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Solubility enhancement of nimodipine through preparation of Soluplus® dispersions

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ABSTRACT

The present work aims to enhance the water solubility of nimodipine, a hydrophobic drug, using a solid dispersion (SD) technique. Soluplus® as a novel hydrophilic polymeric carrier was used. Nimodipine-Soluplus® SDs (1:10) were prepared by impregnation technique using supercritical fluid technology (SCF) and compared with the ones which were prepared by conventional hot-melt (HM) method. The solubility and the *in vitro* release study of the raw drug, solid dispersions, and the corresponding physical mixtures were characterized and compared. The prepared SD by SCF technology showed 77-fold increase in nimodipine solubility, in comparison to 48-fold increase when prepared by HM and 7.7-fold when physically mixed. Moreover, they showed the highest percentage of nimodipine cumulative release within the studied period. The results were confirmed the amorphous transfer of the drug into the polymer matrix which was assured by the powder X-ray diffraction and the thermal analysis. In addition to the hydrogen bond formation between nimodipine and Soluplus®, which was evident in the FTIR spectra; A weakening of peak related to nimodipine N–H stretching and C=O of the ester group. Nimodipine solid dispersion with Soluplus® using the SCF technology might represent a promising formulation for nimodipine to enhance its oral bioavailability.

INTRODUCTION

The poorly aqueous solubility of new chemical entities is increasingly posing a significant challenge in the development of the pharmaceutical industry (Sharma and Joshi, 2007). The biopharmaceutical classification system (BCS) classifies drugs based on the drug solubility and permeability into four classes (Sapkal *et al*., 2013). Class II drugs have dissolution-limited absorption; they have low solubility and high permeability. The limited solubility can lead to failure in reaching the desired concentration of the desired pharmacological action (Savjani *et al*., 2012).

Nimodipine is a (1,4) Dihydro(2,6)dimethyl (4-(3-nitrophenyl)(3,5)pyridine dicarboxylic acid 2-methoxyethyl 1-methyl-ethyl ester, (Fig. 1). It is a dihydropyridine calcium channel blocker (Teng *et al*., 2018). Nimodipine has been proposed as the first choice for prevention and the treatment of delayed ischemic neurological disorders following subarachnoid hemorrhage (Liu *et al*., 2016; Vergouwen *et al*., 2018).

Nimodipine acts mainly by hindering calcium influx through the voltage-dependent calcium channel and inhibiting vascular smooth muscle contraction which causes vasodilatation (Sin *et al*., 2018). It is a highly hydrophobic drug, can pass the blood

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brain barrier, and delivered to brain and also the cerebrospinal fluid (Wessell *et al*., 2017).

Nimodipine belongs to class II of the (BCS) classification. It has mainly poor water solubility with good permeability characteristic due to its high lipophilicity (log p = 3.41) (Masumoto *et al*., 1995). Nimodipine is a basic compound with predicted pka value equals to 5.41. It is freely soluble in methanol, dioxane, ethanol, and DMSO (Urbanetz and Lippold, 2005). It is available in several FDA approved dosage forms, soft gelatin capsules, tablets, liquid for intravenous administration, and oral solution (Sweetman and Martindale, 2002).

Nimodipine has two enantiomers and shows two polymorphic forms. Modification 1 is the commercialized crystal form of the drug. It is a racemic mixture that contains an equal ratio of two enantiomorphs, and it is the metastable form. Modification 2 is the mixture of pure S and R enantiomer, and it is the stable form (Rahman *et al*., 2013). The solubility of the two modifications is entirely different. Modification 1 exhibits double solubility value of (0.36 mg/l) compared to modification 2 (0.18 mg/l) (Grunenberg *et al*., 1995, Riekes *et al*., 2012).

Several techniques had been reported in the literature to improve nimodipine solubility and dissolution rate, such as nanoparticle technology (Fu *et al*., 2013), self-microemulsification (Kale and Patravale, 2008), complexation with cyclodextrins (Kopecký *et al*., 2003), and solid dispersion (SD) (Papageorgiou *et al*., 2006; Thirty *et al*., 2016). Among these methods, SDs had the advantages of scaling up ability and excellent economical outcomes (Kreidel *et al*., 2012).

SD is a type of solid formulations; it consists of two or more components, usually hydrophilic polymer and a hydrophobic active ingredient. These polymeric matrices can be either crystalline or amorphous form (Chiou and Riegelmant, 1971). SD enhances the drug dissolution by various mechanisms, such as reduction of particle size, improving wettability, increasing porosity, and amorphous state formation (Sharma and Jain, 2011). Various methods were used for preparing the SDs. These included the melting method, solvent extraction or evaporation, extrusion, lyophilization method, spray congealing and drying, and supercritical fluid technology (Vo *et al*., 2013). Nimodipine SDs were prepared by using various methods, such as melt mixing and solvent evaporation. They were prepared by using different polymers, such as polyethylene glycol with different molecular weight (Kreidel *et al*., 2012; Papageorgiou *et al*., 2006, Urbanetz, 2006), poloxamer (Kreidel *et al*., 2012), polyvinylpyrrolidone K30 (Gorajana *et al*., 2010), hydroxypropyl methylcellulose, and Eudragit® EPO (Zheng *et al*., 2007).

Soluplus® is a polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer that consists of 13% macrogol (PEG 6000), 57% vinyl caprolactam, and 33% vinyl acetate, (Fig. 2). It is a novel polymer with amphiphilic properties (Vo *et al*., 2013). Due to its bi-functional characters, it acts as a matrix polymer for a solid solution as well as an active solubilizer for drugs that have low solubility in aqueous fluids attributed to micelle formation. Moreover, Soluplus® has a strong potential to improve the oral bioavailability of low water-soluble drugs by enhancing its intestinal absorption (Shamma and Basha, 2013).

Many studies proved the effectiveness of Soluplus® dispersions which were prepared by using different conventional techniques. They improved the rate of dissolution for drugs that have poor water solubility, such as carbamazepine [hot-melt (HM) extrusion] (Djuris *et al*., 2013), camptothecin (solvent evaporation) (Thakral *et al*., 2012), and carvedilol (spray drying and freeze drying) (Shamma and Basha, 2013). Also, Soluplus® enhanced the dissolution of other poorly water-soluble class II drugs, such as tacrolimus and itraconazole, by using the most recent technology; Impregnation using supercritical fluid technology (SCF) (Obaidat *et al*., 2017; Yin *et al*., 2015).

In the present work, the SD of nimodipine with Soluplus® using the conventional HM method and the SCF technology was prepared, characterized, assessed, and compared regarding nimodipine solubility and dissolution rate enhancement ability.

EXPERIMENTAL

Materials

Nimodipine was kindly donated from JPM Company (Naour, Jordan). Soluplus® (polyvinyl caprolactam–polyvinyl

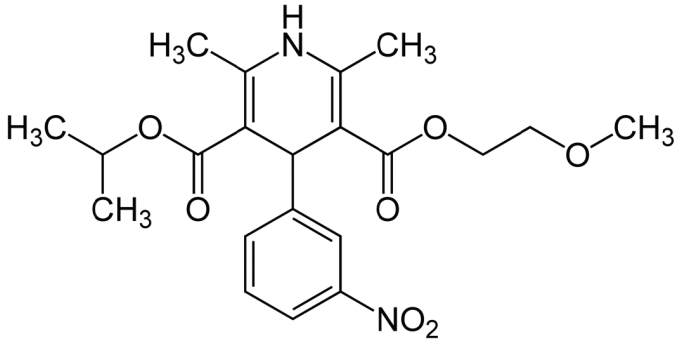

Figure 1. Chemical structure of nimodipine.

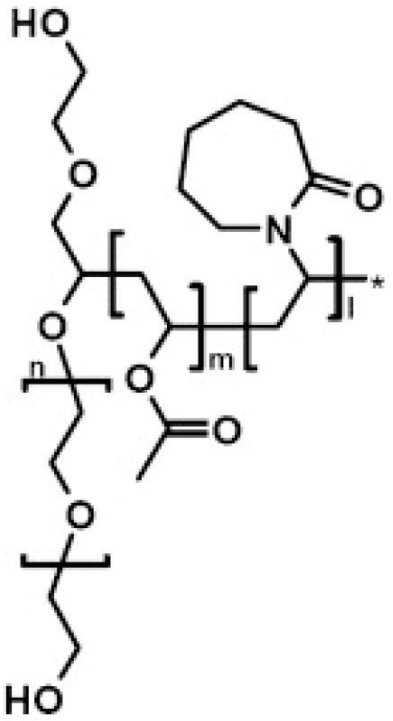

Figure 2. Soluplus® chemical structure.

acetate–polyethylene glycol graft copolymer in the ratios of 57%–33%–13%, respectively) was kindly provided by the BASF company (Ludwigshafen, Germany). Potassium Bromide (IR Spectroscopy grade) and methanol were provided by Fisher chemical, UK. Nylon membrane filters 0.45 µm were from Bonna-Agela Technologies, US. Carbon dioxide (CO_2) that ha 99.995% purification grade was supplied by the Jordanian Gas Co., Amman, Jordan. All the materials were used as provided without any modification.

METHODS

Preparation of nimodipine-Soluplus® SD by the HM method

The Soluplus® carrier was melted separately at a temperature of 70°C. Nimodipine was added with continuous stirring, and the temperature was increased carefully to 120°C until a homogeneous mixture was formed. The mixture was immediately cooled on a water bath. The solidified mass was scrapped, crushed, and pulverized using the mortar and pestle. A mesh screen 300–180 µm was used to sieve the prepared SD powder, after that they were stored at room temperature in the silica gel desiccators until their use. The ratio of nimodipine: Soluplus® was 1:10.

Preparation of nimodipine-Soluplus® SD by the supercritical fluid method

Nimodipine powder was mixed with the Soluplus® at a ratio of 1:10, and then placed in a stainless-steel vessel (Eurotechnica, GmbH, Germany). CO_2 was entered to the vessel using double acting piston pumps at a rate of 100 g/minute until reaching the required pressure (100 bar) at 40°C. The same conditions were continued for two hours. After that, depressurization was started at a rate of around 0.5 bar/s. The formed foamy SDs were then grinded using mortar and pestle and sifted through mesh screen 300–180 µm to get the desirable size. The samples were stored at room temperature in the desiccator.

Preparation of nimodipine-Soluplus® physical mixtures (PMs)

PMs were prepared by mixing nimodipine with Soluplus® (1:10) in a mortar by trituration for 15 minutes. The PMs were kept in the desiccator at room temperature until use.

Physicochemical characterization

Powder X-ray diffraction (PXRD)

PXRD was done by Ultima IV X-ray diffractometer (Rigaku, Japan) using cobalt radiation (CuKα) using voltage of 40 kV and a current of 30 mA at room temperature with diffraction angles of 2θ starting from 0° to 60°. The step scan mode was used with a step size of 0.02°.

Fourier transform infrared spectroscopy (FTIR)

FTIR studies for raw materials, PMs, and SDs were carried out using IRAffinity-1 Spectrophotometer (Shimadzu, Japan) with KBr as a reference. Thirty milligrams of each sample was physically mixed with 270 mg KBr and grinded using mortar and pestle to obtain homogenous samples. The scanning range was from 4,000–450 cm^{-1}.

Differential scanning calorimetry (DSC)

DSC thermograms were recorded using DSC 204 (Netzch, Germany). Indium was used to calibrate temperature and energy scale. An accurately weighed sample was placed in an aluminum pan and sealed, then it was heated up until reaching 200°C under fixed gas flow of nitrogen using a rate of 30 ml/minute. The reference used was an empty sealed aluminum pan.

Thermogravimetric analysis (TGA)

TGA thermograms of pure nimodipine were analyzed using a Shimadzu TGA-50 under nitrogen. The sample was first equlibruimed at 25°C, and then heated under nitrogen at a rate of 10°C $minute^{-1}$, up to final temperature 350°C.

Solubility determination of nimodipine in water

Saturation water solubility of the pure nimodipine, PM, and the SDs by HM and SCF was determined. The known excess samples, which were equivalent to 10 mg of nimodipine, were placed into a volumetric flask (100 ml), and the water was added accurately by volume up to the final mark. The flasks were placed in a water bath shaker at 37°C for 24 hours. Then, samples were filtered through 0.45-µm silicon membrane filter and analyzed by UV spectrophotometer at λ_{max} 237 nm. The test was replicated three times. A calibration curve was performed with R^2 value equals 0.99. The absorbance of Soluplus® at λ_{max} = 237 nm was negligible.

In vitro sissolution studies

Thirty-milligram of pure nimodipine, PM, and SDs by HM and SCF containing 30 mg nimodipine were accurately weighed. The dissolution rate studies were carried out in 900 ml of 0.5% sodium dodecyl sulfate in water with pH 6.4 at 37°C using rotating paddle at 50 rpm (U.S. FDA method). At predetermined time intervals 10, 20, 30, 45, 60, and 120 minutes, 5 ml sample was withdrawn, filtered through a 0.45-µm membrane filter, and assayed spectrophotometrically at 237 nm. Sink condition was maintained by replacing an equal volume of dissolution media after each withdrawn sample. A calibration curve was performed with R^2 value equals 0.99, with the linear range of nimodipine concentration (0.8–2.4) µg/ml, the used solvent was water, and suitable dilution was performed.

RESULTS AND DISCUSSION

Physicochemical characterization of nimodipine

Powder X-ray diffraction (PXRD)

PXRD of pure nimodipine (Fig. 3) illustrated the crystalline nature of nimodipine modification 1. Numerous sharp peaks were visible with original ones at 2θ of 6.10, 11.74, 17.70, 18.20, 20.16, 20.98, and 24.70 and similar to those appeared in Gorajana *et al*. (2011). Moreover, the crystallinity was obvious in the PM as indicated by the presence of the sharp peaks. In the other side, SDs by HM and SCF exhibited complete conversion into the amorphous form of the drug, which was indicated by the presence of an amorphous halo.

Fourier transform infrared spectroscopy (FTIR)

FTIR of nimodipine modification 1 (Fig. 4) showed many main peaks at; 3,297 cm^{-1} due to N–H stretching, 3,097 cm^{-1}

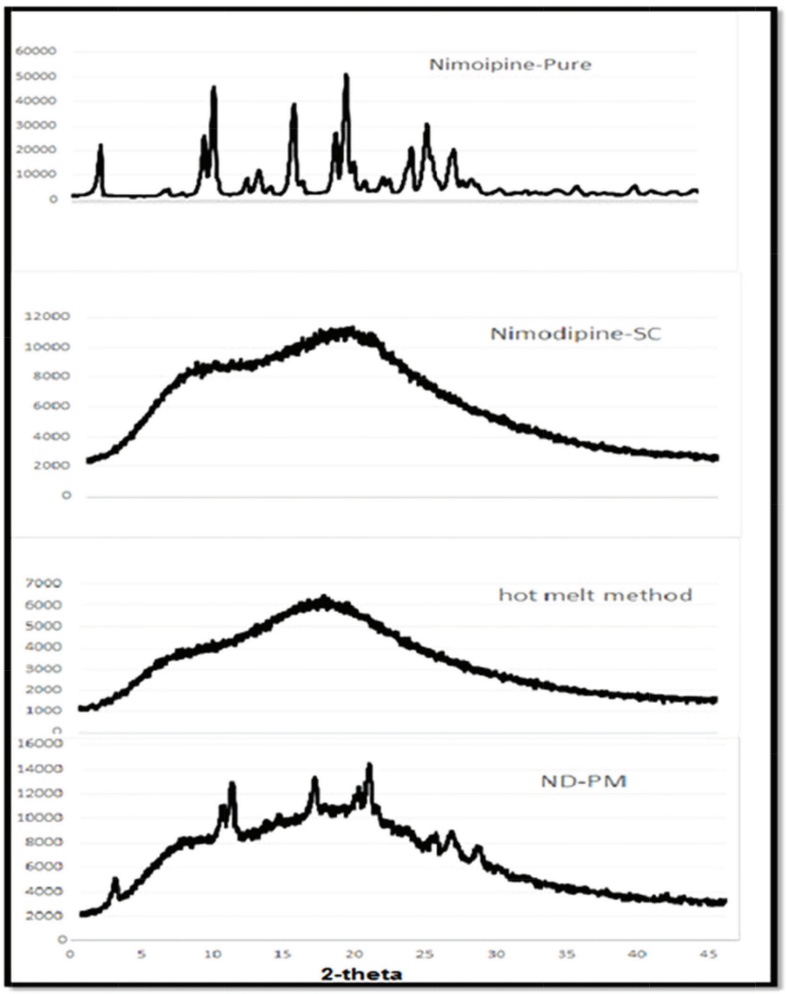

Figure 3. PXRD of pure nimodipine, PM, HM, and SCF solid dispersions with cobalt radiation (CuKα) at a voltage of 40 kV and a current of 30 mA at room temperature with diffraction angles from 0° to 60° of 2-theta.

due to C–H aromatic stretching, 2,933 cm^{-1} due to C–H aliphatic stretching, 1,695 cm^{-1} due to C=O stretching in ester, 1,648 cm^{-1} due to C=C stretching, 1,621 cm^{-1} due to C=C aromatic, 1,523 cm^{-1} due to $-NO_2$, 1,381 cm^{-1} due to $-C-CH_3$, and 1,134 cm^{-1} that can be related to −C–O– ester. All these bands were assigned as the fingerprints of nimodipine in the literature (Semcheddine *et al*., 2015).

By comparing the FTIR spectrum of pure nimodipine with its SD (HM and SCF), it seemed that the intensity of the secondary amide peak (at around 3,297 cm^{-1}) and of the C=O peak (at around 1,696 cm^{-1}) was significantly reduced and almost disappeared. This can be explained by the formation of the hydrogen bonding between Soluplus® hydroxyl group and nimodipine. It was well identified that upon the formation of hydrogen bonding, the bands could shift to different wave lengths with reduced intensities or even could disappear (Xu *et al*., 2009). Moreover, a new peak appeared at 2,500 cm^{-1} in the spectrogram of SCF that reflected the sorption of CO2 as discussed by Obaidat *et al*. (2018).

On the other hand, by comparing the FTIR of pure nimodipine with the PM (Fig. 4), same peaks particularly the amide peak (at around 3,297 cm^{-1}) and the C=O peak (at around 1,696 cm^{-1}) was obvious in both spectra, indicating no interactions between nimodipine and Soluplus® in the PM.

Differential scanning calorimetry (DSC)

DSC thermograms of the PM (Fig. 6) showed that they had the same endothermic peaks of raw materials. A peak at approximately 126°C possibly represented the melting point of nimodipine as shown in Figure 5. The findings matched with the previous studies performed by Papageorgiou *et al*. (2006) and Mowafaq and Abulfadhel (2017). The presence of this peak indicated the appearance of nimodipine in its crystalline form. Another endothermic peak was obvious at temperature 70°C that represents the polymeric glass transition temperature as declared by Mendiratta *et al*. (2011). On the other hand, DSC thermograms of SDs indicated that the morph of nimodipine in the solid dispersion is amorphous form, and the anticipated melting

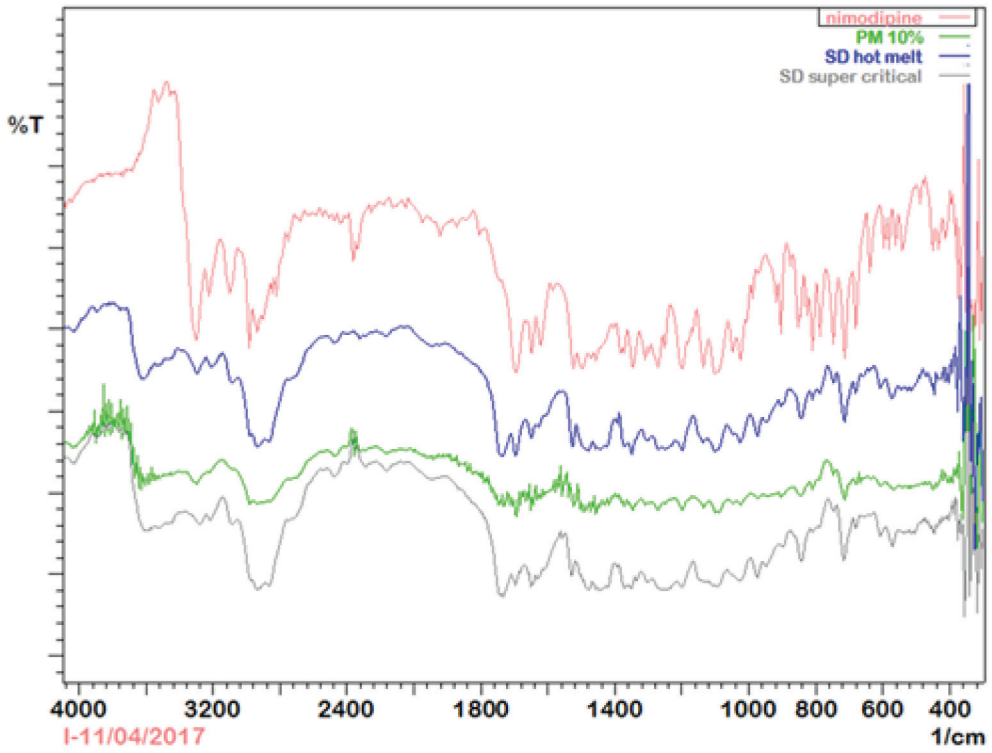

Figure 4. FTIR spectra of nimodipine, PM, solid dispersions by HM and SCF.

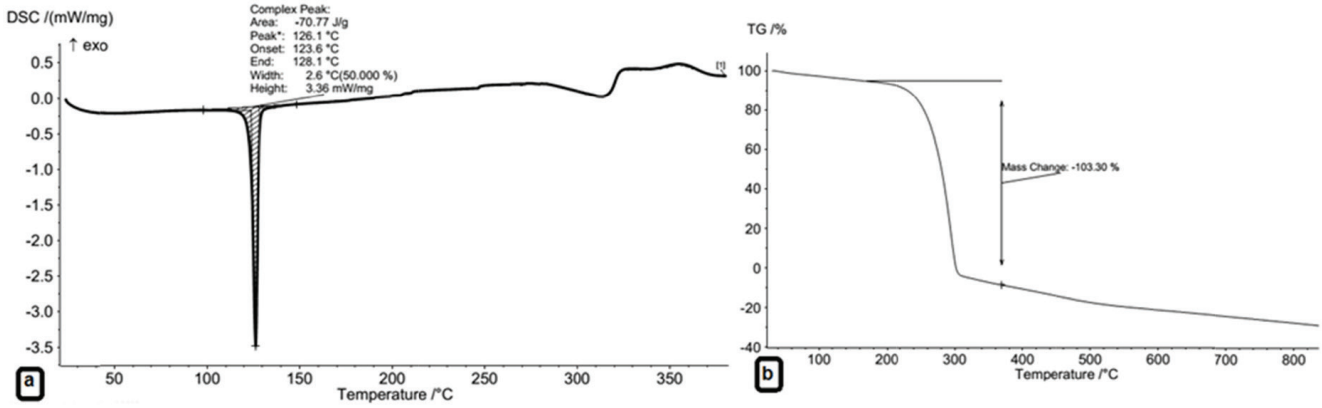

Figure 5. DSC of nimodipine pure powder.

endotherm was not appeared in melting point range when the SDs prepared by HM and SCF.

Thermogravimetric analysis (TGA)

Figure 5 shows the TGA results of the raw nimodipine drug. It shows the thermal behavior of nimodipine. A significant mass loss started after 200°C and was related to the decomposition of nimodipine. Similar results were reported in the previous studies of Kiwilsza *et al*. (2015).

Solubility determination of nimodipine in water

Since the poor solubility of nimodipine is cosidered a major problem in the pharmaceutical formulations of this drug, it was expected that the use of amphiphilic Soluplus® polymer would enhance nimodipine solubility significantly and would enhance consequently its bioavailability. Table 1 shows the solubility values of nimodipine in water at 37ºC. The solubility of raw nimodipine (modification 1) was determined to be 0.0653 mg/100 ml. Accordingly, nimodipine is classified based on the solubility expressions as slightly soluble drug as expressed in U.S. Pharmacopeia and National Formulary. The solubility value was increased in nimodipine-Soluplus® PM (the physical mixture) by 7.7-folds. This increment was probably due to a wettability improvement by the Soluplus® polymer (Fule and Amin, 2014).

Moreover, nimodipine-Soluplus® solid dispersions results showed a significant improvement in the solubility of nimodipine, especially with supercritical dispersion method which demonestrated remarkable highest increase in solubility.

Around 77-folds and 48-folds increase were observed using SCF and HM methods, respectively. These results could be attributed to the conversion of nimodipine to the amorphus form inside the Soluplus® polymer which confirmed by the DSC and PXRD results. However, this enhancement in solubility found to be more significant when the SCF technology was used. This could be referred to the cosolvent impact of Soluplus®, as well the foaming effect that occurred for the sample while using this particular method. This could be related to the increase in the porosity and the surface area that occurred in the supercritical fluid samples (Charoenchaitrakool *et al.*, 2000). In this experiment, the absorbance of Soluplus® at λ_{max} = 237 nm was negligible.

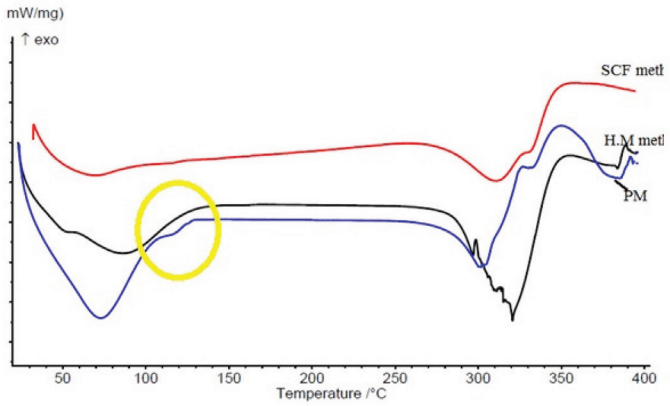

Figure 6. DSC of PM, solid dispersion of HM method and SCF method.

Table 1. Solubility of nimodipine, PM, hot melt SD, and SCF SD.

Sample name	Conc mg/100 ml (*n* = 3)
Pure nimodipine	0.065 ± 0.06
10% nimodipine-soluplus PM	0.5 ± 0.05
Hot melt SD	3.16 ± 0.04
Super critical fluid SD	5.03 ± 0.02

In vitro dissolution studies

Figure 7 shows the dissolution profiles of nimodipine. The results corresponded with the solubility data, as the solubility-improved, the dissolution rate increased as well. Pure nimodipine showed a cumulative release of approximately 16% within 2 hours and 17% for PM. At the same time, SDs exhibited higher cumulative release; 33% and 41% for the SDs which were prepared by HM and SCF methods, respectively. The increment could be attributed to the improved wettability and dispersibility, in addition to the complete conversion of Nimodipine to the amorphous form in the presence of Soluplus® (Homayouni *et al.*, 2012). As a future study, the *in vitro* release results would be compared with the marketed formulation of nimodipine.

CONCLUSION

Soluplus® increased the solubility of nimodipine in the physical mixture, as well as the solid dispersions forms prepared either by conventional hot melt (HM) method or impregnation by SCF method. Saturation solubility study revealed the superior result obtained by SCF where the solubility was increased by 77-folds comparing to 48-folds increment by using the HM method. This increment was attributed to nimodipine-Soluplus® hydrogen bond interactions which were postulated using FTIR spectra of the solid dispersion. In addition to the amorphous transfer which was confirmed by DSC and PXRD. The use of Soluplus® with nimodipine to prepare solid dispersions found to be promising technique to enhance both nimodipine solubility and the dissolution profile. This enhancement was more pronounced in the dispersions prepared using the supercritical

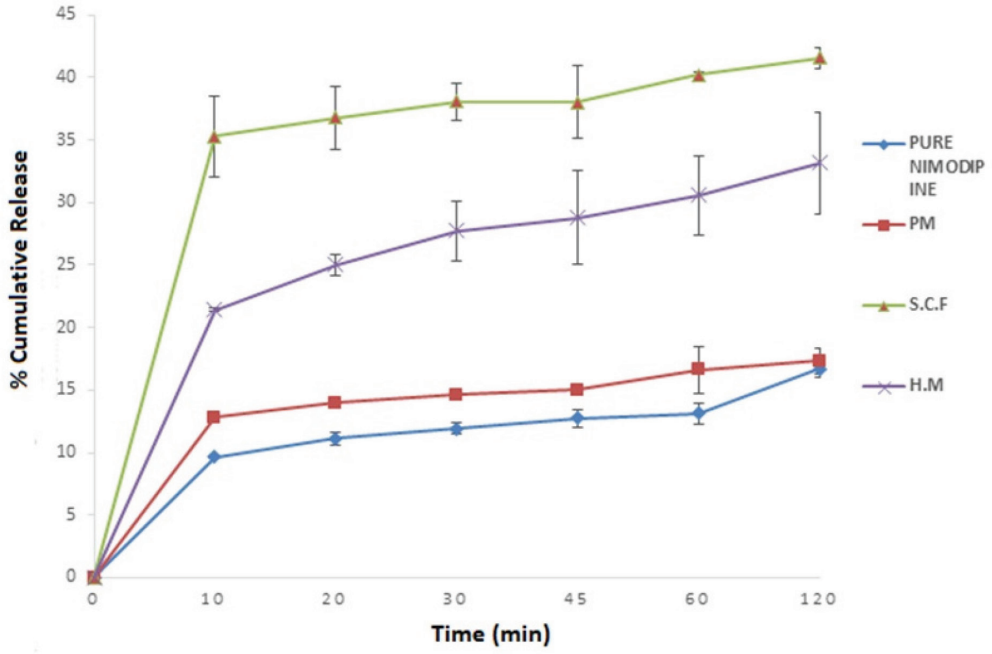

Figure 7. Dissolution profiles of pure nimodipine, PM, solid dispersions by HM and SCF at the dissolution tests were performed using USP apparatus (rotating paddle) with 50 rpm and 37°C using 900 ml of 0.5% sodium dodecyl sulfate in water (U.S. FDA method).

fluid technique. Future work should be designed to study such formulations through quality by design approach, in addition to performing accelerated stability studies for the selected formulations.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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