

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF NIMESULIDE USING SOLUBILIZATION, SOLID DISPERSION AND COMPLEXATION TECHNIQUES

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بر النيمسوليد أحد مضادات الالتهابات غير الستيرويديه المسكنة للألم وبالرغم من أن له اختبارية أكثر لانزيم السيكلووكسيجيناز- إلا أن له الكثير من الآثار الجانبية وخاصة على المعدة مع الاستخدام الطويل للدواء عن طريق الفم بالإضافة إلى تأثير الكبد السلبي على التوافر الحيوي للدواء في الدم. لذلك فإن استخدام الدواء موضعياً مباشرة على مكان الألم يعتبر من الوسائل البديلة للتغلب على هذه المشاكل. ولأن العقار شحيح الذوبان في الماء تمت محاولة تحسين ذائبته باستخدام المذيبات المساعدة والعوامل ذات النشاط السطحي غير المتأينة. أظهرت النتائج أن ثنائي ميثيل الإسيتاميد (% ح/ح) أعطى أعلى تأثير على ذائبية العقار (مرات) مقارنة مع المذيبات المساعدة الأخرى. أما بالنسبة للمواد ذات النشاط السطحي غير المتأينة فإن بريج (% و/ح) قد حسن كثيراً من ذائبية العقار (مرة). كذلك تمت دراسة ذوبان النيمسوليد من مشتقات صلبة. تم تحضير متشابات في الحالة الصلبة من النيمسوليد مع البيتا سيكلوديكسترين وهيدروكسي بروبيل بيتا سيكلوديكسترين عند نسبة عيارية (:). ولقد تم الحصول على المخاليط الانصهارية والتي لها أذ درجة انصهار عند نسبة وزنية : . أظهرت نتائج دراسة ذوبان العقار أن درجة الذوبان كانت أعلى من المشتقات الصلبة مقارنة بالمخاليط الفيزيائية والنيمسوليد بمفرده وكانت أعلى قيمة الذوبان من المشتقات الصلبة من الفينيل بيروليدونات عند نسبة وزنية من نيمسوليد:البوليمر (:) وعلى ذلك تمت دراسة الخصائص الفيزيوكيميائية لعقار النيمسوليد والفينيل بيروليدون والمشتت الصلب وكذا الخليط الفيزيائي من الفينيل بيروليدون عند هذه النسبة. أثبتت نتائج التحليل الحراري واشعة الحيوذ السينية بوجود النيمسوليد بشكل غير بللوري. كما أثبتت نتائج الأشعة تحت الحمراء أن هناك رابطة هيدروجينية تكونت بين العقار والبوليمر وأوضح التحليل بالميكروسكوب الالكتروني غياب الشكل البللوري للنيمسوليد في المشتت الصلب.

Nimesulide is a preferential COX-2 inhibitor. It has high anti-inflammatory, antipyretic and analgesic activities. It has poor aqueous solubility (0.01mg/ml). Solubility of nimesulide was studied using different cosolvent mixtures and various classes of nonionic surfactants. Dimethylacetamide (DMA); at 10% v/v exhibited the highest solubilizing effect (10-fold) towards nimesulide as compared with other cosolvents. Among the tested nonionic surfactants at 10% w/v, brij 58 which exhibited the highest solubilization effect (39-fold). The dissolution of nimesulide from solid dispersions was also studied. Solid inclusion complexes of nimesulide with β -cyclodextrin (β -CD) and hydroxypropyl β -cyclodextrin (HP β -CD) were prepared at a molar ratio of 1:1. Eutectic mixtures were obtained at weight ratio of 1:9 binary systems as confirmed by DSC studies. The dissolution studies indicated that the highest relative amounts dissolved were obtained from solid dispersions as compared with physical mixtures or pure nimesulide. Also higher relative amounts dissolved were obtained with polyvinylpyrrolidones (PVPs) at weight ratio of nimesulide/PVP 40000 1:7. Physicochemical characterization of pure drug, PVP 40000, nimesulide/PVP 40000 solid dispersion and the physical mixture at this ratio were conducted by DSC, FTIR, X-RPD and SEM. The DSC thermograms and X-RPD patterns demonstrated that nimesulide existed in an amorphous form and there is an intermolecular hydrogen bond between the drug and the carrier as shown from FTIR analysis. SEM images confirmed the absence of the crystalline structure of nimesulide in the solid dispersion.

INTRODUCTION

The dissolution enhancement of poorly water-soluble drugs can be achieved by several

techniques, such as micronization^{1&2}, recrystallization³, inclusion complexation⁴, cogrinding⁵ and solid dispersion⁶. Cosolvents as ethanol, propylene glycol, polyethylene glycols

and glycerin are routinely used as a means for solubilization of drugs in aqueous vehicles⁷. Dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been widely used because of their large solubilizing capacity for poorly water-soluble drugs⁸. They are organic compounds that are substantially miscible with water and having small hydrocarbon regions. This leads to a reduction of the ability of water to squeeze out nonpolar hydrophobic compound and consequently enhance its aqueous solubility⁹.

Micellization is the technique by which the water insoluble or slightly water soluble drugs are solubilized by the aid of surfactants above their respective critical micelle concentration¹⁰. In virtue of their relatively low toxicity and high solubilizing power; nonionic surfactants have been awarded major attention for promoting solubilization¹¹.

Solid dispersion in which the compound is dispersed as a molecular form combines the benefits of increasing the solubility and maximizing the surface area of the compound that comes in contact with the dissolution medium into which the carrier freely dissolves¹². It is considered a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs when incorporated in dosage forms¹³. The most commonly used water soluble carriers in solid dispersion technique are solid polyethylene glycols, polyvinyl pyrrolidones¹⁴ and poloxamers¹⁵.

Cyclodextrins (CDs) have attracted growing interest in the pharmaceutical industry as complexing agents, because of their low toxicity and ability to produce stable complexes. Cyclodextrins play an important role in formulation of poorly water-soluble drugs by acting as hydrophilic carriers. Reduction of drug crystallinity on complexation with CDs also contributes to increase apparent drug solubility and dissolution rate¹⁶.

Nimesulide is a preferential selective COX-2 inhibitor; it inhibits the prostaglandin synthesis from arachidonic acid by inhibiting the COX pathway. It is 5-16 fold selective for COX-2 than COX-1¹⁷. The drug is poorly water soluble and its aqueous solubility is 0.01 mg/ml. It is a weakly acidic NSAID having a pKa of 6.4-6.8¹⁸. It has some gastrointestinal

adverse effects especially on long term administration. Furthermore, it is extensively metabolized in the liver when administered orally. Consequently, topical application of nimesulide is desirable to alleviate pain without systemic adverse effects. Moreover, nimesulide has a poor aqueous solubility belonging to class II drugs of low solubility and high permeability. Thus, the aim of this study is to enhance the solubility and the dissolution of nimesulide using cosolvency, micellar solubilization, solid dispersion and complex formation techniques so as to formulate it in suitable semisolid dosage forms.

EXPERIMENTAL

Materials

Nimesulide was kindly supplied by Alkan Pharma Co., Egypt; Dimethylsulphoxide (DMSO), BDH Chemicals Ltd. Poole, England; Isopropanol, ethanol, methanol, dimethyl formamide (DMF), propylene glycol (PG) and glycerol, El-Nasr Pharmaceutical Chemicals Co. Egypt; polyoxyethylene (20) sorbitan monolaurate (Tween 20), polyoxyethylene (20) sorbitan monopalmitate (Tween 40) and Polyoxyethylene (20) sorbitan monooleate (Tween 80), Polyoxyethylene (50) stearate (Myrj 53), polyoxyethylene (40) stearate (Myrj 52), Polyvinyl pyrrolidone 40000 (PVP 40000), polyvinyl pyrrolidone K25 (PVP K25), pluronic F-68 and pluronic F-127, Sigma Chemical Co., USA; polyoxyethylene (23) lauryl ether (Brij 35), polyoxyethylene (20) cetyl ether (Brij 58), Ethylene Glycol (EG), polyethylene glycol 200 (PEG 200), polyethylene glycol 300 (PEG 300) Polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000), and N,N-dimethylacetamide (DMA), Merk-Schuchardt, Germany; Formamide, Analar[®] Searle Co. Hopkin and Williams, England; Propanol, Aldrich Chemical Co. Ltd., England; -cyclodextrin (-CD), Acros Organics, USA and 2-hydroxypropyl -cyclodextrin (HP-CD), Fluka, Japan. All other chemicals used were of analytical grade.

Methods

Assessment of nimesulide solubility

Solubility of nimesulide in phosphate buffer pH 6.8 in presence of different

concentrations 2-10% (v/v or w/v) of some selected cosolvents was investigated. The selected cosolvents were: formamide, DMF, DMA, DMSO, ethanol, propanol, isopropanol, glycerol, EG, PG, PEG 200, PEG 300, PEG 400 and PEG 600. In addition, the solubility in presence of different concentrations 2-10% (w/v) of different nonionic surfactants (tween 20, tween 40, tween 80, myrj 52, myrj 53, brij 35 and brij 58) was also studied. An excess amount of nimesulide was added to 50-ml stoppered glass bottles containing 10 ml cosolvent solutions or surfactant solutions. The bottles were shaken in a mechanical shaking water bath previously equilibrated at 32°C. Aliquots were withdrawn after three hours (equilibrium time), filtered using a 0.45 µm membrane disc filter and assayed spectrophotometrically at λ_{\max} 392 nm (λ_{\max} was determined practically) after appropriate dilution employing the same concentration of the cosolvent or surfactant as a blank. The results are the mean values of three determinations.

Assessment of dissolution of nimesulide from solid dispersions and inclusion complexes

Preparation of physical mixtures

Nimesulide and the selected carriers were sieved through a sieve no. of 60 (250 µm pore size), then the physical mixtures containing PEG 4000, PEG 6000, pluronic F-68 and pluronic F-127 at a weight ratio of nimesulide/carrier of 1:9 were prepared. Physical mixtures of nimesulide and carriers PVP K25 as well as PVP 40000 were prepared at a weight ratio of 1:7. -CD and HP -CD physical mixtures were prepared at equimolar ratio of 1:1 by simple mixing using spatula and paper.

Preparation of nimesulide solid dispersions

1- Fusion method

Solid dispersions of nimesulide with PEG 4000, PEG 6000, pluronic F-68 and pluronic F-127 in different weight ratios of nimesulide/carrier were prepared by fusion method. Nimesulide was fused until melted then the carrier was added and the mixture was stirred until completely mixed and the stirring was continued at room temperature until cooled, then stored in a desiccator containing

anhydrous calcium chloride for 24 hrs (this time was found to be sufficient for complete drying of the powder). The obtained solid mass was ground in a mortar and passed through sieve no. 60 (250 µm pore size).

2- Coprecipitation method

Since fusion method can not be applied due to the high glass transition temperature (T_g) of PVP K25 and PVP 40000, coprecipitation method was used to prepare solid dispersions of nimesulide with these carriers. Different drug/carrier ratios: 1:1, 1:3, 1:5 and 1:7 were used to prepare the solid dispersions. The calculated amounts of nimesulide and the carrier were dissolved in a minimum amount of methanol. The solvent was allowed to evaporate at room temperature and the residue was dried at 40°C in a hot air oven until constant weight of the residue is obtained (24 hrs). The dried mass was placed in a desiccator containing anhydrous calcium chloride for further 24 hrs. The obtained solid mass was ground and passed through sieve no. 60 (250 µm pore size).

Preparation of solid inclusion complexes

The complexation of nimesulide with -CD and HP -CD both in solution and solid state to improve the dissolution behavior of nimesulide was previously studied^{19&20}. The solubility phase diagrams of nimesulide/CDs solutions from these studies revealed 1:1 molar ratio complexation of nimesulide with these CDs. Accordingly nimesulide/-CD and nimesulide/HP -CD coprecipitated solid complexes and physical mixtures were prepared in 1:1 molar ratio. An equimolar ratio of 1:1 of nimesulide and -CD was prepared by adding the aqueous -CD solution to the methanolic solution of nimesulide. The obtained mixture was stirred for one hour and allowed to evaporate at 40°C in a hot air oven until dry. The dried mass was placed in a desiccator containing anhydrous calcium chloride for further 24 hrs then ground and passed through sieve no. 60 (250 µm pore size).

The inclusion complex of nimesulide with HP -CD was prepared by dissolving an equimolar ratio of 1:1 of nimesulide and HP -CD in methanol and then the solvent was allowed to evaporate at room temperature and

the residue was dried at 40°C in a hot air oven for 24 hrs. The dried mass was placed in a desiccator containing anhydrous calcium chloride for further 24 hrs. The obtained solid mass was ground and passed through sieve no. 60 (250 µm pore size).

Construction of phase diagrams

The phase diagrams of nimesulide with the tested carriers were constructed. This was achieved by using a melting point apparatus (Stuart scientific melting point SMP1, UK). The samples were placed in glass capillary tubes and heated at a rate 5°C/minute. The melting points were recorded by visual observation of complete melting of the samples using a high power magnifying glass lens fixed on the mount of the samples and a heating stage. The results are the mean values of two determinations.

Dissolution studies

The dissolution of nimesulide alone, from its solid dispersions and the corresponding physical mixtures were studied using USP XXIV type II dissolution apparatus, paddle type (Electrolab, TDT-06N, India). Accurately weighed amounts equivalent to 20 mg of nimesulide were dispersed over the dissolution medium, 900 ml phosphate buffer at pH 6.8, and at 32±0.2°C, stirred at 50 rpm. At appropriate time intervals, 5 ml samples were withdrawn over a period of 3 hrs and replaced by an equal volume of fresh dissolution medium at the same temperature. The samples were filtered using a 0.45 µm membrane disc filter and assayed spectrophotometrically at λ_{\max} 392 nm. The results are the mean values of three determinations.

Characterization of nimesulide solid dispersion with PVP 40000

1- Differential scanning calorimetry (DSC)

Differential Scanning Calorimetric (DSC) analysis of the pure drug, carriers, solid dispersions and physical mixtures of nimesulide with PEG 4000, PEG 6000, pluronic F-68 and pluronic F-127 at a weight ratio of 1:9 was performed using Shimadzu-Thermal analyzer DSC-T50, Japan, calibrated with indium. 4-5 mg samples heated under nitrogen atmosphere on a sealed aluminum pans at a rate of 10°C/minute over the

temperature range of 30-300°C. Solid dispersion and physical mixture of nimesulide with PVP 40000 at a weight ratio of 1:7 were also measured.

2- X-Ray powder diffraction analysis (X-RPD)

X-ray powder diffraction patterns of pure nimesulide, PVP 40000, solid dispersion and physical mixture of nimesulide with PVP 40000 at a weight ratio of 1:7 were performed using Philips PW1710 diffractometer, USA. The samples were irradiated with CuK radiation with a wavelength of 1.5418 Å at 40 Kv and 40 mA, then analyzed between 2 angles of 4-60° at a scan rate of 0.06°/min.

3- Infrared spectrophotometry (IR)

The IR spectra of pure drug, PVP 40000, solid dispersion and physical mixture of nimesulide with PVP 40000 at a weight ratio of 1:7 were recorded using Shimadzu IR-470 spectrophotometer, Japan, at a range of 4000-400 cm⁻¹ using KBr disk method. The samples were mixed with KBr and compressed into discs using IR compression machine.

4- Scanning electron microscopy (SEM)

Samples of pure drug, PVP 40000, solid dispersion and the corresponding physical mixture at weight ratio of 1:7 were mounted onto the stub using double-sided adhesive tape and then coated with gold palladium alloy using fine coat ion sputter. The samples were subsequently analyzed under the electron microscope (JSM 5400LV, Jeol, Japan) to obtain digital images of the samples.

RESULTS AND DISCUSSION

Assessment of nimesulide solubility using cosolvency technique

The equilibrium solubility of nimesulide in phosphate buffer at pH 6.8 and 32°C was determined. It was found that nimesulide achieved an equilibrium solubility of 8.827 µg/ml after 3 hrs.

The effect of different concentrations of various cosolvents: DMA, DMF, DMSO, formamide, isopropanol, propanol, ethanol, PG, EG, glycerol, PEG 200, PEG 300, PEG 400 and PEG 600 at concentrations ranging from 2-10% on the aqueous solubility of nimesulide

are presented in Table 1. All cosolvents displayed an increase in the solubility and there was a direct relationship between the solubility and the concentration of the cosolvents used. The order of increasing solubility using cosolvents at 10% concentration is shown in Table 1; DMA exhibited the highest value of 85.306 $\mu\text{g/ml}$ (9.7-fold) whereas glycerol showed the lowest value of 14.877 $\mu\text{g/ml}$ (1.7-fold) among the investigated cosolvents. This can be explained by the fact that glycerol is quite a polar solvent. Since the less polar cosolvent, is the more effective one in disrupting hydrogen bonding between water molecules. This in turn, reduces the ability of a newly formed solvent (aqueous-cosolvent mixture) to squeeze out nonpolar drugs. As a result, nonpolar drugs such as nimesulide can be solubilized more efficiently by DMA, the least polar cosolvent. These results are in agreement with those obtained by Kawakami *et al.*⁸ on phenytoin and Zhao and Yalkowsky²¹ on fluasterone, in which the increase in solubility of drugs depends on concentration and the polarity of cosolvents used.

Table 1: Solubility of nimesulide in phosphate buffer containing 10% cosolvents.

Cosolvent	Solubility ($\mu\text{g/ml}$)	[#] Solubility efficiency
DMA*	85.31	9.7
DMF*	71.17	8.1
DMSO*	48.09	5.4
Formamide*	45.49	5.2
PEG 600**	37.41	4.2
PEG 400**	34.81	3.9
PEG 300**	32.07	3.6
Isopropanol*	31.98	3.6
Propanol*	30.25	3.5
Ethanol*	29.19	3.3
PEG 200**	28.78	3.3
PG**	21.05	2.4
EG**	15.74	1.8
Glycerol**	14.88	1.7

* (% v/v). **: (% w/v).

N.B.: The solubility of nimesulide in phosphate buffer pH 6.8 and 32°C is 8.827 $\mu\text{g/ml}$.

[#]Solubility efficiency=

$$\frac{\text{The solubility of nimesulide in presence of cosolvent}}{\text{Solubility of nimesulide in phosphate buffer}}$$

The solubility of nimesulide was enhanced markedly by increasing cosolvents concentrations. At 10% of DMA, DMF, DMSO and formamide, the solubility was enhanced to about 9.7, 8.1, 5.4 and 5.2 fold, respectively. This is in accordance with the cosolvent polarity. Alkylation of formamide increases the solubilizing effect. In alcoholic cosolvents, the solubility of nimesulide was increased by increasing the concentration of alcohols. Isopropanol; the least polar cosolvent exhibited 31.98 $\mu\text{g/ml}$ (3.6-fold) whereas ethanol; the most polar cosolvent among investigated alcoholic cosolvents exhibited 29.19 $\mu\text{g/ml}$ (3.3-fold). Similar results were obtained when fluasterone was solubilized in methanol, ethanol and propanol, in which methanol exhibited the lowest solubilizing effect and propanol exhibited the highest solubilizing effect on fluasteron²². PG, EG and glycerol exhibited solubility effect of 21.049 $\mu\text{g/ml}$, 15.74 $\mu\text{g/ml}$ and 14.88 $\mu\text{g/ml}$, respectively. On comparing the effect of PEGs on the aqueous solubility of nimesulide, it could be ranked in the following descending order: PEG 600 > PEG 400 > PEG 300 > PEG 200. It is evidenced that by increasing the chain length of PEGs suggesting an interaction between nimesulide and the tested PEGs²³.

Assessment of nimesulide solubility using micellar solubilization technique

The solubilizing effect of different nonionic surfactants; polysorbates (tweens), polyoxyethylene stearates (myrjs) and polyoxethylene alkyl ethers (brijs) was investigated at 2-10% (% w/v) concentrations. A marked increase in the drug solubility was obtained with all tested surfactants and was increased with an increase in the surfactants concentrations. At 10% concentration, brij 58 showed the highest solubilizing value of 343.15 $\mu\text{g/ml}$ (39-fold) while tween 20 enhanced nimesulide solubility up to 171.79 $\mu\text{g/ml}$ (19.5-fold) (Table 2). The increase in nimesulide solubility by the investigated tweens could be ranked in a descending order as tween 80 > tween 40 > tween 20. Tweens have the same hydrophilic portion in their molecules but differ in the length of the lipophilic portion. Nonpolar compounds are generally solubilized in the hydrocarbon interior of the micelle²⁴. It is clearly evidenced that the solubilization

effects of these micelle forming agents is increased as the hydrophobic chain length of the surfactant is increased. This is due to an increase in the volume of the hydrocarbon in the micelle interior. In addition, the increase in the alkyl chain length increases the size of the surfactant micelle which accommodates more quantity of nonpolar solute and hence increases its solubilization effect. Similar results were obtained with carbamazepin²⁴ and nalidixic acid²⁵.

Table 2: Solubility of nimesulide in phosphate buffer containing 10% (w/v) nonionic surfactants.

Surfactant	Solubility (µg/ml)	#Solubility Efficiency
Brij 58	343.149	38.9
Myrj 52	291.944	33.1
Brij 35	267.930	30.4
Tween 80	212.20	24.0
Myrj 53	197.337	22.4
Tween 40	190.69	21.6
Tween 20	171.79	19.5

N.B.: The solubility of nimesulide in phosphate buffer pH 6.8 and 32°C is 8.827 µg/ml.

#Solubility efficiency =

$$\frac{\text{The solubility of nimesulide in presence of surfactant}}{\text{Solubility of nimesulide in phosphate buffer}}$$

The effect of myrj 52 and myrj 53 on the solubility of nimesulide is shown in Table 2. It is clearly observed that the effect of myrj 52 (291.94 µg/ml); (33-fold) was greater than myrj 53 (197.34 µg/ml); (22-fold). It could be noticed that the ability of solubilization decreases with increasing the length of polyoxyethylene chain. This may be explained by the fact that the micellar size of surfactant decreased as polyoxyethylene chain length increased^{24&26}.

The effect of two different brij on the aqueous solubility of nimesulide is shown in Table 2. Higher increase value 343.15 µg/ml (39 fold) in drug solubility was obtained by brij 58 while brij 35 exhibited a lower solubilizing effect 267.93 µg/ml; (30 fold). This is due to the difference in the hydrocarbon chain length

of each surfactant. Lengthening of the hydrocarbon chain causes an increase in the micellar size. The larger hydrocarbon chain provides a greater driving force for micellization than a short one^{24&27}. Obviously, the effect of these classes of nonionic surfactants on the solubility of nimesulide can be arranged in the following descending order: brij 58 > myrj 52 > brij 35 > tween 80 > myrj 53 > tween 40 > tween 20 (Table 2).

Construction of phase diagram

As shown in Figure 1, the presence of the carriers causes a depression of the melting point of nimesulide in all binary mixtures and the melting points of both nimesulide and the carriers were depressed at a ratio of 1:9. The eutectic points were found to be 55, 58, 50 and 52°C for nimesulide/PEG 4000, nimesulide/PEG 6000, nimesulide/pluronic F-68 and pluronic F-127, respectively.

The DSC thermograms of pure nimesulide, PEG 4000, PEG 6000, pluronic F-68 and Pluronic F-127, solid dispersions and physical mixtures at weight ratio of 1:9 are shown in Figures 2 and 3, respectively. Nimesulide trace showed a single endothermic peak with a melting point of 151.4°C. Whereas the carriers; PEG 4000, PEG 6000, pluronic F-68 and pluronic F-127 traces have single endothermic peaks at 58.7°C, 63.4°C, 53.4°C and 56.2°C, respectively which are corresponding to the melting points of these carriers. These revealed the existence of nimesulide and these carriers in a crystalline state. DSC thermograms of solid dispersions of nimesulide with these carriers showed single endothermic peaks shifted to lower melting points than nimesulide and the carriers, confirm the formation of eutectic systems. On the other hand physical mixtures showed one endothermic peaks, corresponding to the melting points of the carriers and the disappearance of nimesulide endothermic peak may be due to its solubility in the melted carriers during heating^{15,28&29}. Bikiaris *et al.*²⁹ concluded that the absence of melting peak of felodipin and hesperetin in the case of solid dispersions was not because the drugs were amorphous, but due to the increase in drug solubility in the liquid PEG at elevated temperature.

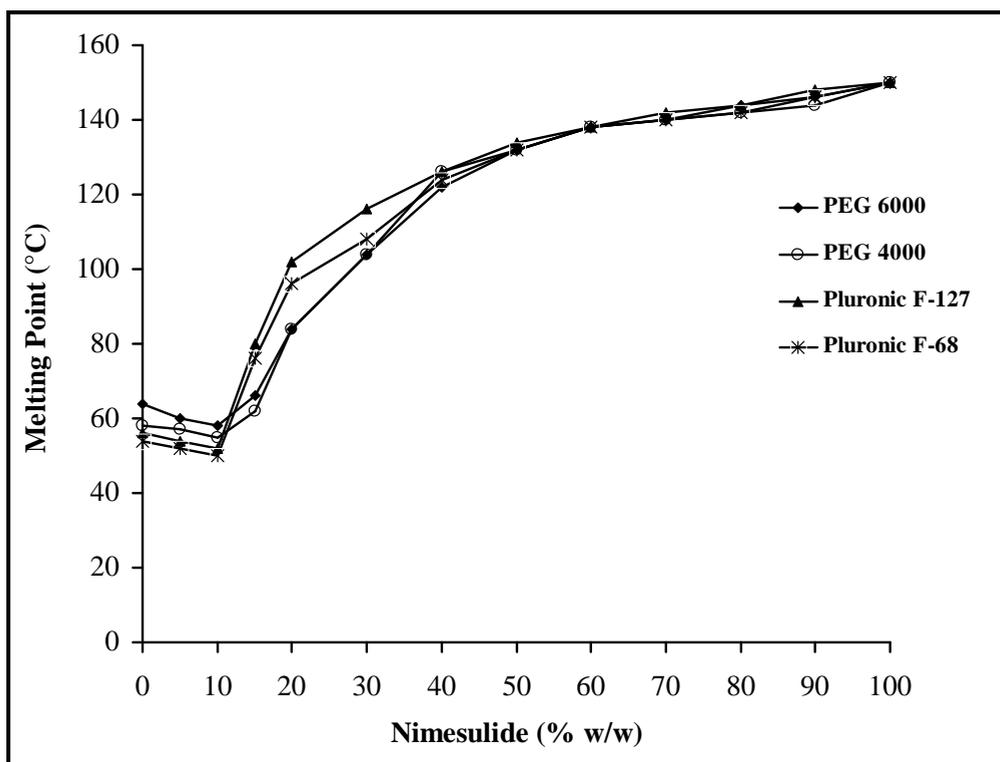


Fig. 1: Phase diagram of nimesulide/polyethylene glycol 6000, nimesulide/polyethylene glycol 4000, nimesulide/pluronic F-127 and nimesulide/pluronic F-68 solid dispersions.

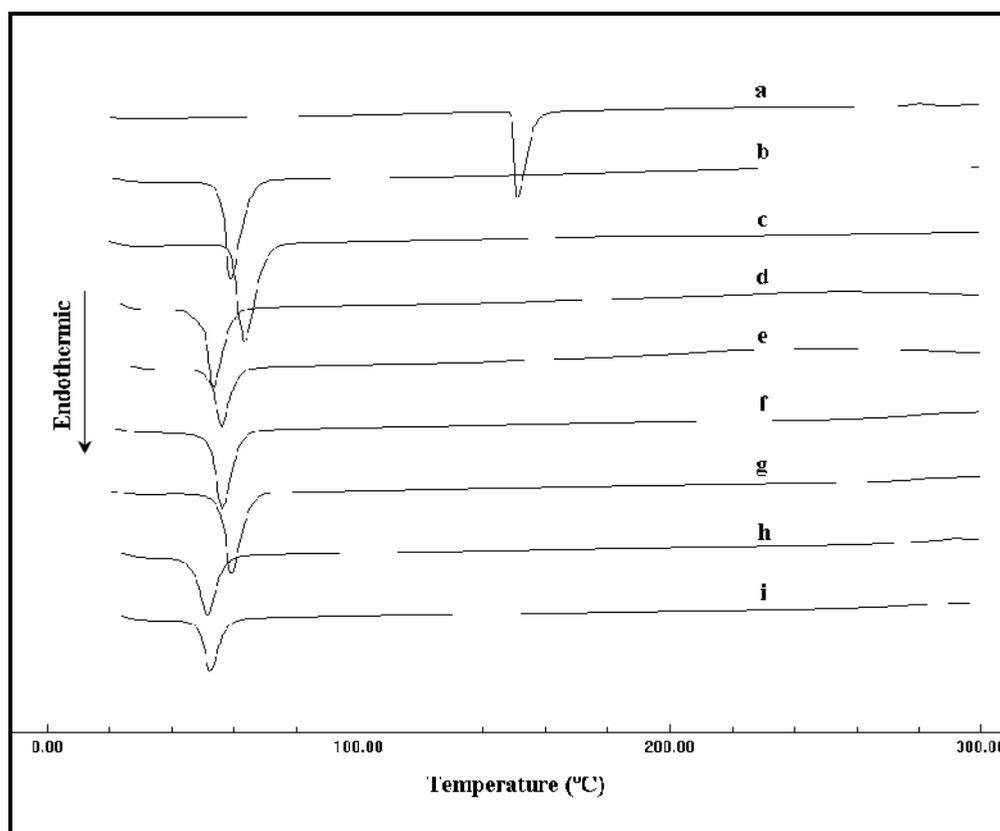


Fig. 2: DSC thermograms of (a): nimesulide, (b): PEG 4000, (c): PEG 6000, (d): pluronic F-68, (e): pluronic F-127, and solid dispersions at weight ratio of 1:9 of (f): nimesulide/PEG 4000, (g): nimesulide/PEG 6000, (h): nimesulide/Pluronic F-68 and (i): nimesulide/pluronic F-127.

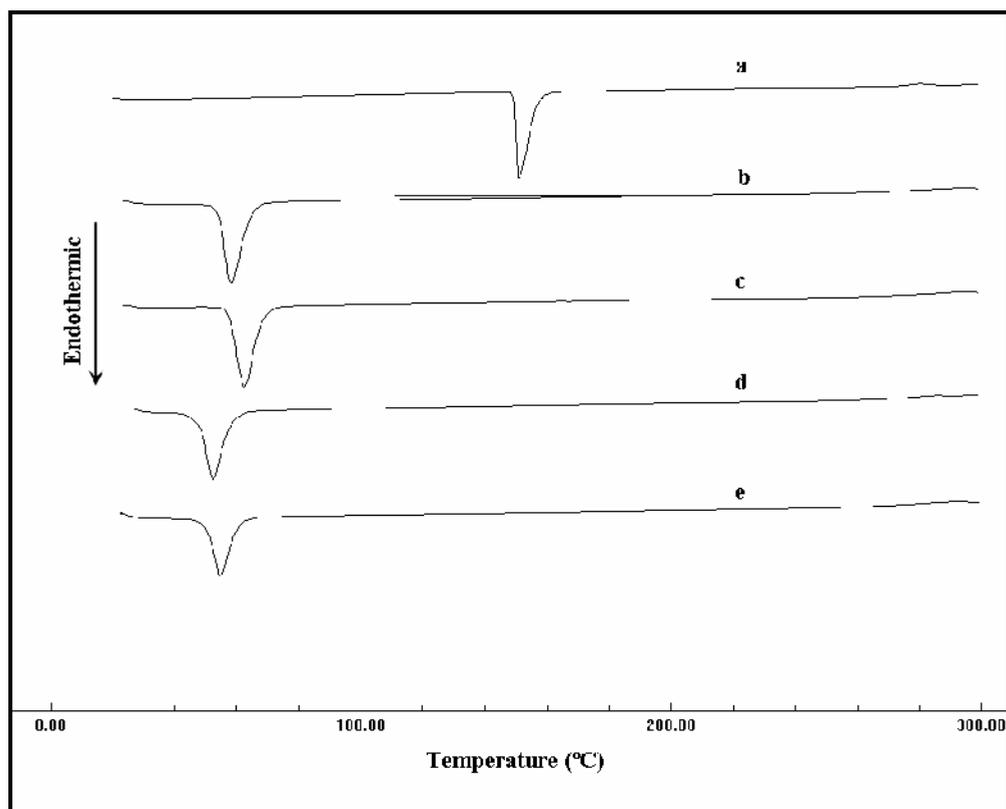


Fig. 3: DSC thermograms of (a): nimesulide, and physical mixtures at weight ratio of 1:9 of (b): nimesulide/PEG 4000, (c): nimesulide/PEG 6000, (d): nimesulide/pluronic F-68 and (e): nimesulide/pluronic F-127.

Dissolution studies

Figure 4 illustrates the dissolution of nimesulide from its solid dispersions and physical mixtures with PEG 4000 and PEG 6000. It is evident that the dissolution of pure nimesulide is very slow, about 1.99 mg after 15 minutes. Dispersion of nimesulide in these hydrophilic carriers considerably enhanced the dissolution. Table 3 shows the relative amount dissolved (R.A.D) of nimesulide from the solid dispersion and inclusion complexes as well as the physical mixture after 15 minutes. It is clearly obvious that nimesulide/PEG 4000 and nimesulide/PEG 6000 solid dispersions exhibited faster dissolutions of about 6.40 mg (3.2-fold) and 7.36 mg (3.7-fold), respectively after 15 minutes as compared with the pure drug. The observed increase in the dissolution of nimesulide from its solid dispersions could be attributed to improved wettability, local solubilization and drug particles size reduction. Similar observation by Khan and Jiabi for ibuprofen solid dispersion with PEG 10000 was obtained³⁰. Dissolution from the physical mixture was faster than pure drug. Drug mixing

brings the drug in close contact with the hydrophilic carrier resulting in increased wettability and dispersibility of nimesulide. During dissolution experiments, it was noticed that the physical mixtures immediately sink to the bottom of the dissolution vessels, whereas the pure drug floats for a long period of time on the surface of the dissolution medium, thereby, decreasing effective surface area of the particles exposed to the dissolution medium.

The results of dissolution tests of nimesulide from its solid dispersions and physical mixtures with pluronic F-68 and pluronic F-127 is shown in Figure 5. Nimesulide/pluronic F-68 and nimesulide/pluronic F-127 solid dispersions exhibited faster dissolutions of about 8.22 mg (4.1-fold) and 9.05 mg (4.5-fold), respectively after 15 minutes compared with the pure drug (Table 3). The fact that the solid dispersions were miscible in the liquid state and immiscible in the solid state indicate that they might have been crystallized out simultaneously as microfine crystals from the molten mixtures resulting in an increase in nimesulide surface

Table 3: Relative amounts of nimesulide dissolved after 15 minutes from solid dispersion, inclusion complexes and physical mixtures with different carriers.

System	Preparation	R.A.D* after 15 minutes
PEG 4000	Physical mixture	1.7
	Solid dispersion	3.2
PEG 6000	Physical mixture	2.2
	Solid dispersion	3.7
Pluronic F-68	Physical mixture	3.8
	Solid dispersion	4.1
Pluronic F-127	Physical mixture	4.2
	Solid dispersion	4.5
PVP K 25	Physical mixture	2.4
	Solid dispersion	5.6
PVP 40000	Physical mixture	2.5
	Solid dispersion	5.6
-CD	Physical mixture	2.0
	complex	3.0
HP -CD	Physical mixture	2.8
	complex	3.0

$$*(R.A.D) = \frac{\text{Amount of the drug dissolved in presence of carrier}}{\text{Amount of the drug dissolved alone}}$$

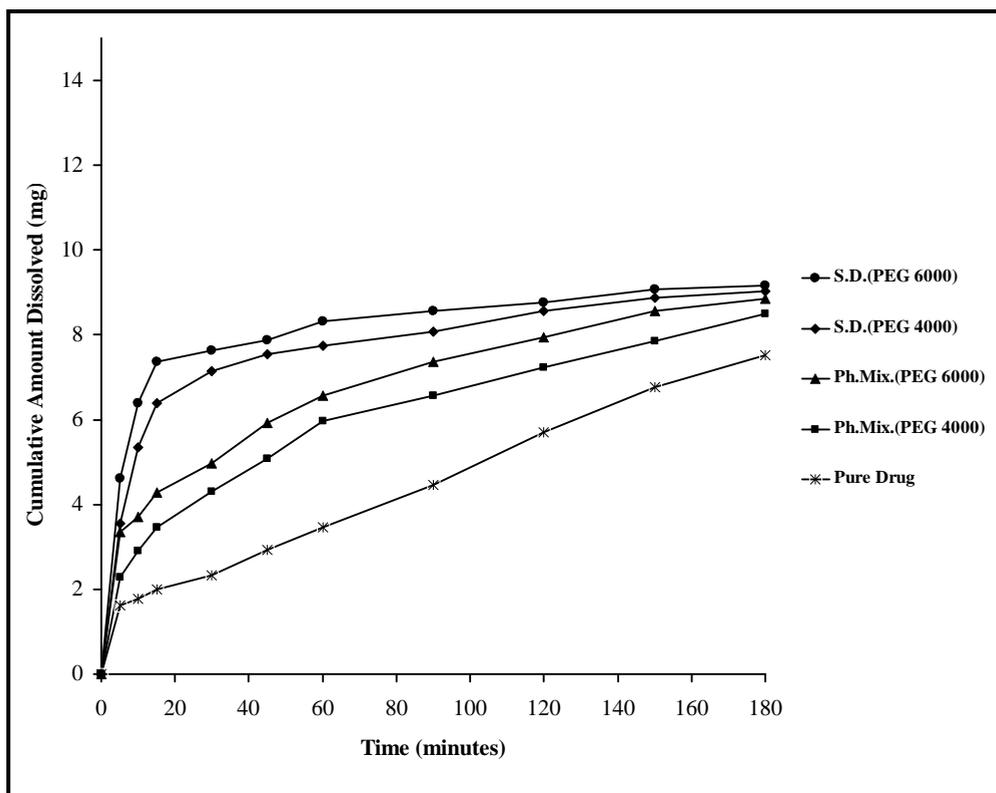


Fig. 4: Dissolution profiles of nimesulide from its physical mixtures (Ph. Mix.) and solid dispersions (S.D.) with PEG 4000 and PEG 6000.

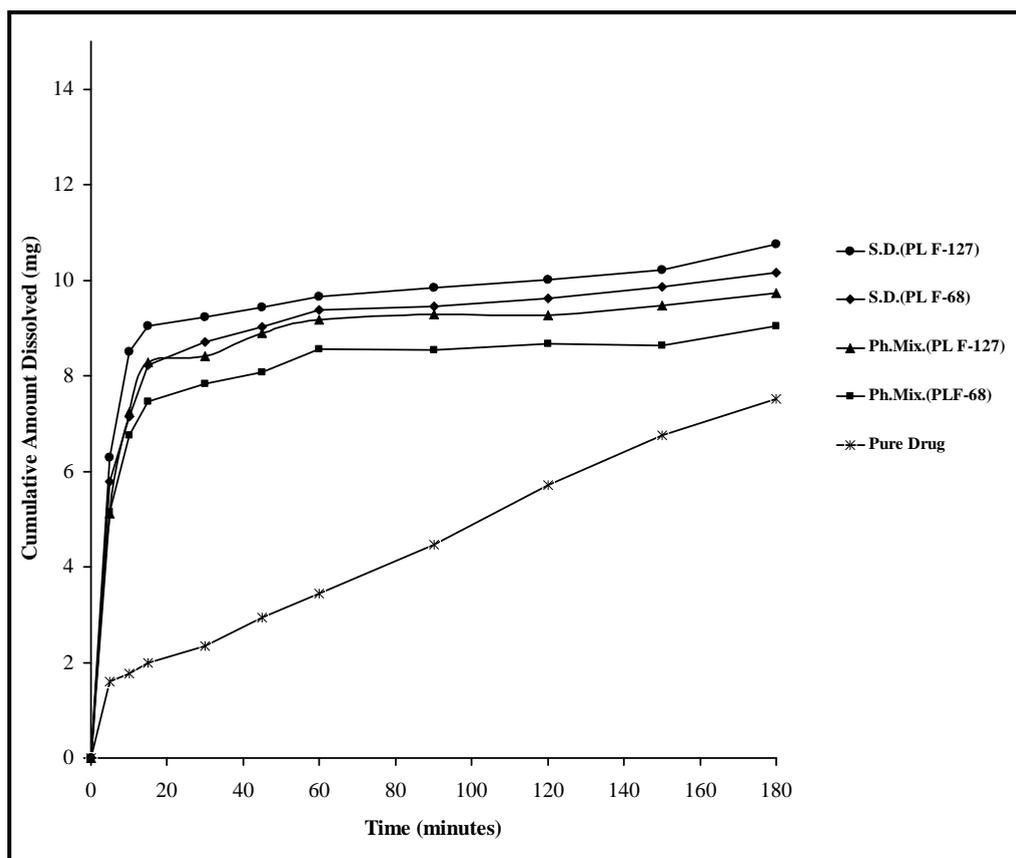


Fig. 5: Dissolution profiles of nimesulide from its physical mixtures (Ph. Mix.) and solid dispersions (S.D.) with pluronic F-68 (PL F68) and pluronic F-127 (PL F-127).

area. The enhancement of dissolution from solid dispersions may be attributed partly to the reduction in particles size of nimesulide crystals due to formation of eutectic mixtures with pluronics, along with eutectic mixtures, surface activity, wetting and solubilization effect of pluronics. Enhanced dissolution of nimesulide from physical mixtures could be correlated to the chemical structures of highly water soluble pluronics. Reportedly, the hydrophobic core can act as reservoir for the drug while the hydrophilic portion acts as interface between the aqueous medium and the drug. Consequently, enhancement in dissolution could be possibly of combined action of surface activity, solubilization and wettability effects of pluronics³¹⁻³⁴.

The dissolution of nimesulide from its solid dispersions with PVP K25 and PVP 40000 at ratios of 1:1, 1:3, 1:5 and 1:7 and from physical mixtures at a weight ratio of 1:7 is shown in Figures 6 and 7. It can be noticed that the dissolution of the drug is increased as

the amount of the tested carrier is increased in the solid dispersions. Previous studies indicated that the increase in dissolution can be achieved by increasing in the amount of PVP in the solid dispersions³⁵. Solid dispersions and physical mixtures prepared in a weight ratio of 1:7 PVP K25 or PVP 40000 exhibited a faster dissolutions of about 11.13 mg (5.6-fold) and 11.07 mg (5.6-fold), respectively after 15 minutes as compared with the pure drug (Table 3). This may be attributed to the changes in the solid state during the formation of dispersion and the formation of high-energy amorphous phase as supported by DSC and X-RPD data. Similar results were obtained by several authors when they used PVPs in preparation of solid dispersions of different drugs and confirmed the formation of amorphous phases of these drugs³⁵⁻³⁹. The increase in the dissolution observed for the physical mixtures may be due to the wetting properties of the carriers to the hydrophobic surface of the drug particles.

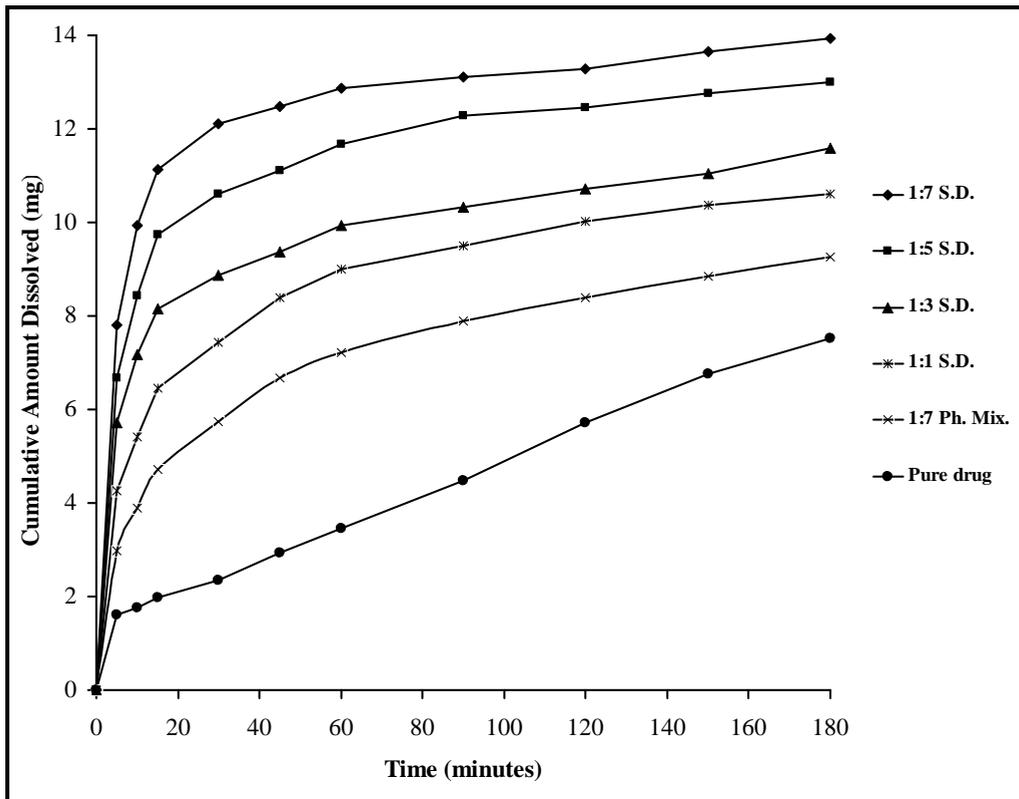


Fig. 6: Dissolution profiles of nimesulide from its physical mixture (Ph. Mix.) and solid dispersions (S.D.) with PVP K25.

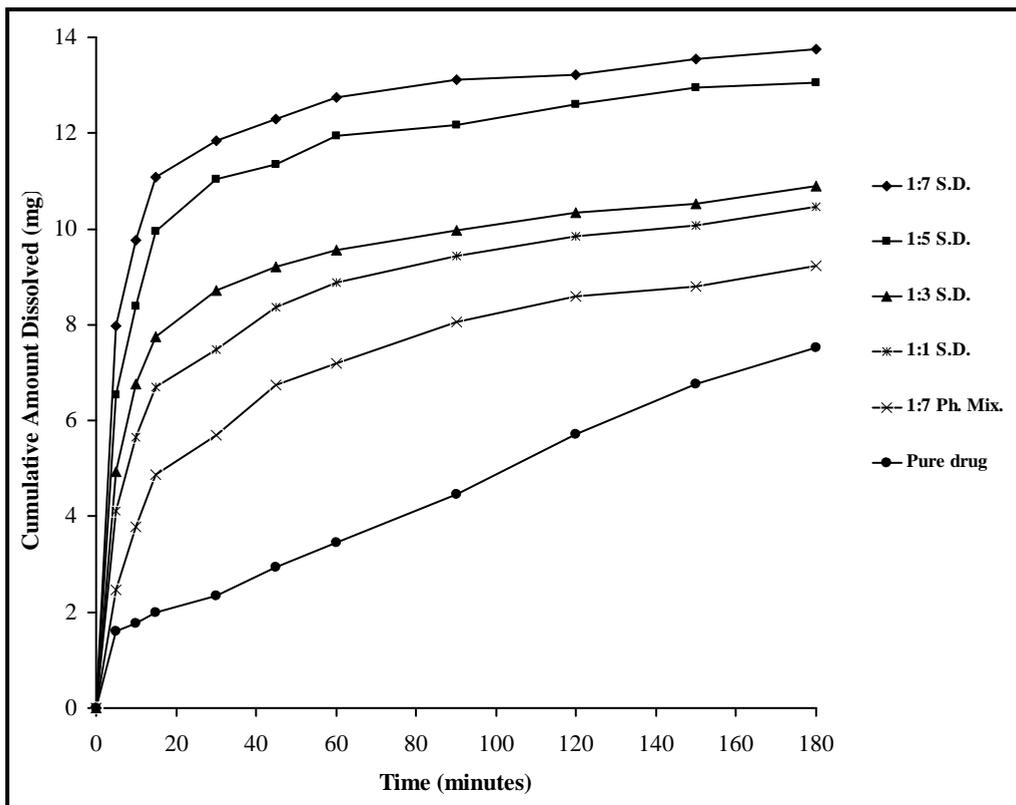


Fig. 7: Dissolution profiles of nimesulide from its physical mixture (Ph. Mix.) and solid dispersions (S.D.) with PVP 40000.

The results of the dissolution studies of nimesulide/ β -CD and nimesulide/HP β -CD solid inclusion complexes and physical mixtures are graphically illustrated in Figure 8. It is observed that solid inclusion complexes of β -CD and HP β -CD exhibited higher dissolutions of 6.05 (3-fold) and 6.73 (3.4-fold) after 15 minutes, respectively compared with the pure drug (Table 3). This could be attributed to the improved solubility and/or reduction in crystallinity of nimesulide. The increase in the dissolution of nimesulide when it is physically mixed with CDs may be due to an improvement in the wettability and solubility of the drug in the aqueous CDs solutions resulting from the coexistence in the dissolution medium and the formation of inclusion complexes in solution⁴⁰.

Characterization of nimesulide solid dispersion with PVP 40000

The dissolution rates of nimesulide were enhanced markedly when it was dispersed with PVPs. DSC, infrared spectroscopy, X-ray powder diffraction were conducted in order to examine the solid state characterization and the possible mechanism of the enhanced dissolution rate of the drug from its solid dispersion with PVP 40000.

1- Differential scanning calorimetry (DSC)

The DSC thermograms of pure nimesulide, PVP 40000, solid dispersion and corresponding physical mixture at weight ratio 1:7 are presented in Figure 9. Because of the amorphous structure of PVP 40000, no melting point peak was seen in the thermogram. The endothermic broad peak was attributed to the removal of water from PVP 40000. The DSC trace of the physical mixture shows the melting peak of nimesulide and the observed peak was reduced due to the low drug content. Solid dispersion did not show such peak, suggesting that nimesulide was molecularly dispersed in an amorphous form.

2- X-Ray powder diffraction (X-RPD)

The X-RPD patterns of pure nimesulide, PVP 40000, solid dispersion and physical mixture are shown in Figure 10. Nimesulide was found to exhibit a strong and characteristic X-RPD pattern, showing the crystalline nature

of the powder. PVP 40000 is an amorphous powder and characterized by the absence of any diffraction peaks. The X-RPD peaks of nimesulide physical mixture was detected but with reduced intensity, indicating that the crystallinity of nimesulide did not change. On the other hand, no peak was displayed from solid dispersion X-RPD pattern, indicating the presence of nimesulide in an amorphous form. Sekikawa *et. al.*⁴¹ pointed out that PVP might inhibit the crystallization of drug and confirmed the DSC results.

3- Infrared Spectroscopy (IR)

Figure 11 depicts IR spectra of pure nimesulide, pure PVP 40000, nimesulide/PVP 40000 solid dispersion and the corresponding physical mixture at weight ratio of 1:7. Nimesulide (trace a) showed the N-H stretching vibration at 3255 cm^{-1} . This region of interest showed the evidence of interaction between nimesulide and PVP 40000 via intermolecular hydrogen bonding between the N-H group of nimesulide with the N- or C=O groups on pyrrolidone moiety.

On the other hand the IR spectrum of PVP 40000 displayed (trace b) broad peak at about 3440 cm^{-1} due to the presence of moisture and at 1645 cm^{-1} due to the C=O stretching. The IR spectrum of the physical mixture still showed peak of N-H stretching vibration of nimesulide and seemed to be only the summation of both components which reflected that there was no interaction occurred. In solid dispersion the N-H stretching vibration of nimesulide was not detected and a single absorption band at 3430 cm^{-1} and at 1641 cm^{-1} was observed. These peaks were shifted toward lower wave number, indicating the presence of intermolecular hydrogen bond between nimesulide and PVP 40000. Therefore, the amorphousness of nimesulide within the PVP 40000 might be predicted by the disappearance of the N-H peak of nimesulide. This IR pattern was previously observed by Tantishaiyakul *et. al.*³⁸ who demonstrated the presence of intermolecular hydrogen bonding between piroxicam and PVP in solid dispersion. Therefore, piroxicam presence in amorphous state was confirmed by the disappearance of N-H or O-H peak of piroxicam.

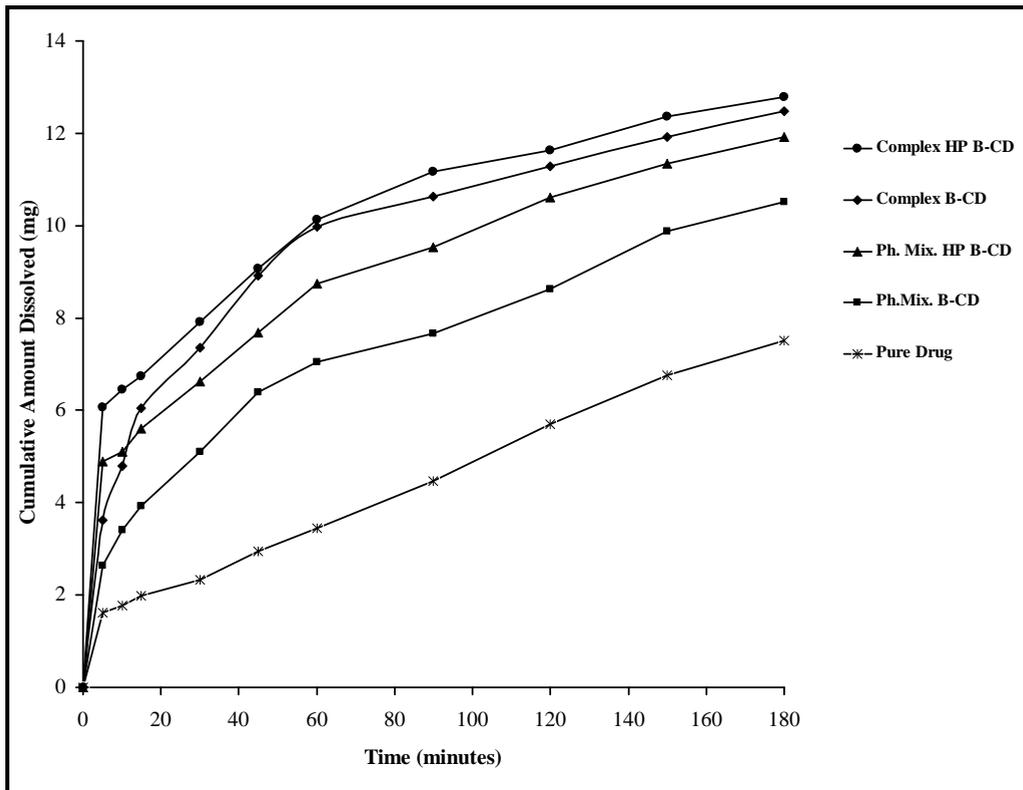


Fig. 8: Dissolution of nimesulide from its physical mixtures (Ph. Mix.) and inclusion complexes with β -CD and HP β -CD.

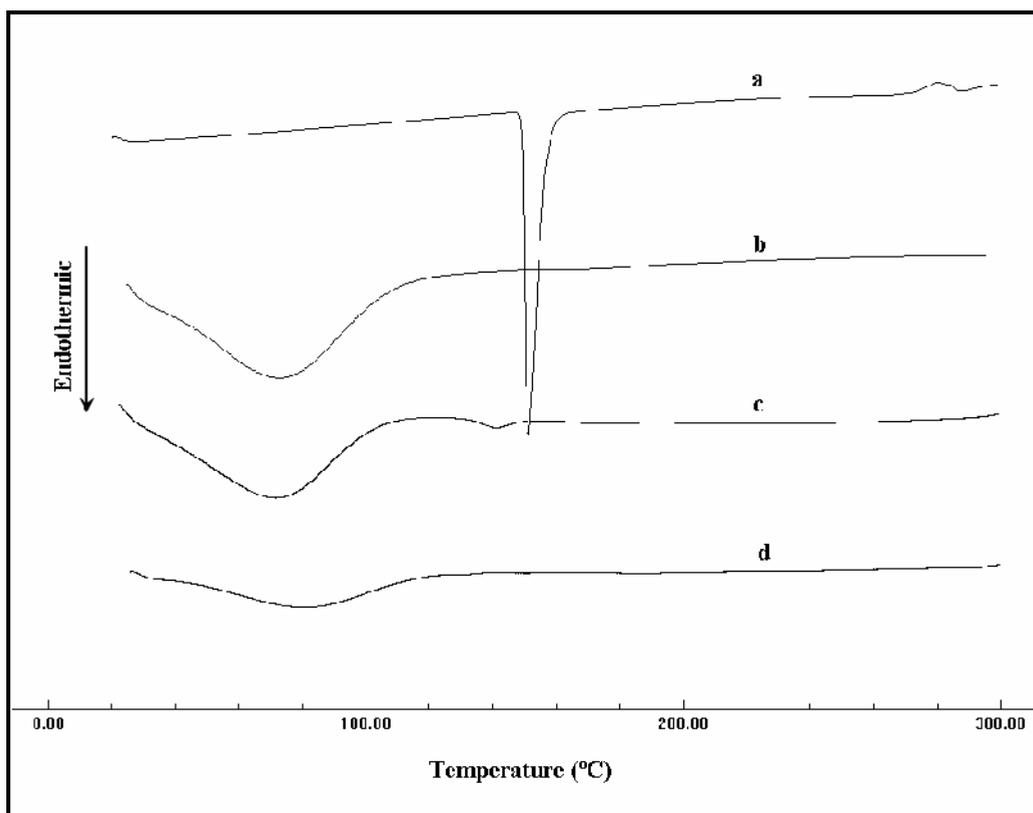


Fig. 9: DSC thermograms of (a): nimesulide (b): PVP 40000, (c): 1:7 nimesulide/PVP 40000 physical mixture and (d): 1:7 nimesulide/PVP 40000 solid dispersion.

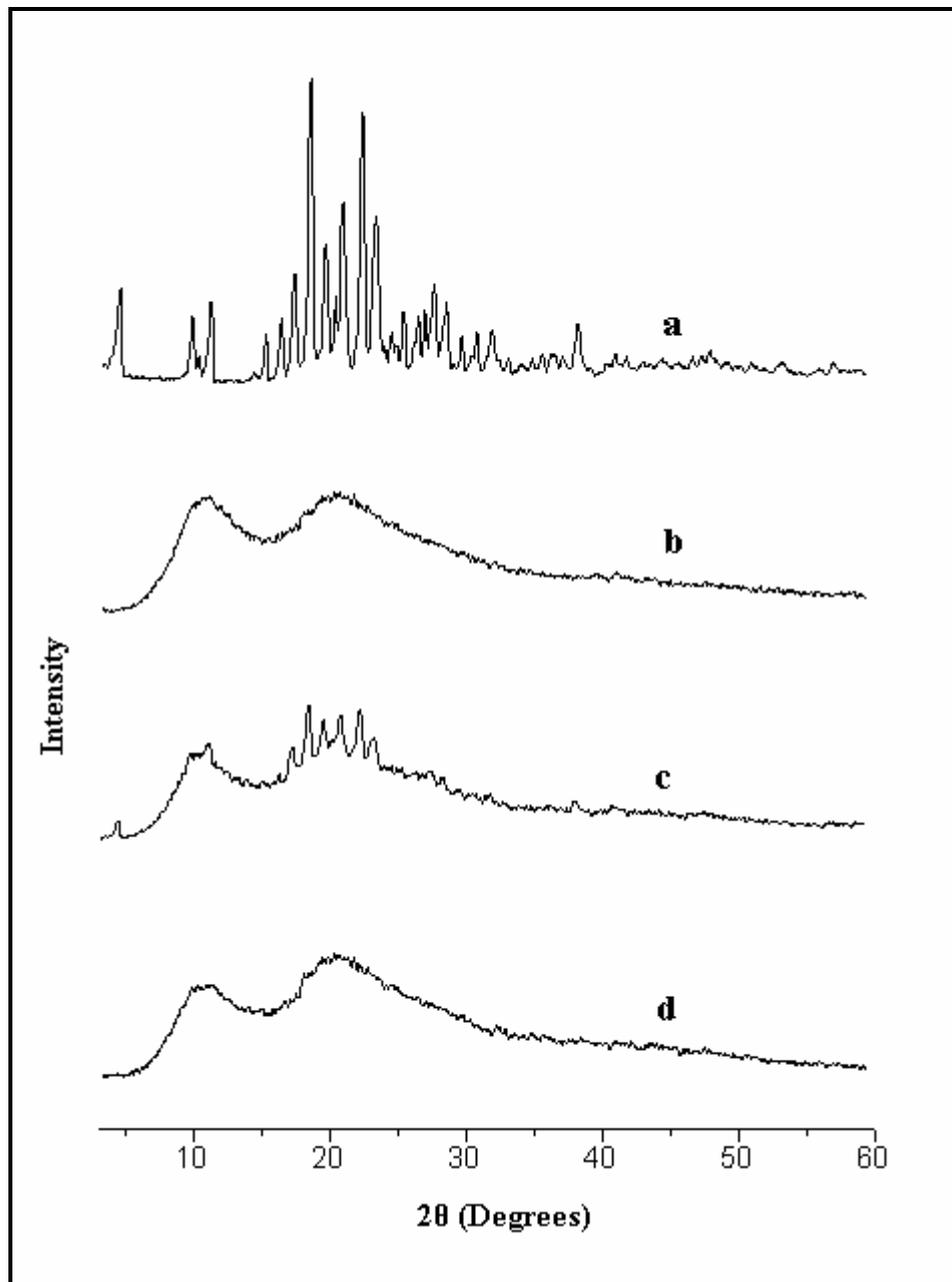


Fig. 10: X-Ray powder diffraction patterns of (a): nimesulide, (b): PVP 40000, (c): 1:7 Nimesulide/PVP 40000 physical mixture and (d): 1:7 nimesulide/PVP 40000 solid dispersion.

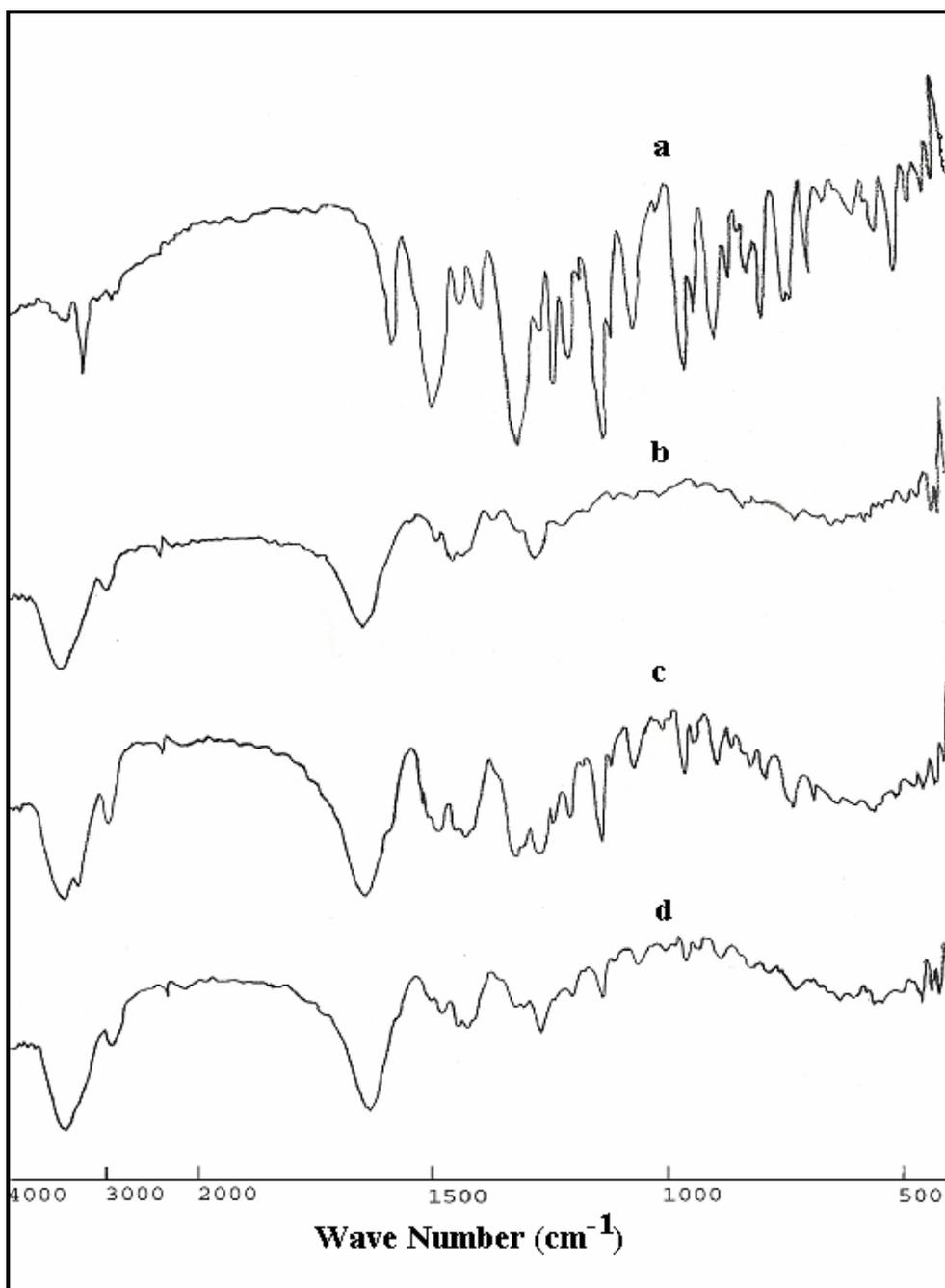


Fig. 11: IR spectra of (a): nimesulide, (b): PVP 40000, (c): 1:7 nimesulide/PVP 40000 physical mixture and (d): 1:7 nimesulide/PVP 40000 solid dispersion.

4- Scanning electron microscope (SEM)

Scanning electron microscope (Fig. 12) showed that nimesulide particles are in the form of tabular shaped crystals with smooth surfaces, while PVP 40000 appeared as large spherical particles of smooth surfaces. The SEM image of the physical mixture showed the individual nimesulide and PVP 40000 particles. The adherence of small crystal particles of

nimesulide onto the surface of the larger particles of PVP 40000 indicating no interaction takes place between them. The solid dispersion revealed absence of crystalline structure of the drug. It is difficult to differentiate between particles of both components, indicating that there was an interaction between them.

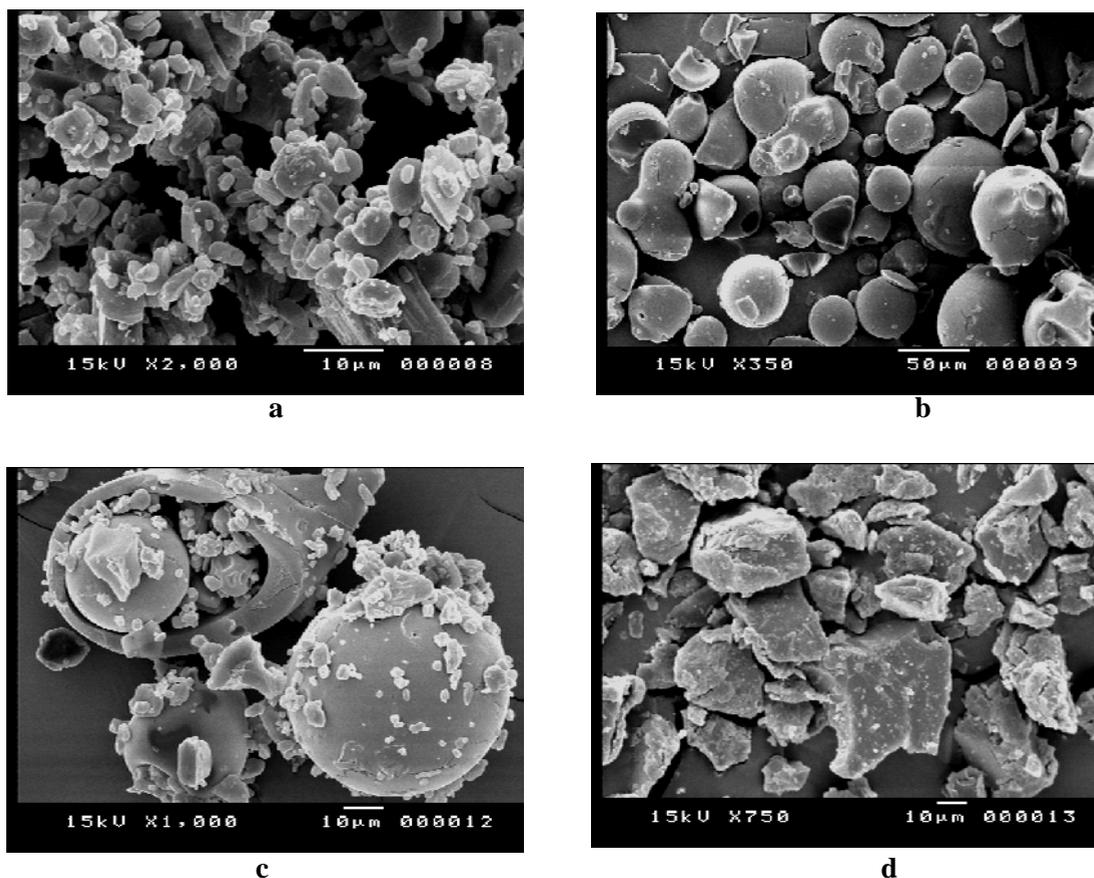


Fig. 12: Scanning electron micrographic of (a): nimesulide, (b): PVP 40000, (c): 1:7 nimesulide/PVP 40000 physical mixture and (d): 1:7 nimesulide/PVP 40000 solid dispersion.

Conclusion

From this study, it could be concluded that DMA and brij 58 showed the highest solubilizing power among the investigated solubilizers. Eutectic mixtures were obtained by solid dispersion of nimesulide with PEGs and pluronics at a weight ratio of 1:9. The dissolution of nimesulide from its solid dispersions and inclusion complexes with the investigated hydrophilic polymers as well as cyclodextrins was clearly improved. PVPs exhibited the highest dissolution at weight ratio of 1:7. The presence of nimesulide in an amorphous form in its solid dispersion with PVP 40000 might be responsible for the enhancement in the dissolution as confirmed by DSC, X-RDP, IR and SEM. These systems will be further investigated in the release of nimesulide from different topical formulations.

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