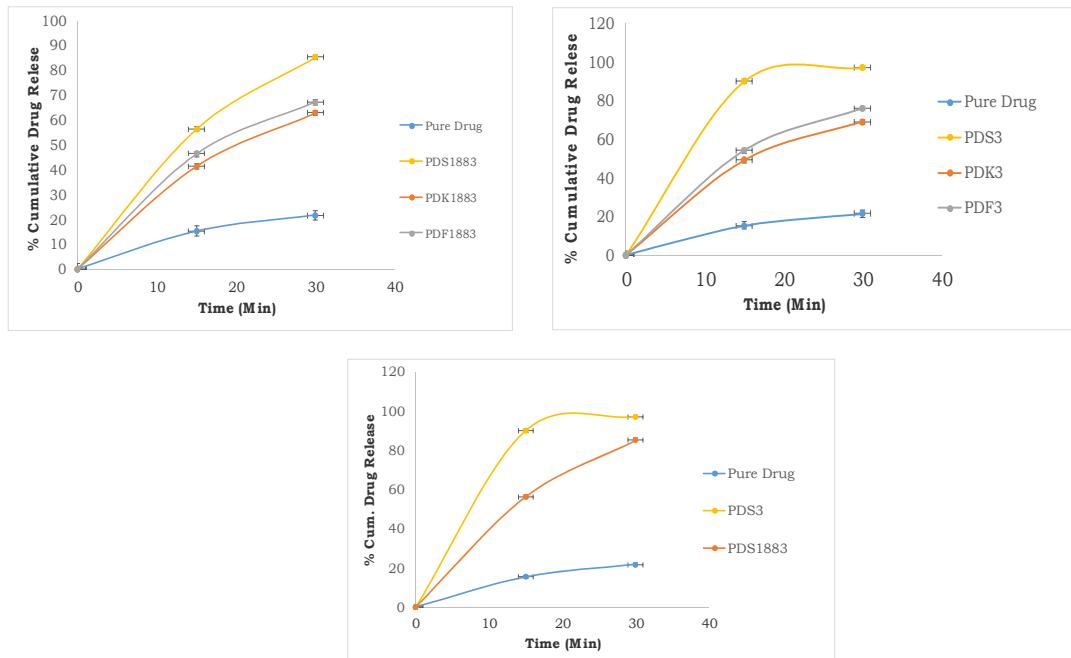


Fig – 11 & 12: Comparative Drug Release Profile of Optimized formulation of Mesalazine using Poloxamer 188 & Poloxamer 407 in Hydrochloric Acid Buffer pH 2.0.

Fig – 13: Comparative Drug Release Profile of Optimized formulation of Mesalazine by Solvent Evaporation Method using Poloxamer 188 & Poloxamer 407 in Hydrochloric Acid Buffer pH 2.0.

RESULTS AND DISCUSSION

To investigate the potentiality and performance of Poloxamer-188 and Poloxamer-407-based systems for enhancement of drug solubility and dissolution, the solid dispersion of Mesalazine-Poloxamer-188 and Mesalazine - Poloxamer-407 binary systems were prepared by

different methods. These techniques include, Fusion Method, Kneading Method and Solvent Evaporation Method.

Characterization of prepared Solid Dispersion: Solubility Analysis:

The solubility profile of Mesalazine and its different dispersions with polymers are shown in

table -1. The solubility of Mesalazine in water was found to be approximately 1.34 mg/ml. Significantly increase in solubility was obtained for all dispersions of Mesalazine with hydrophilic carriers. Maximum solubility was observed in PDS3 in Hydrochloric Acid pH 2.0 prepared by Solvent Evaporation Method, which considered as optimized solid dispersion of drug. Increase in solubility may be due to hydrophilic nature of the polymers, decreased agglomeration and aggregation of drug particles, particle size reduction to molecular size. Another probable theory concerns to an increase effective solubilisation process by carriers in the microenvironment (diffusion layer) immediately surrounding the drug particles. Solubility increases with increase in carrier concentration. In summary, the order of solubility was found to be SEM>FM>KM both in Hydrochloric Acid Buffer pH 2.0.

FTIR: The fig - 2 shows the FTIR spectra of Mesalazine, PXM, and solid dispersion systems. The infrared spectrum of pure mesalazine exhibited the characteristic bands corresponding to the functional groups of the drug at 3,433 cm⁻¹ (due to the mutual overlapping of NH and OH stretching), 1,651 cm⁻¹ (corresponds to the C=O stretch), 1,620 cm⁻¹ (corresponds to NH bending), and 1,354 cm⁻¹ (corresponds to CN stretching). The characteristic peaks at 2887, 1343 and 1124 are assigned due to C-H, O-H and CO groups of poloxamer. Solid dispersions showed the characteristics peaks of Mesalazine with decreased intensity and little shifting of peaks. The IR spectrum of dispersion shows shifting of the characteristic peak of N-H from 3429 to 3419 due to hydrogen bonding. However the IR spectrum does not show any additional peak indicating the absence of any chemical interaction between Mesalazine and poloxamers. From the above data it was assumed that physical interaction of drug with polymer is responsible in dissolution enhancement. Fig - 2 indicates that drug and excipient (polymer) interaction was not seen in the formulation.

Scanning Electron Microscopy Studies:

Morphology of the pure drug, Poloxamer 188, Poloxamer 407 and Solid Dispersions of optimized formulation was investigated by scanning electron microscopy. Fig - 4 shows the surface morphology of Mesalazine, Poloxamer 188, Poloxamer 407 and Solid Dispersions of optimized formulation. Mesalazine was characterized by different size of prism shaped crystals, whereas Poloxamer-188 and Poloxamer-407 was characterized by spherical particles with very smooth surface. Figure - 4 shows SEM photographs of drug: polymer ratios 1:3. All solid dispersion systems showed drastic change in the surface of the prepared micro-particles. The photomicrographs of solid dispersion systems prepared by solvent method (SM), Fusion method (FM) and kneading

method (KM) showed agglomerates of micro-crystals of drug particles were uniformly dispersed in the matrices of Poloxamer 188 and Poloxamer-407 (Figure - 4). This change of particles shape was indicative of the presence of a new solid phase. The obtained results were in agreement with those from previous reports.

DSC: Differential scanning calorimetry (DSC) is frequently used in the pharmaceutical field as a thermal analysis technique, to provide detailed information about both the physical and energetic properties of substances. The thermal behaviour of Mesalazine, Mesalazine-Poloxamer188, Mesalazine-Poloxamer-407 solid dispersion systems prepared by different methods and carriers are shown in Figure - 3. Mesalazine displayed an endothermic peak at 285 °C corresponding to its melting point. Poloxamer 188 and Poloxamer 407 showed endothermic peak at 54°C and 55°C due to its melting point. Thermal traces for Solid dispersion at 1:3 ratio showed very weak peak shifted to lower melting point. The peak appeared at 279°C with heat of fusion -76.3 mJ and -68.5 mJ respectively for the ratio 1:3 in case of Fusion Method, while lower intensity of peak appearance in case of Solvent Evaporation Method. The decrease of the intensity of the peak may be due to the dilution effect by the carrier used. Other SD systems prepared using different drug: polymer ratios showed the disappearance of the characteristic peak of the drug. This may be due to decreased crystallinity of the drug. These results were in agreement with that found by Shin and Cho. It is worthy to note that the heat of fusion for all solid dispersions systems decreased which might indicate that Mesalazine has been transformed to an amorphous or less crystalline form in its-polymer Solid Dispersion systems.

XRD: Figure - 2 show XRD Photographs of pure drug and formulations. XRD study reveals the physical interaction between the drug and polymers. Mesalazine is a highly crystalline powder with several characteristic diffraction peaks that appeared at diffraction angle 2θ (6.0, 13.0, 14.2, 19.1, 22.1 and 26.2). While Poloxamer 188 and Poloxamer-407 copolymers produced two characteristic peaks at 19.2 and 24.0. All prepared dispersions showed changes in the number of peaks or few diffuse peaks were observed in all dispersions as compared to XRD spectra of raw Mesalazine drug, which indicate decrease in crystallinity in dispersed Mesalazine. The intensities of the major drug peaks of Mesalazine were slightly decreased in Solid Dispersions of Solvent Evaporation Method ratio 1:3. But the most of drug peaks were disappeared in all different solid dispersion systems. This means that in Solid Dispersion, the drug was still in a crystalline state but the intensity was decreased due to the dilution effect of the carrier, but in all Solid Dispersion

systems the disappearance of the characteristic peaks of drug may be due to change into amorphous one, as observed in the DSC studies. The decreased drug crystallite size can explain the faster dissolution and increased solubility, which indicates that there is physical interaction between drug and polymers

Drug Content Analysis:

The drug content was found in the range of 95.14 ± 2.24 to 99.62 ± 1.56 % in Hydrochloric Acid pH 2.0 and the % yield was within 100% to 101% indicating the acceptability of method for preparation of solid dispersions. Low values of standard deviation of drug content in SDs indicates uniform drug distribution in all the prepared batches. The values are given in Table -1.

In-vitro Drug Release:

The release of the drug from all the solid dispersions was increased significantly ($p<0.05$) than from pure drug alone as indicated by values of $T_{50\%}$ and $T_{80\%}$ in Table -1. As shown in Figures - 5 to 10, the release of drug from the solid dispersions prepared with Poloxamer 188 and Poloxamer 407 in the ratio of 1:3 by Solvent Evaporation Method was quickest in comparison to other Solid Dispersions. Values of $T_{50\%}$ and $T_{80\%}$ are shown in Table-1. The dissolution profiles of Mesalazine-Poloxamer-188 and Mesalazine-Poloxamer-407 solid dispersions (SDs) prepared using different methods were compared with drug itself (Figures - 5 to 10). All the prepared SD systems showed a remarked enhancement of the in-vitro drug dissolution rate. In particular, SD systems prepared by Solvent Evaporation method in ratio 1:3 by using both Poloxamer 407 was able to produce 98 % of the drug in solution within 6min in case of Hydrochloric Acid Buffer pH 2.0 in comparison with Poloxamer 188 which release 96% 11min in same dissolution medium. Similarly, Fusion method was able to produce about 92 % in 60min and the Kneading method was able to produce about 85% of the drug in solution within 120 min in Hydrochloric acid pH 2.0. It was noticed that SD systems prepared by Solvent Evaporation Method were capable of improving drug dissolution in a rate higher than those produced by Fusion and Kneading Method significantly ($p< 0.01$). On the other hand, the corresponding percentage of the drug was only about 38 %. An increased in Mesalazine dissolution rate was achieved by the other ratios for the different systems but this increase was less than this ratio (1:3). $T_{50\%}$ and $T_{80\%}$ of all solid Dispersion was kept in table -1. It could be seen that, Poloxamer-407 has effectively enhanced the drug dissolution and this effect depends on the ratio of the carrier used and the method of the preparation of solid dispersion. In addition, Figure - 11 to 13 showed the comparison between the dissolution behaviors of the drug from all different systems. It has shown that the Solvent Evaporation

method had the priority of the enhancing of the dissolution rate. It is evident that, in all solid dispersion preparation methods, increasing the Poloxamer-407 weight ratio was followed by increasing the amount of Mesalazine dissolving property.

The enhancement of dissolution of Mesalazine from solid dispersion systems may be due to lack of crystallinity, amorphization, increase wettability and dispersibility and particle size reduction. Furthermore, Kneading produces a uniform distribution of drug in the copolymer carrier crust in highly dispersed state. Thus, when such system becomes in contact with dissolution medium, the hydrophilic carrier dissolves rapidly. In addition, the Poloxamer-407 has surface activity so it reduces the interfacial tension between the solid dispersion and dissolution medium and decreases the aggregation of drug particles and enhances the dissolution rate of drug.

Conclusion:

Solid dispersion of Mesalazine in Poloxamer- 188 and Poloxamer-407 could be prepared by different methods. Mesalazine solid dispersion systems prepared by Solvent Evaporation Method using Poloxamer-407 in comparasion to other two techniques had showed higher solubility and dissolution rate than the drug alone. The Solvent Evaporation Method had a priority to enhance the solubility and dissolution rate over the other studied methods.

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