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Physicochemical Characterization and *In Vitro* Evaluation of Solid Dispersions of Nimodipine With PEG 8000

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Solid dispersions of nimodipine were prepared in an attempt to enhance solubility and dissolution rate. Solid dispersions of nimodipine were prepared with polyethylene glycol (PEG 8000) using melting method. Solid dispersions were characterized using differential scanning calorimetric and X-ray powder diffraction analysis. Dissolution characteristics were determined by using pH 4.5 acetate buffer containing 0.3 % SDS. Differential scanning calorimetric and X-ray powder diffraction studies reflected that no chemical incompatibility between the drug and polymeric. It is also indicated that crystallinity of the drug in solid dispersions was significantly decreased and the possibility of existence of amorphous entities of the drug in solid dispersions. The solid dispersions and physical mixtures showed higher solubility and dissolution rate than nimodipine due to improved wettability and dispersibility of nimodipine. It is concluded that the solid dispersions of nimodipine in PEG 8000 considerably enhanced the dissolution rate of nimodipine.

Key Words: Nimodipine, PEG 8000, Differential scannning calorimetry, X-Ray powder diffraction study, Dissolution enhancement.

INTRODUCTION

In 21st century, an increasing numbers of new drugs that exhibit poorly water-soluble property in biological media. These poorly water-soluble drugs contribute to slower dissolution rate when they are dissolved in biological media. The therapeutic efficacy of a drug product intended to be administered by the oral route depends on its absorption through the gastro-intestinal tract. Other drawbacks of use of poorly water-soluble drugs include increasing the dosage, administration frequency and the resultant occurrences of side effects[1]. There are numerous techniques can be applied to enhance the solubility and dissolution rate of poorly water-soluble drugs such as liquisolid, nanomorph, *in situ* micronization, salt formation, formation of inclusion compound with cyclodextrin, change in physical form, use of pro-drug and drug deviation, alteration in pH, addition surfactants and solid dispersions[2,3]. A common approach to improve the dissolution rate of poorly water soluble drugs and, therefore, improve bioavailability is by formulation of solid dispersions[4] with a water-soluble rate-enhancing polymer. Nimodipine is isopropyl-2-methoxyethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylate, a dihydropyridine calcium antagonist. It is a highly permeable drug but slower dissolution rate in biological media and resulting in low bioavailability and low therapeutic effects after oral administration[5]. Hence, the slow dissolution rate must be accelerated in order to achieve a better bioavailability. These properties have been contributed to the reasons of nimodipine was chosen in this research study. The objective of the present study is to prepare, characterize and evaluate solid dispersions of nimodipine using PEG 8000 as water soluble carrier.

EXPERIMENTAL

Nimodipine powder (Batch No. 200704004) was received as gift sample from China. PEG 8000 (product of Germany) was received from Italy. All other chemicals used are of the analytical grade and purchased from local supplier.

Preparation of physical mixtures and solid dispersions: The physical mixtures of nimodipine and PEG-8000 were obtained by weighing and simple blending nimodipine and polymer in ratios of 1:1, 1:2 and 1:3 (drug:polymer) with a spatula, respectively.

Solid dispersions of nimodipine were prepared by using water soluble polymer PEG 8000 in the ratios of 1:1, 1:2 and 1:3 by melting method. The required quantity polymer was melted on a hot plate stirrer (HTS-1003 Harmony, Korea) for 10 min. Then, the required quantity of nimodipine was added with constant stirring until clear solution is obtained. The liquid was cooled by rapid cooling in an ice bath for 10 min. The

dried solid dispersion was stored in refrigerator for 24 h. The dried samples were then pulverized uniformly in a mortar and sieved into defined particle size fractions. The sample passed through Sieve No. 60 and retained on sieve No. 100 was used for the present study.

Phase solubility study for nimodipine: Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors[6]. An excess amount of nimodipine was added in screw-cap vials containing aqueous solution of PEG 8000 in various concentrations. The samples were shaken in a water bath shaker at 37 ± 0.5 ºC for 72 h. The samples were filtered through 0.45 µm membrane filter. After suitable dilution, the absorbance was measured at 236 nm[7] and the concentration of nimodipine was determined. The value of apparent stability constant, K_s, between drug-carrier combinations were computed from the phase-solubility profiles, as shown in eqn. 1.

$$K_s = \frac{\text{Slope}}{\text{Intercept}\,(1-\text{Slope})} \quad (1)$$

Gibbs free energy of transfer (ΔG_{tr}^{o}) of nimodipine from pure water to the aqueous solutions of carrier was calculated as in eqn. 2:

$$\Delta G_{tr}^{o} = -2.303RT \log\left(\frac{S_0}{S_s}\right) \quad (2)$$

where S_0/S_s is the ratio of molar solubility of nimodipine in aqueous solution of PEG 8000 to that of the same medium without PEG 8000.

Differential scanning calorimetry (DSC) curves were obtained by a differential scanning calorimeter ((Mettler Toledo DSC 823e, Switzerland) at a heating rate of 10 ºC/min from 30-300 ºC in a nitrogen atmosphere.

The X-ray powder diffractometry patterns of nimodipine, PEG 8000 and solid dispersions were recorded using diffractometer with tube anode Cu over the 5-70 º/2θ interval at a scanning speed of 2º min^{-1}. The generator tension (voltage) and generator current were kept at 40 kV and 30 mA, respectively.

***In vitro* drug release study:** Dissolution characteristics of nimodipine pure drug, physical mixtures and different solid dispersions were studied in pH 4.5 acetate buffer containing 0.3 % sodium dodecyl sulfate[7]. A sample of physical mixtures, solid dispersions equivalent to 30 mg of nimodipine was used in each test. The dissolution rate of prepared solid dispersion was carried out using USP XXI dissolution rate test apparatus in 900 mL of dissolution medium at 37 ± 0.5 ºC with rotation speed of 100 rpm. 5 mL of aliquot of dissolution medium was withdrawn with time intervals at 5, 10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 min by a syringe with Millipore filter with pore size of 0.45 µg. The percentage of drug release was measured by UV spectrophotometer (Shimadzu 1240, Japan) at λ_{max} 236 nm. The test was repeated three times.

RESULTS AND DISCUSSION

The phase-solubility results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drug[8]. The phase-solubility diagram investigated was linear over a wide range of PEG 8000 concentrations and corresponds to A_L-type profiles[9]. The stability constant K_c was 0.305 mL^{-1} mg. At 20 % w/v concentration of PEG 8000, the solubility of nimodipine increased by 4.80-fold. This is due to well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs. An indication of the process of transfer of nimodipine from pure water to the aqueous solution of PEG 8000 may be obtained from the values of Gibbs free energy change. ΔG_{tr}^{o} values were all negative for PEG 8000 at various concentrations indicating the spontaneous nature of drug solubi-lization.

The thermal behaviour of the prepared solid dispersions of nimodipine with PEG 8000 was studied by DSC. The differential scanning calorimetric thermograms for pure nimodipine, PEG 8000 and solid dispersions are shown in Fig. 1. Nimodipine showed a melting peak at 125 ºC. The differential scanning calorimetric scan of PEG 8000 showed a melting peak at 60 ºC. Differential scanning calorimetric thermograms of nimodipine and PEG 8000 (1:1, 1:2 and 1:3) showed the melting peaks at 60 ºC due to melting point of PEG 8000 and absence of drug peak at 125 ºC. This indicates that nimodipine is in amorphous or in a solid solution dispersed in PEG 8000 matrix. This type of interaction was also observed in the XRD studies.

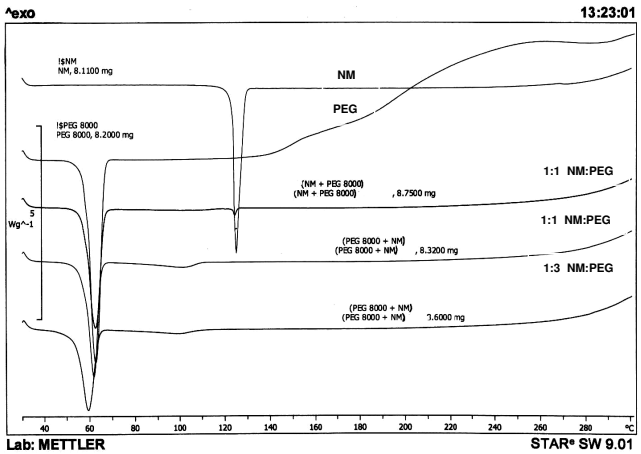

Fig. 1. Differential scanning calorimetric thermogrames of nimodipine, PEG 8000 and solid dispersions

Powder X-ray diffractograms of nimodipine, PEG 8000 and their solid dispersions are shown in Fig. 2. The presence of numerous distinct peaks in the XRD spectrum indicate that nimodipine was present as a crystalline material with major characteristic diffraction peaks appearing at a diffraction angle of 2θ at 11.906, 17.788, 20.771 and 25.350. PEG 8000 exhibited a distinct pattern with diffraction peaks at 2θ at 19.084 and 23.265. The diffraction patterns of all the samples of solid dispersion show peaks due to PEG 8000 are similar and an absence of major diffraction peaks corresponding to nimodipine, with most of the diffraction indicating nimodipine was present as amorphous material inside the PEG 8000 matrix. Moreover, no peaks other than those that could be assigned to pure nimodipine and PEG 8000 were detected in the solid dispersions of nimodipine and PEG 8000 in ratio 1:3 indicating no chemical interaction in the solid state between the two entities. Dissolution

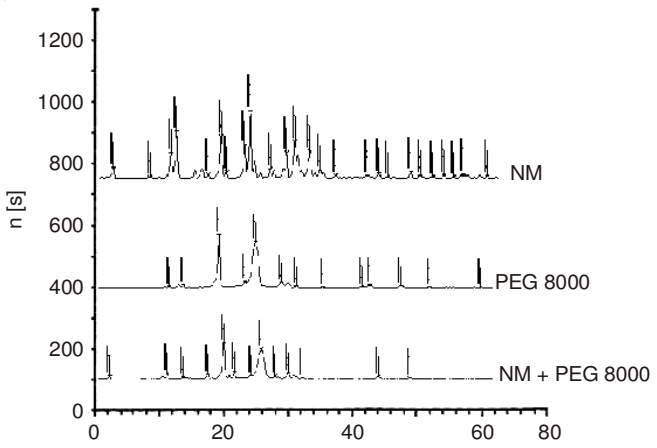

Fig. 2. XPRD pattern of nimodipine, PEG 8000 and nimodipine + PEG (1:3) solid dispersion

profiles of nimodipine from capsules containing nimodipine (without PEG 8000), physical mixtures of nimodipine with PEG 8000 and its solid dispersions of nimodipine with PEG 8000 are shown in Fig. 3. Percent drug dissolved in 10, 20 and 30 min are calculated and reported in Table-1. Nimodipine dissolution is very slow and as evident from Table-1. The dissolution rate of nimodipine from solid dispersions was increased significantly ($p > 0.01$) when compared to nimodipine and its physical mixtures. PEG 8000 enhanced the dissolution rate of nimodipine in sold dispersions. Dissolution efficiency (% DE 10 min) values for nimodipine (2.60%), physical mixture of 1:3 ratio (12.96 %) and solid dispersions of 1:3 ratio (34.64 %) were observed. Dissolution efficiency 30 min values are increased subsequently to as high as 29.59 % for physical mixture of ratio 1:3 and 49.91 % for SD of ratio 1:3. The solubilization effect of PEG 8000 results in the reduction of particle aggregation of the drug, elimination of crystallinity, increased wettability, dispersibility, alteration of the surface properties of the drug particles and this is probably responsible for the enhanced solubility and dissolution rate of nimodipine in the solid dispersions[9,10].

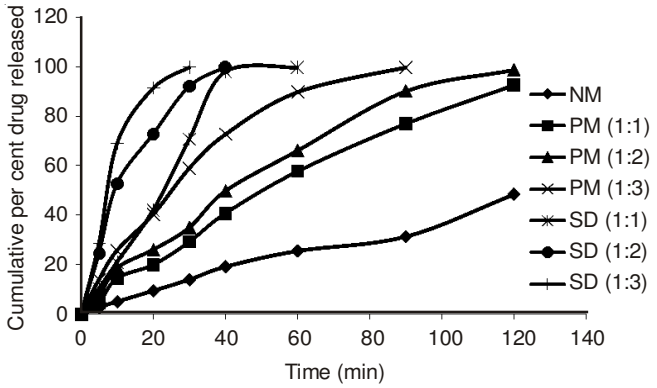

Fig. 3. Dissolution profiles of nimodipine, its physical mixtures and solid dispersions

TABLE-1
DISSOLUTION PARAMETERS OF NIMODIPINE, ITS PHYSICAL MIXTURES AND SOLID DISPERSIONS

Formulation	Dissolution parameter				
	$PDR_{10\ min}$	$PDR_{30\ min}$	$PDR_{90\ min}$	$DE_{10\ min}$ (%)	$DE_{30\ min}$ (%)
NM	5.20	14.08	31.5	2.60	7.25
PM (1:1)	14.7	29.4	77.2	7.36	14.72
PM (1:2)	18.8	35.1	90.2	9.41	17.40
PM (1:3)	25.9	59.1	99.9	12.96	29.59
SD (1:1)	21.2	70.8	99.9	10.61	35.51
SD (1:2)	52.8	92.1	99.9	26.43	48.20
SD (1:3)	69.2	99.9	99.9	34.64	49.91

PM = Physical mixtures; NM = Nimodipine, SD = Solid dispersions; DE = Dissolution efficiency.

Conclusion

The solubility and dissolution rate of nimodipine is enhanced by the use of PEG 8000 as water soluble carrier. Differential scanning calorimetric thermograms of nimodipine solid dispersions did not show any presence of crystallinity for nimodipine. XRD studies results also supported this. Nimodipine-PEG 8000 solid dispersions provided a promising approach to enhance the solubility and dissolution rate of nimodipine. The study shows that the dissolution rate of nimodipine can be enhanced to a great extent by solid dispersion technique using an industrially feasible melting method. This in turn can reduce the doses of drug reduction in dose related adverse effects and improved bioavailability.

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