

PREPERATION AND *IN VITRO* EVALUATION OF SOLID DISPERSIONS OF NIMODIPINE USING PEG 4000 AND PVP_{K30}

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ABSTRACT

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability, of a range of hydrophobic drugs. The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug, nimodipine, by a solid dispersion technique. Solid dispersions were prepared by using polyethylene glycol 4000 (PEG- 4000) and polyvinylpyrrolidone K30 (PVP_{K30}) in different drug-to-carrier ratios. The solid dispersions were prepared by melting method. Morphology of solid dispersions was characterised by scanning electron microscope. The pure drug, physical mixtures and solid dispersions were characterized by *in vitro* dissolution study. Dissolution characteristics were determined by using pH 4.5 acetate buffer

containing 0.3% SDS. The very slow dissolution rate was observed for pure nimodipine and the dispersion of the drug in the polymers considerably enhanced the dissolution rate. This can be attributed to improved wettability and dispersibility, as well as decrease of the crystalline and increase of the amorphous fraction of the drug. Solid dispersions prepared with PEG-4000 and PVP_{K30} showed the highest improvement in wettability and dissolution rate of nimodipine. Even physical mixtures of nimodipine prepared with both polymers also showed better dissolution profile than that of pure nimodipine. In conclusion, dissolution of nimodipine can be enhanced by the use of hydrophilic carriers PEG-4000 and PVP_{K30}.

Key Words: Nimodipine, PEG-4000, PVP_{K30}, solid dispersions, dissolution enhancement.

INTRODUCTION

Nimodipine is a dihydropyridine calcium channel blocker. It has been shown to selectively regulate calcium channels to increase cerebral blood flow. Because of its high permeability, nimodipine can pass through the blood–brain barrier to protect brain cells by increasing their ability to tolerate hypoxia. The major therapeutic indication of nimodipine is for the prevention and treatment of delayed ischemic neurological disorders, which often occur in patients with subarachnoid hemorrhages [1]. Nimodipine has also been used in other cerebrovascular disorders, such as ischemic stroke and multi-infarct dementia [2,3].

Nimodipine is a poorly water-soluble drug and has a low bioavailability and limited clinical efficacy. For “low solubility/high permeability” drugs, dissolution plays an important role in their absorption [4]. Recently, for the purpose of improving oral bioavailability, a variety of techniques have been used to enhance the solubility in water and in biological fluids at physiological pH values, such as salt formation, solubilization, particle size reduction, solid dispersion, self-dispersing lipid formulations and the use of inclusion compounds based on cyclodextrin [5]. Among these methods, solid dispersions is the most efficient. The use of solid dispersions to increase the dissolution rate and the bioavailability of poorly water-soluble drug is now well established [6,7,8]. An important influence on the properties of such solid dispersions is the method of preparation and the type of the carrier used [9,10,11,12]. The increase in dissolution rate from solid dispersions can be attributed to one or a combination of the following factors: a reduction of particle size of the drug, a solubilizing effect on the drug by the water soluble carrier, enhancement of the wettability and dispersibility of the drug by the carrier material, and the possible formation of a metastable dispersion that has a greater solubility resulting in a faster dissolution rate [13].

The popular carriers used in the formation of solid dispersions are polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) [14,15,16]. Both polymers are freely soluble in water and are available in various molecular weights. The molecular size of both polymers favors the formation of interstitial solid solutions [17]. Studies were carried out to enhance the dissolution of nimodipine using modified gum karaya, HPMC as carriers [18, 19]. The purpose of our study was to formulate the nimodipine solid dispersions using fusion method employing freely water-soluble carriers, PEG-4000 and PVP_{K30} and to evaluate the effect of the polymers on the dissolution rate of the drug.

MATERIALS AND METHODS

Materials:

Nimodipine powder (Batch No. 200704004) was received as gift sample from China. PEG-4000 (product of Germany) and PVP_{K30} (product of U.S.A) were supplied by Essen-Haus Sdn. Bhd., Malaysia. All other chemicals used are of analytical grade.

Phase solubility studies:

Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors [20]. Pure nimodipine (50 mg) and a quantity of physical mixtures equivalent to 50 mg of nimodipine prepared using PEG-4000 and PVP_{K30} were stirred vigorously in a water bath shaker at $37 \pm 0.5^\circ \text{C}$ in sealed vials with 25 ml of acetate buffer (pH 4.5) containing 0.3% sodium dodecyl sulfate for 24 h. The sample was then centrifuged and filtered through 0.45 μm membrane filter. After suitable dilution, the absorbance was measured at 236 nm [21]. For the saturation solubility study, the same treatment was applied to solid dispersions and the concentration of nimodipine was determined.

Preparation of physical mixtures in various drug and polymer ratios:

Physical mixtures were prepared by homogeneous blending of previously sieved and

weighed nimodipine and polymer in ratio of 1:1 with a spatula in a mortar.

Preparation of solid dispersions in various drug and polymer ratios:

The solid dispersions of nimodipine and polymer were obtained by using drug and polymer in ratio of 1:1 by melting method. Nimodipine was added to the molten base comprising PEG-4000 or PVP_{K30}. The blend was heated 10 °C above the melting point of each carrier for 5 min with continuous stirring. The systems were placed in a freezer at -20 °C for 24 h. The mass was crushed, ground gently with a mortar and pestle and passed through 500 µm sieve. The samples were kept in a desiccator until the next experiments.

Scanning electron microscopy (SEM) analysis:

Morphology of the solid dispersions was investigated using SEM study. The sample was individually glued on the brass sample holder with double-sided adhesive tape. The image was captured at an excitation voltage of 15kV from magnification 100x and 500x.

Determination of nimodipine content:

An accurately weighed amount of each preparation was dissolved in small volume of methanol and further diluted with pH 4.5 acetate buffer containing 0.3% sodium dodecyl sulfate. The content of nimodipine was determined spectrophotometrically at 356 nm using UV spectrophotometer (Shimazu 1240, Japan).

In vitro drug release study:

Dissolution characteristics of nimodipine pure drug and different solid dispersions were studied in pH 4.5 acetate buffer containing 0.3% sodium dodecyl sulfate [21]. The drug, physical mixtures or solid dispersions (nimodipine and polymer in the ratio 1:1) equivalent to 30 mg of NM were filled in empty hard gelatin capsules. The dissolution rate was carried out using USP XXI dissolution rate test apparatus with rotating basket in 900ml of dissolution medium. The stirring speed was 100 rpm and the temperature was maintained at 37°C ± 1°C. 5ml of aliquot of dissolution medium was withdrawn at time intervals 5,

10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 minutes by a syringe with Millipore filter with pore size of 0.45 µg. The volume withdrawn at each time was replaced with dissolution medium (5 ml). The percentage of drug release was measured by UV spectrophotometer (Shimazu 1240, Japan) at λ_{\max} 356 nm. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The complexation of nimodipine (NM) with PEG-4000 and PVP_{K30} was investigated using phase solubility studies. The phase-solubility diagram for the complex formation between nimodipine, PEG-4000 and PVP_{K30} is presented in Fig 1. This plot shows that the aqueous solubility of the drug increases linearly as a function of PEG-4000 and PVP_{K30} concentrations. It is clearly observed that the solubility diagram of nimodipine in the presence of PEG-4000 and PVP_{K30} can be classified as the A_L type [20,22]. The linear host-guest correlation with slope of less than 1 suggested the formation of a complex with respect to PEG-4000 and PVP_{K30} concentrations. The solubility of NM did not increase appreciably below 1% concentration of polymer. The increase in solubility was linear with respect to the weight fraction of the carrier above 1%. The increase in solubility of NM by PEG-4000 and PVP_{K30} may probably be due to the formation of soluble complexes between water-soluble polymeric carrier and poorly soluble drug. The increase in NM solubility at 15% concentration of PEG-4000 and PVP_{K30} was seen to be approximately 4.6- and 5.2-fold respectively after.

The SEM of NM, NM:PEG-4000, NM:PVP_{K30} systems were shown in Fig 2. Pure drug scanning electron microscopic image showed crystalline drug of irregular shapes and sizes whereas in physical mixture, the PEG-4000 and PVP_{K30} existed as individual particles in which NM dispersed in its native crystalline form. In the solid dispersion products, the original morphology of the raw materials disappeared, and it was not possible to differentiate

the two components. The freeze-dried samples appeared as agglomerates. The drastic change of the particles' shape and aspect in the freeze-dried samples was indicative of the presence of a new solid phase as opposed to the physical mixture, these particulates displayed much larger and rougher, presumably due to NM incorporated into the swelled polymer.

The content of NM in each preparation was assayed by UV spectroscopy. The assay values were between 96% and 99% of the theoretical values. Dissolution profiles of are shown in Figure 3. Dissolution of solid dispersions (SDs) prepared using PEG-4000 and PVP_{K30} was more rapid and higher when compared to corresponding physical mixtures and pure drug. In the first 30 minutes, percent drug dissolved from NM pure drug was 2.4%, from physical mixtures was 19.9% (PEG-4000+NM) and 24.5% (PVP_{K30}+NM). Significant increase ($P < 0.01$) in dissolution rate of SDs prepared by melting method in weight ratio 1:1 was observed. Percent drug dissolved in 30 minutes from PEG-4000+NM SDs was 88.2% and from PVP_{K30}+NM was 91.4%. This was due to the effect of molecular dispersion of drug in PEG-4000 and

PVP_{K30}, the decreased crystallinity of NM existing in solid dispersions.

It was reported that molecular dispersion is one of the important roles of drug release from the polymer-drug system. The present work shows that the dissolution rate of nimodipine from solid dispersions with PEG 4000 and PVP_{K30} improved to more than 80% compared to the pure drug. Further, solid dispersions performed better than the corresponding physical mixtures. Various studies have shown that freely water soluble carriers inhibits crystallization of drugs in solid dispersions resulting in amorphous form of the drug in the solid dispersions [17,23]. Crystallization inhibition is attributed to two effects: interactions, such as hydrogen bonding between the drug and the polymer and the entrapment of the drug molecules in the polymer matrix during solvent evaporation or a combination of both. The present study confirmed the advantage of improved aqueous solubility of NM in its solid dispersions form, which can be formulated as tablets with better dissolution characteristics.

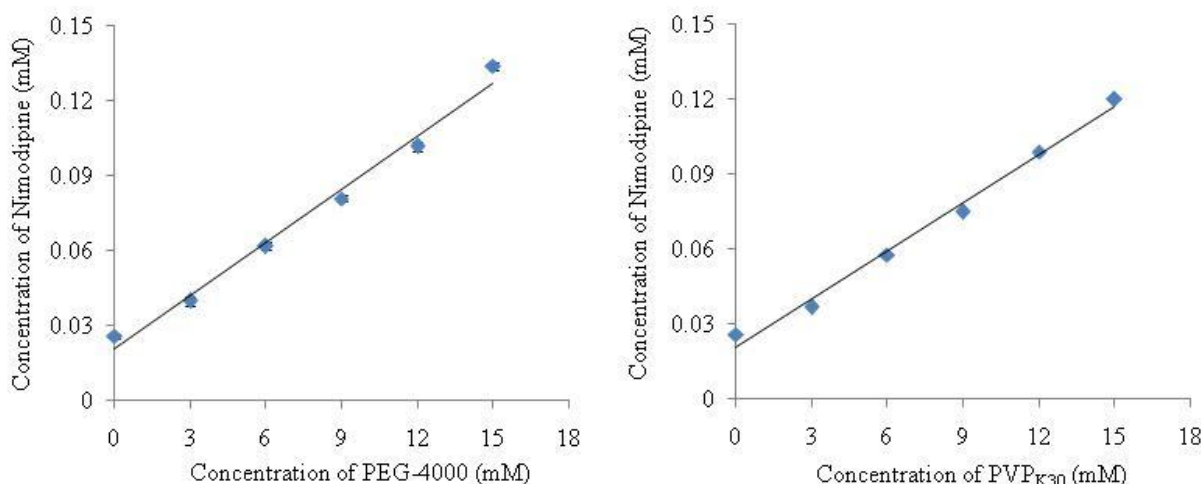


Fig 1. Phase solubility diagrams of nimodipine with PEG-4000 and PVP_{K30}

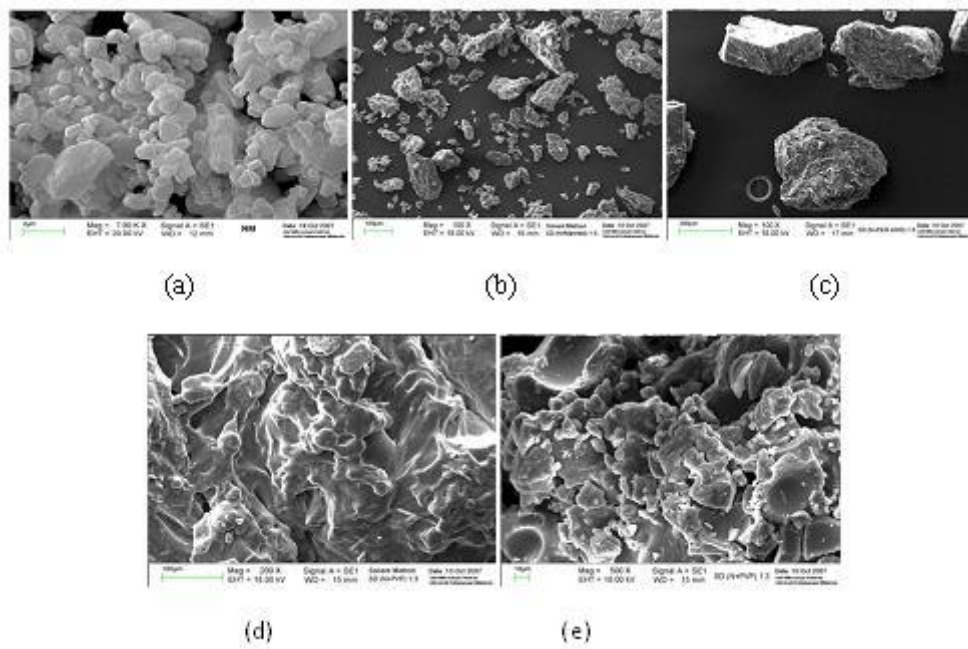


Fig 2. Scanning electron micrographs of (a) Nimodipine; (b) PEG - 4000 + Nimodipine physical mixture; (c) PVPK30 + Nimodipine physical mixture (d) PEG - 4000 + Nimodipine solid dispersion and (e) PVPK30 + Nimodipine solid dispersions

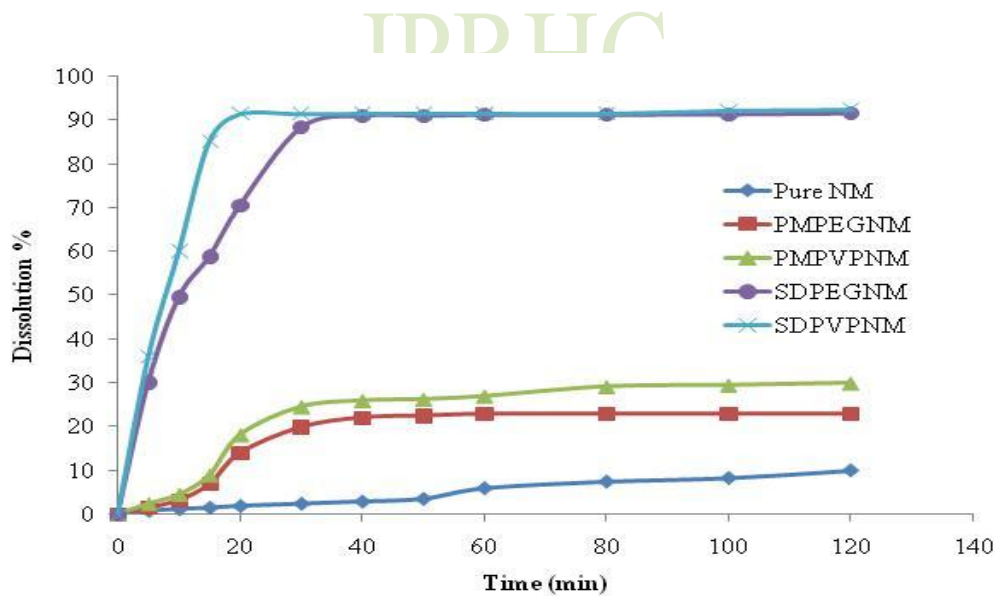


Fig 3. Dissolution profile of (♦) NM, (■) PEG 4000 + NM physical mixture, (▲) PVP_{K30} + NM physical mixture, (●) PEG 4000 + NM solid dispersion and (*) PVP_{K30} + NM solid dispersion in pH 4.5 acetate buffer containing 0.3% SDS.

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