

PERFORMANCE OF POLOXAMER 407 AS HYDROPHILIC CARRIER ON THE BINARY MIXTURES WITH NIMESULIDE

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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, nimesulide (Nims), was chosen as a model for non-steroidal anti-inflammatory drugs. It was dispersed in a water-soluble carrier poloxamer 407. Different methods were employed to prepare such dispersion, namely: Solvent method (SM), Melting method (MM) and Kneading method (KM) in different drug: carrier ratios. Nims solid dispersions were characterized for their physicochemical properties using scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and the powder X-ray diffractometry (XRD). In addition to dissolution studies, the results revealed that Nims was converted to its amorphous state. The dissolution rate of the prepared solid dispersion systems was determined in phosphate buffer pH 7.4. The solubility of drug from different systems was also determined in water. This study revealed that, the presence of the hydrophilic carrier allows improving the drug solubility. The dissolution rate was enhanced in the following order KM > MM > SM. The enhancement of dissolution rate may be due to increase in wettability, dispersibility as well as particle size reduction of the drug.

Rezumat

În prezentul articol s-a realizat un studiu privind obținerea dispersiilor solide, în vederea creșterii ratei de dizolvare a medicamentelor, prin îmbunătățirea solubilității lor în apă. Nimesulidul, un medicament insolubil în apă, a fost ales ca substanță activă model din clasa antiinflamatoarelor nesteroidiene. Acesta a fost dispersat în Poloxamerul 407, un transportor hidrosolubil. Au fost folosite diferite metode pentru a se realiza dispersiile, dintre care: metoda solventului (SM), metoda topirii (MM), metoda triturării (KM), utilizându-se proporții diferite de medicament / transportor.

Dispersiile solide cu nimesulid au fost caracterizate din punct de vedere al proprietăților lor fizico-chimice, cu ajutorul microscopiei electronice (SEM), a calorimetriei dinamice diferențiale (DSC) și a difracției cu raze X (*powder X-ray diffractometry*). Pe lângă studiile de dizolvare, rezultatele au demonstrat că nimesulidul a trecut în starea sa amorfă. Rata de dizolvare a sistemelor solide pregătite a fost determinată în tampon fosfat pH 7,4. De asemenea, a fost determinată solubilitatea în apă a medicamentului din diferite

sisteme. Acest studiu a arătat că prezența diferiților transportori hidrofilici permite îmbunătățirea solubilității medicamentului.

Rata de dizolvare a crescut în ordinea următoare, în funcție de metodele folosite: KM > MM > SM. Îmbunătățirea ratei de dizolvare se poate datora atât sporirii capacității de înmuiere și a capacității de dispersare, cât și unei reduceri a dimensiunii particulelor de medicament

Keywords: Poloxamer 407, nimesulid, solid dispersion, SEM, DSC, XRD

Introduction

Solid dispersions have been used for a long time to solve many problems related to poor water solubility, low bioavailability and stability of many drugs [1, 2]. Many procedures can be used to prepare solid dispersions such as fusion, solvent evaporations and solvent-fusion methods [3]. Other relevant methods can be used to prepare solid dispersions such as spray drying [4], freeze-drying [5] and microwaves [6]. 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 solvent [7, 8].

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 structure resulting in an amphiphilic structure [9-11]. 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 407 [9-11]. Poloxamer 407 was used to enhance the dissolution rate of several drugs such as atenolol [12], piroxicam [9] and ibuprofen [13].

Nimesulide (Nims) is an acidic nonsteroidal anti-inflammatory drug (NSAID) that differs from many similar compounds in that it is acidic by virtue of a sulfonanilide rather than a carboxyl group [14]. It is an inhibitor of cyclooxygenase 2, hence inhibits the synthesis of destructive prostaglandins and spares cytoprotective prostaglandins. Nims belongs to the class II biopharmaceutical classification scheme [15, 16] a low solubility-high permeability drug. Nims is very sparingly soluble in water (0.01 mg/mL) [16] and its poor aqueous solubility and wettability gives rise

to difficulties in pharmaceutical formulations for oral and parenteral delivery, which may lead to variable bioavailabilities. Enhancement of dissolution and bioavailability of Nims solid dispersion systems was carried out using different hydrophilic carriers such as polyethylene glycol, polyvinyl pyrrolidone [17], tromethamine [18]. In this study, Nims was used as model drug for NSAIDs.

The aim of the present investigation was to enhance the solubility, dissolution rate of Nims with solid dispersion technique using Poloxamer 407 as a hydrophilic carrier. Solid dispersion systems of the drug with Poloxamer 407 were prepared in different ratios by melting, kneading and solvent techniques. The physicochemical properties of the prepared solid dispersion were evaluated using different methods.

Materials and Methods

Materials

Nimesulide (Nims) was kindly supplied by Medical Union Pharmaceuticals (MUP) Co., Abu-Sultan, Ismaillia Egypt. Poloxamer- 407 (Pluronic F-98) was obtained from C.H. Erbesloh, Krefeld, Germany. All other reagents were of analytical grade.

Methods

Preparation of Nims solid dispersions (SDs) using different techniques

Different drug: polymer ratios were used for preparing Nims solid dispersions in Poloxamer-407 matrix, *via* melting method (MM), solvent method (SM) and kneading method (KM).

Solvent method (SM)

The weighed amounts of Nims and polymer were dissolved in a minimum amount of methanol. Then, the organic solvents were removed by evaporation at room temperature [19]. The dried mass was taken, pulverized, sieved. The samples were kept in desiccators until the experiment.

Melting method (MM)

The formula weights of the drug and the polymer heated in a beaker on a thermostatically controlled hot plate (Gallenkamp, United Kingdom) at 70-80°C until the solution had completely cleared. The molten mixture was then stirred until having cooled.

Kneading method (KM)

Nims and the polymer weight ratios were kneaded with appropriate amounts of water and methanol using a mortar and pestle for 10 min. The

mass was dried (room temperature overnight), crushed, sieved and dried again in an oven (Heraeus, Germany) at 40 °C for 24h.

Preparation of binary mixtures

Physical mixtures (PMs) of different drug to polymer ratios were prepared by gentle mixing the drug and the carriers in a mortar.

Characterization of Nims-polymer binary mixtures

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-Poloxamer 407 solid dispersions and their selected physical mixtures compared to the individual components were generated using a wide-angle Rigaku Ultima IV X-ray diffractometer (Rigaku Corporation, Tokyo, Japan). The instrument was operated on the 2 θ scale. The angular range was 10° to 50° (2 θ) and counts were accumulated for 1 sec at each step.

Dissolution study

The dissolution of Nims from different samples was carried out in 900 mL phosphate buffer pH 7.4 maintained at 37±0.5 °C under 50 rpm stirring rate (Erweka DT-D6, Heusenstamm Germany). Twenty milligrams of the drug or its equivalent in PM or SD was dispersed on the surface of the dissolution medium. Five mL were withdrawn at appropriate time intervals, and filtered. The content was determined spectrophotometrically at 392 nm. [18]. Triplicate runs were carried out and the amount of drug dissolved was calculated.

Solubility study

For determination of solubility of Nims alone, PM with Poloxamer-407 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 392 nm for Nims content.

Statistical analysis

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

Results and Discussion

To investigate the potential of Poloxamer-407-based systems for enhancement of drug solubility and dissolution, the solid dispersion of Nims-Poloxamer-407 binary systems were prepared by different methods. These techniques include, melt, kneading and solvent method.

Characterization of prepared solid dispersion

Scanning electron microscopy (SEM)

SEM microphotographs of the drug, Poloxamer-407, physical mixture 1:4 and its solid dispersions were illustrated in Figure 1 (1A, 1B, 1C, 1D, 1E and 1F).

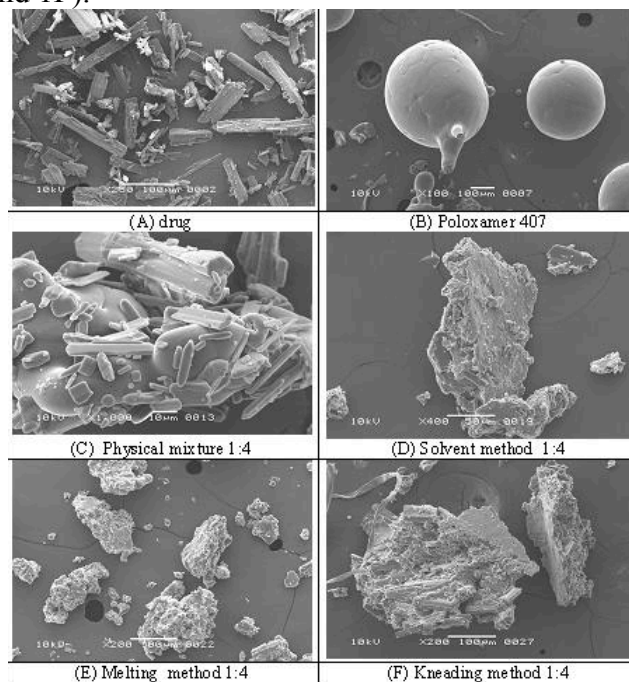


Figure 1

Photomicrographic scanning electron images for: (A) drug, (B) poloxamer 407 (C) PM 1:4 drug: Poloxamer-407 (D) Solid dispersion 1:4 solvent method (E) SD 1:4 melting method (F) SD 1:4 kneading method.

Nims was characterized by different size of prism shaped crystals, whereas Poloxamer-407 was characterized by spherical particles with very smooth surface. The physical mixture of drug and carrier in a drug: polymer ratio 1:4 showed mixture of spherical smooth surface and prism crystals, Figure 1C. While all the 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), melting method (MM) and kneading method (KM) showed agglomerates of micro-crystals of drug particles were uniformly dispersed in the matrices of Poloxamer-407 Figure 1 (D, E and F). 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 [20 -22].

Differential Scanning Calorimetry (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 [21]. The thermal behavior of Nims, Nims-Poloxamer-407 solid dispersion systems prepared by different methods as well as their corresponding physical mixtures with the used carrier are shown in Figures 2–4. Nims displayed an endothermic peak at 149 °C corresponding to its melting point [18, 23] with heat of fusion about – 431.78 mJ.

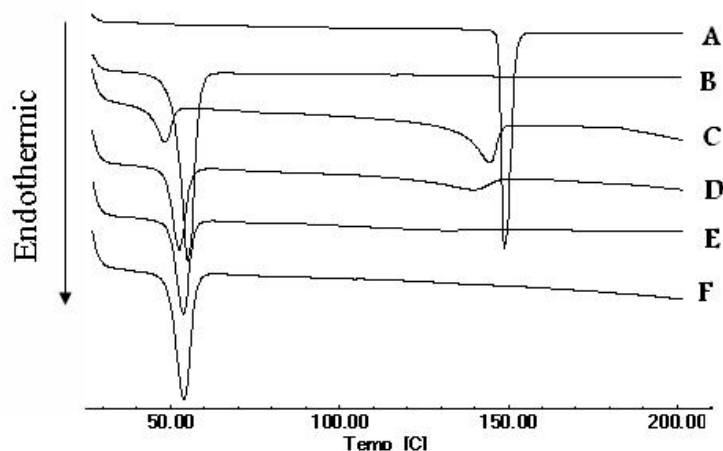


Figure 2

DSC thermograms for (A) Nims (B) Poloxamer-407 (C) PM 1:4 (D) SM 1:1 (E) SM 1:2 (F) SM 1:4.

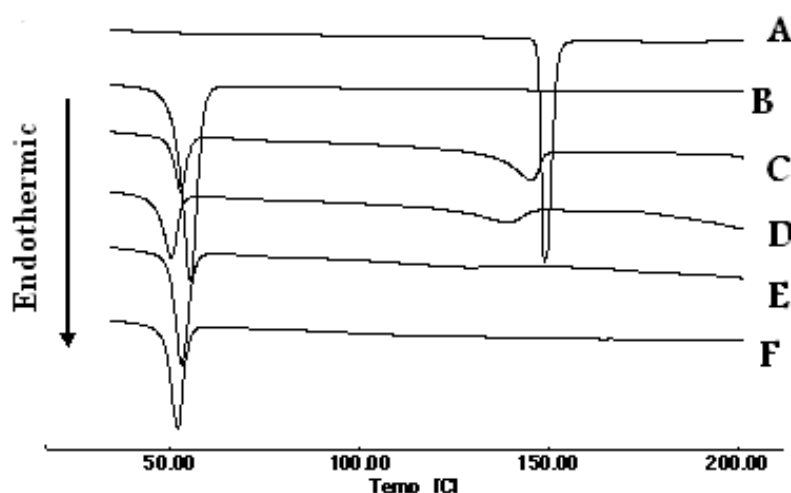


Figure 3

DSC thermograms for (A) Nims (B) Poloxamer-407 (C) PM 1:4 (D) MM 1:1 (E) MM 1:2 (F) MM 1:4.

Poloxamer 407 showed endothermic peak at 55°C due to its melting point. Thermal traces for PM at 1:4 ratio showed very weak peak shifted to lower melting point. The peak appeared at 145°C with heat of fusion – 144 mJ. The decrease of the intensity of the peak may be due to the dilution effect by the carrier used. For the ratio 1:1 for the solvent method and melting method, the characteristic peak of the drug was shifted to lower melting point at 138.8°C with heat of fusion about -76.3 mJ and -68.5 mJ respectively. Other SD systems prepared using different drug: polymer ratios showed the disappearance of the characteristic peak of the drug. This may be due to decrease the crystallinity of the drug. The endothermic peak of the Poloxamer-407 in all SDs systems appeared sharp and at the same position as that of pure copolymer. This revealed the existence of Poloxamer-407 in crystalline state. These results were in agreement with that found by Shin and Cho [24]. It is worthy to note that the heat of fusion for all SD systems decreased which might indicate that Nims has been transformed to an amorphous or less crystalline form in its-polymer SD systems [20].

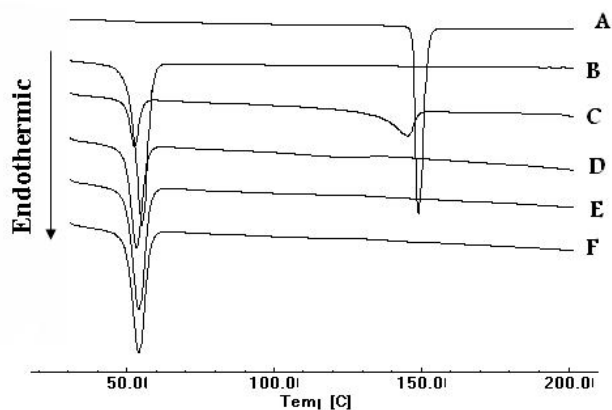


Figure 4

DSC thermograms for (A) Nims (B) Poloxamer-407 (C) PM 1:4 (D) KM 1:1 (E) KM 1:2 (F) KM 1:4.

X-ray powder diffraction (XRD)

The XRD patterns of Nims, Poloxamer-407, PM 1:4 and solid dispersion prepared by different methods in ratio 1:4 are displayed in Figure 5.

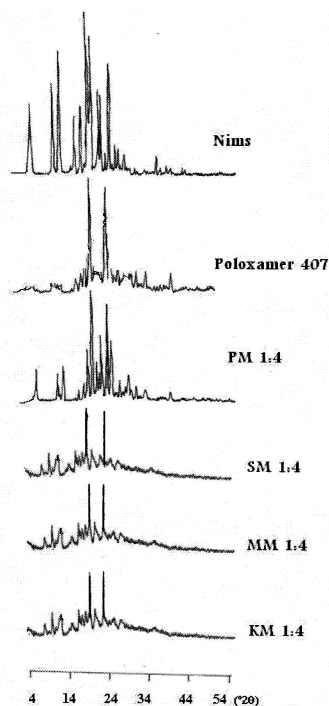


Figure 5

X-ray diffraction patterns for the drug, Poloxamer-407, PM 1:4 and different solid dispersion system at ratio 1:4.

Nims 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-407 copolymer produced two characteristic peaks at 19.2, 24.0. The intensities of the major drug peaks of Nims were slightly decreased in physical mixture ratio 1:4, but the most of drug peaks were disappeared in all different solid dispersion systems. This means that in PM the drug was still in a crystalline state but the intensity was decreased due to the dilution effect of the carrier, but in all SD systems the disappearance of the characteristic peaks of drug may be due to change into amorphous one, as observed in the DSC studies.

***In vitro* dissolution studies**

The dissolution profiles of Nims-Poloxamer-407 solid dispersions (SDs) prepared using different methods for Nims were compared to those of the PM and drug itself (Figures 6-8). All the prepared SD systems showed a remarked enhancement of the in-vitro drug dissolution rate. In particular, SD systems prepared by kneading method in ratio 1:4 was able to produce 98 % of the drug in solution, while the melting method produce about 89 % and the solvent method produce about 71% of the drug in solution within 120 min. It was noticed that SD systems prepared by kneading were capable of improving drug dissolution in a rate higher than those produced by melting method significantly ($p < 0.01$). On the other hand, the PM produced about 55 % of the drug in solution. The corresponding percentage of the drug was about 38 %. An increased in Nims dissolution rate was achieved by the other ratios for the different systems but this increased was less than this ratio (1:4). The relative dissolution rate at 10 and 120 minutes (RDR_{10} , RDR_{120}) were summarized in table 1. It could be seen that, Poloxamer-407 has effectively enhanced the drug dissolution and this effect depended on the ratio of the carrier used and the method of the preparation of solid dispersion. In addition, Figure 9 showed the comparison between the dissolution behavior of the drug from all different systems. It has shown that the kneading 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 Nims dissolved.

The enhancement of dissolution of Nims from solid dispersion systems may be due to lack of crystallinity, amorphization, increase wettability and dispersibility and particle size reduction [1-2]. 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.

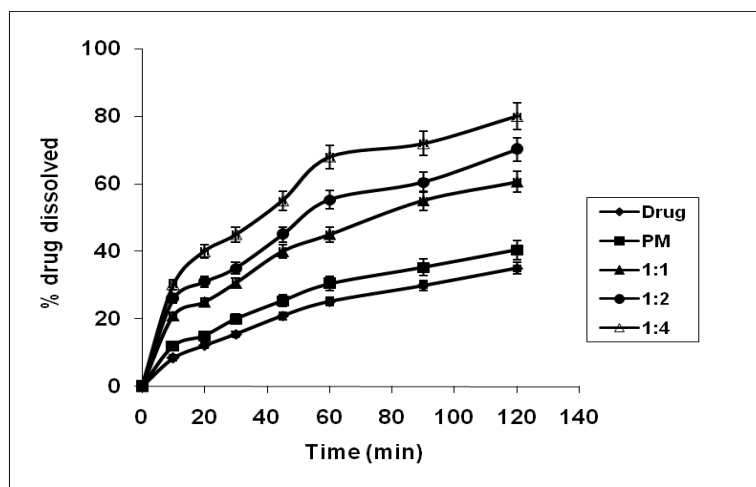


Figure 6

Dissolution profile of Nimesulide, PM and different solid dispersions with Poloxamer-407 prepared by solvent method.

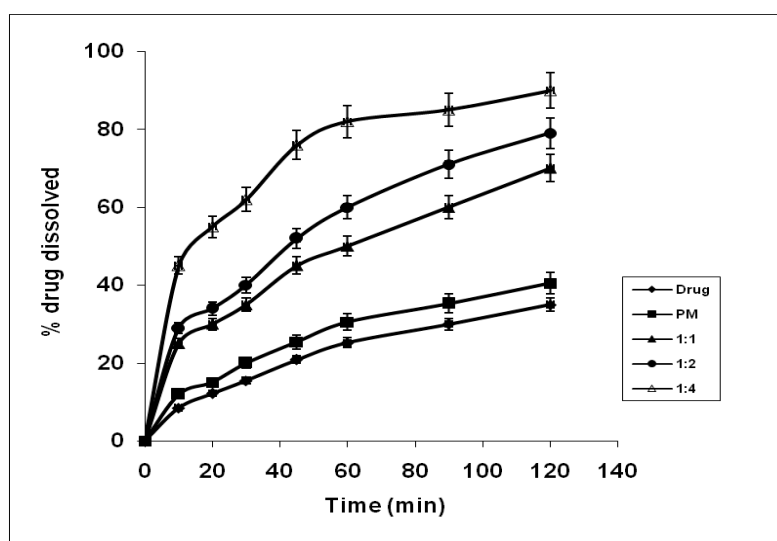


Figure 7

Dissolution profile of Nimesulide, PM and different solid dispersions with Poloxamer-407 prepared by melting method.

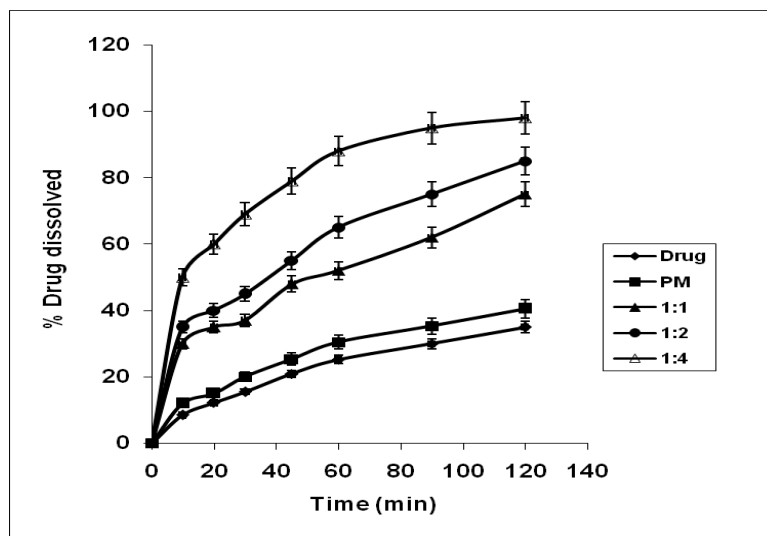


Figure 8

Dissolution profile of Nimesulide, PM and different solid dispersions with Poloxamer 407 prepared by kneading method.

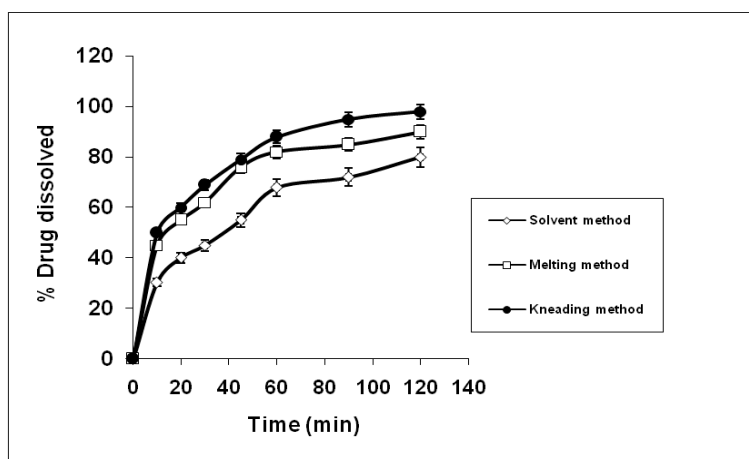


Figure 9

Dissolution profile of the Nimesulide in different solid dispersion systems

Solubility determination

The aqueous solubility of a drug is a prime determinant of its dissolution rate and compounds with aqueous solubility less than 0.1 mg/mL often present dissolution limitation to absorption. Nims is considered

practically as an insoluble drug in water. The solubility of Nims in water was markedly increased in presence of the used carrier as solid dispersion (Table I). For instance, the solubility of Nims at 37 °C increased 11- folds or 10-fold when it was formulated as SD at 1:4 ratio by either kneading method or melting method, respectively. On the other hand, the solubility of drug increased 7-fold by the solvent method in the same ratio. In general, the increase in solubility of Nims was enhanced in all other SDs ratio compared to the corresponding PMs, Table I. It was shown that, the kneading method had a priority in enhancing drug aqueous solubility.

Table I

Solubility and relative dissolution rate (RDR) after 10 and 120 minutes of different solid dispersion systems and its physical mixture.

System type	Ratio	Solubility (mg/mL)	RDR ₁₀ (after 10 minutes)	RDR ₁₂₀ (after 120 minutes)
Drug	===	0.010	===	===
Physical mixture	1:4	0.030	1.41	1.14
Solvent system	1:1	0.042	2.47	1.72
	1:2	0.061	3.06	2.01
	1:4	0.072	3.55	2.29
Melting system	1:1	0.060	2.94	2.03
	1:2	0.078	3.41	2.26
	1:4	0.105	5.29	2.57
Kneading system	1:1	0.070	3.53	2.15
	1:2	0.082	4.12	2.43
	1:4	0.110	5.89	2.80

Conclusion

Solid dispersion of Nims in Poloxamer-407 could be prepared by different methods. Nims solid dispersion systems had a higher solubility and dissolution rate than the drug alone or the physical mixture. The kneading method had a priority to enhance the solubility and dissolution rate over the other studied methods.

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References

- 1- Vasconcelos T, Sarmiento B, Costa, P, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov Today*. 2007, 12:1068-1075.

- 2- Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 2000, 50: 47-60.
- 3- EL-Badry M, Fathy M. Properties of solid dispersion of piroxicam in pluronic F-98. *J Drug Del Sci. Tech.* 2004, 14 (3) :199-205.
- 4- Fouad E A, EL-Badry M, Mahrous G M, AL-Anazi F K, Neau S H, Alsarra, I A. The use of spray drying to enhance celecoxibe solubility. *Drug Dev Ind Pharm.* 2011, 37 (12): 1463-1472.
- 5- EL-Badry M. Preparation and characterization of albendazole microparticles prepared by freeze-drying technique. *Bull. Pharm. Sci. Assiut University.* 2008, 31 (1) :123-135.
- 6- Moneghini M, Zingone G, De-Zordi N. Influence of the microwave technology on the physical-chemical properties of solid dispersion with nimesulide. *Powder technology.* 2009, 195: 259-263.
- 7- Craig D Q. The mechanisms of drug release from solid dispersions in water soluble polymers. *Int J Pharm.* 2002, 231:131-144.
- 8- Karavas E, Georgarakis E, Sigalas MP, Avgoustakis K, Bikiaris D. Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug polymer interactions. *Eur J Pharm Biopharm.* 2007, 66: 334-347.
- 9- Shin SC, Cho CW. Physico chemical characterization of piroxicam-poloxamer solid dispersions. *Pharm Dev Tech.* 1977, 2: 403- 407.
- 10- Narasimha S. Managoli, Raghavendra V. Kulkarni, N. Ramarao, I. S. Muchandi, Crosslinked chitosan hydrogel matrix tablets for controlled release of gabapentin, *Farmacia*, 2012, 60(2), 272-286
- 11- A Wade; PJ Weller; Handbook of Pharmaceutical *Excipients*, American Pharmaceutical Association, Washington, DC, 907, 1994.
- 12- Monti S, Burgalassi S, Rossato M S, Albertini B , Passerini N , Rodriguez L, Chetoni P. Poloxamer 407 microspheres for orotransmucosal drug delivery. Part II: In vitro/in vivo evaluation. *Int J Pharm.* 2010, 400:32–36.
- 13- Nawa M, Bhandari KH , Oh D H , Kim YR, Sung JH, Kim JO, Woo JS, Choi H G, Yong CS. Enhancement dissolution of ibuprofen using solid dispersion with poloxamer 407. *Arch Pharm. Res.* 2008, 31: 1497-1507.
- 14- Singla AK, Chawla M, Singh A. Nimesulide: some pharmaceutical and pharmacological aspects—an update. *J Pharm Pharmacol.* 2000, 52:467-475.
- 15- Meriani F, Cocceani N, Sirotti C, Voinovich V, Grassi M. Characterization of a quaternary liquid system improving the bioavailability of poorly water soluble drugs. *J Colloid Interface Sci.*,2003, 263: 590-596.
- 16- Piel G, Pirotte B, Delneuveille I. Study of the influence of both cyclodextrins and L-lysine on the aqueous solubility of nimesulide: isolation and characterization of nimesulide-L-lysine-cyclodextrin complexes. *J Pharm Sci.* 1997, 86: 475-480.
- 17- Dutet J, Lahiani-Skiba M , Didier L, Jezequel SO., Bounoure F, Barbot C, Arnaud F, Skiba M. Nimesulide/cyclodextrin/PEG 6000 ternary complexes: physico-chemical characterization, dissolution studies and bioavailability in rats. *J Incl Phenom Macrocycl Chem.* 2007, 57: 203–209.
- 18- Abdelkader H, Abdallah O, and Salem H S. Comparison of the effect of tromethamine and polyvinylpyrrolidone on dissolution properties and analgesic effect of Nimesulide. *AAPS Pharm. Sci. Tech.* 2007, 8 (3): E2-E8.
- 19- Fülöp Ibolya, Árpád Gyéresi, Piroska Szabó-Révész, Zoltán Aigner, Solid dispersions of flufenamic acid with PEG 4000 and PEG 6000, *Farmacia*, 2011, 59(1), 60-69.
- 20- Fernandes CM , Vieira MT, Veiga FJB. Physicochemical characterization and *in vitro* dissolution behavior of nicardipine-cyclodextrins inclusion compounds. *Eur J Pharm Sci.* 2002, 15:79–88.
- 21- Naidu NB, Chowdary KPR., Murthy KVR, Satyanarayana V, Hayman AR, Backet G. Physicochemical characterization and dissolution properties of meloxicam-cyclodextrin binary systems. *J Pharm Bio Med Anal.* 2004, 35:75–86.

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- 22- Clas S, Dalton CR, Hancock BC. Differential scanning calorimetry: Applications in drug development. *Res Focus*. 1999, 2: 311–320.
 - 23- Nalluri NB, Chowdary KPR, Murthy KVR, Hayman AR and Becket G. Physicochemical Characterization and Dissolution Properties of Nimesulide-Cyclodextrin Binary Systems. *AAPS PharmSciTech*, 2003, 4 (1):1-12.
 - 24- Shin SC, Cho CW. Physicochemical characterization of piroxicam –poloxamer solid dispersion, *Pharm Dev Tech*.1999, 4:403-407

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