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Preparation and Evaluation of Solid Dispersions of Naproxen

M. GOPAL RAO*, R. SUNEETHA, P. SUDHAKARA REDDY AND T. K. RAVI
Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, 395, Sarojini Naidu Street, Siddapudur, Coimbatore-641 044

The main objective of the present study is to improve the dissolution rate of naproxen using carriers such as PVP, PEG_{4000}, PEG_{6000}, PEG_{20000}, methylcellulose and β-cyclodextrin with a view to develop fast release formulations of naproxen. Solid dispersions of naproxen were prepared by solvent evaporation method and the dispersions were evaluated for drug content uniformity, dissolution rate, moisture absorption, thin layer chromatography and X-ray diffraction analysis. The particle shape and topography were studied using scanning electron microscopy. A marked increase in dissolution rate was observed with all solid dispersions. Among the carriers studied, naproxen-β-cyclodextrin gave the highest improvement in dissolution rate. All the solid dispersions except naproxen-PVP were found to be non-hygroscopic. Naproxen was found to be in an amorphous form in solid dispersions. Selected dispersions of naproxen-β-cyclodextrin and naproxen-methylcellulose were formulated into capsules with usual additives and evaluated for drug release characteristics.

Naproxen[1], a non-steroidal antiinflammatory drug (NSAID) used in the treatment of musculoskeletal disorders is practically insoluble in water and shows poor dissolution characteristics. Hence, an attempt was made to improve the dissolution characteristics using the solid dispersion method. Among the various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of solid dispersion has often proved to be successful[2-6]. In solid dispersion, the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as mannitol, polyethylene glycols (PEGs)[7], citric acid, succinicacid and polyvinyl pyrolidone[6] are used as carriers for preparing solid dispersions. In the present work, solid dispersion of naproxen with different carriers such as polyvinylpyrolidone (PVP), PEG_{4000}, PEG_{6000}, PEG_{20000}, methylcellulose and β-cyclodextrin were prepared and evaluated. Selected dispersions were formulated into capsules and studied for drug release characteristics. The main objective of this work is to study and compare naproxen-β-cyclodextrin complex and the dissolution rate of naproxen-carrier dispersions.

*For correspondence
E-mail: mgrao_vp@pharmacist.ms

MATERIALS AND METHODS

Naproxen was obtained from Brown and Burk Pharmaceuticals Pvt. Ltd., Bangalore, as a gift sample. Methylcellulose and polyvinyl pyrolidone were purchased from Loba Chemie Private Limited, Mumbai. β-cyclodextrin and chloroform were purchased from S. D. Fine Chem, Mumbai. Magnetic stirrer and vacuum pump were purchased from Gelman Sciences, Mumbai. All the carriers and solvent used were of analytical or pharmacopoeial grade.

Preparation of solid dispersion:

Solvent evaporation method was used for the preparation of solid dispersions. Five different drug:carrier ratios (90:10, 75:25, 50:50, 25:75, 10:90) were used. The respective amounts of carrier were dissolved in chloroform (30 ml), and naproxen was added in parts with continuous stirring. The solvent was then removed by evaporation at 40° under vacuum. The solid dispersions prepared were pulverized and sifted (80#) and stored in a desiccator.

Preparation of physical mixture and drug content uniformity:

Drug carrier ratio of 1:1 was used for preparation of physical mixture. One gram of naproxen and 1000 mg of respective carriers were used for the preparation of physical mixture using the geometric dilution technique. The drug content uniformity was estimated using solid dispersion of 100 mg equivalent of naproxen in 0.1M, 7.4 pH buffer as solvent. The estimation was done in a Jasco V-530 UV/Vis spectrophotometer.

Powder X-ray diffraction:

X-ray diffraction spectra of simple eutectic systems show peaks of each crystalline component. Any change in the crystal lattice parameter will displace the diffraction peaks. Solid solutions exhibit a gradual shift in the positions of the diffraction lines with changes in composition. The lattice parameters of complexes are markedly different from those of pure components.

Dissolution rate studies:

Naproxen, pure drug, and all its solid dispersions and physical mixtures were subjected to dissolution test using *in vitro* dissolution rate apparatus of USP XXII. This test was performed using 900 ml of dissolution medium (0.1M, 7.4 pH phosphate buffer) and a sample equivalent to 100 mg of naproxen[8] was taken in a hard gelatin capsule. A stainless steel wire was wound around the capsule as sink. Paddle was adjusted to a speed of 50 rpm and temperature of 37+1°. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals. It was suitably diluted and assayed spectrophotometrically by measuring absorbance at 332 nm. The percentage of drug dissolved at various time intervals was calculated and plotted against time. The T_{50} min. T_{90} min values were calculated from plots. Also K values were obtained by plotting log percent drug undissolved against time; the results are shown in fig. 1. Powder X-ray diffraction patterns were recorded using a XDS-2000 (Scintac Inc, USA) powder X-ray diffractometer (CUKα- radiation) at a scan rate of 2° per min, wavelength of 1.54060A°, 30 kV. 20 mA and 2θ range. All solid dispersions prepared with a drug carrier ratio 1:1 were subjected to thin layer chromatography (tlc) studies using toluene tetrahydrofuran and glacial acetic acid as solvent system and spots detected by short and long wavelengths of UV light.

All solid dispersions were kept in an evacuated desiccator for 48 h to remove water content, if any. An accurately weighed sample 3 g of the solid dispersion was then transferred to a butter paper. The solid dispersion was then subjected to moisture absorption in a closed dessicator at 84% relative humidity at room temperature. The difference in weights of the sample gave the amount of moisture absorbed.

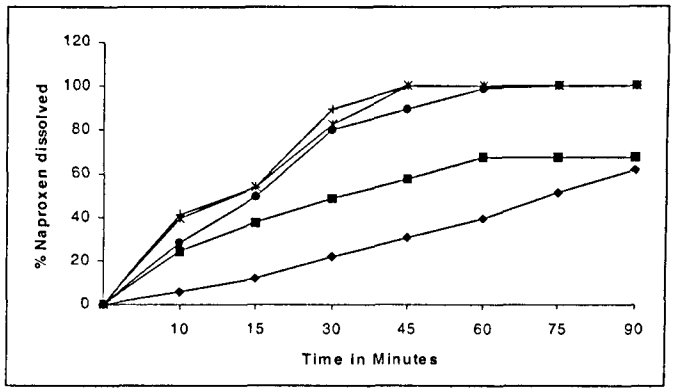

fig. 1: Dissolution of naproxen-β-cyclodextrine solid dispersion of different drug carrier ratios

The dissolution rate of naproxen-β-cyclodextrin solid dispersion with naproxen pure (–♦–) physical mixture (50:50) 100 mg of NAP (–■–), solid dispersion (90:10) of naproxen:β-cyclodextrine (–▲–), solid dispersion (75:25) of naproxen:b-cyclodextrine (–×–), solid dispersion (50:50) of naproxen:β-cyclodextrine (–∗–), solid dispersion (25:75) of naproxen:β cyclodextrine (–●–) and solid dispersion (10:90) of naproxen:β-cyclodextrine (–+–)

Shape and size of the solid dispersion:

The surface morphology and the internal texture of naproxen solid dispersions were observed by scanning electron microscope (SEM)[9]. SEM photographs were taken on a JSM6400 scanning electron microscope at the 120X magnifications and at room temperature. Before scanning, the solid dispersions were sputtered with gold to make the surface conductive.

RESULTS AND DISCUSSION

All solid dispersions were found to be fine and free flowing powders. Naproxen-PVP solid dispersions were found to be slightly hygroscopic. All solid dispersions of naproxen gave a single spot in tlc studies and the same R_f values were obtained for pure naproxen and its solid dispersions. X-ray diffraction patterns of pure drug and physical mixture showed intense peaks indicating the crystalline nature of naproxen, which is reduced in the solid dispersion. The peaks are broadened in the solid dispersion indicating the amorphous nature of naproxen, which might also

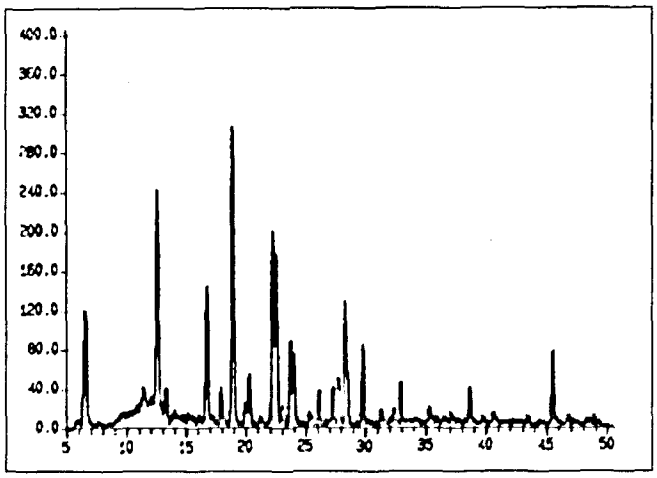

Fig. 2: X-ray diffraction patterns of pure sample of naproxen.

The graphs are more intense peaks indicating the crystalline nature of naproxen.

be the reason for enhanced dissolution which is shown in fig. 2, 3 and 4. Melting points of both solid dispersions and pure naproxen were found to be identical. It was observed in the SEM studies that in the physical mixture, naproxen and β-cyclodextrin remained as separate crystals and were clearly differentiable. The Scanning Electron Microscope photographs of solid dispersions as shown in fig. 5 revealed that the particle sizes were reduced.

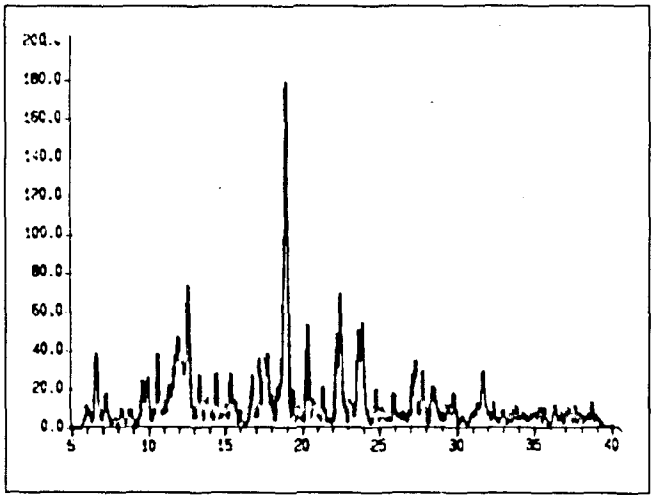

Fig. 4: X-ray diffraction pattern of solid dispersion of naproxen and β-cyclodextrin (1:1)

The graphs are shows intense peaks and are broadened, indicating the amorphous nature of naproxen.

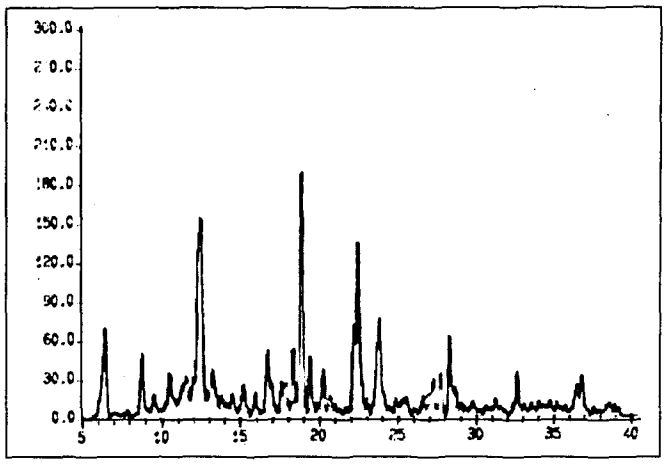

Fig. 3: X-ray diffraction patterns of physical mixture of naproxen and β-cyclodextrin.

Physical mixture graph shows intense peaks.

Dissolution rate of naproxen from all its solid dispersions as compared to the pure naproxen and physical mixture was found to have increased. In the case of β-cyclodextrin and methylcellulose solid dispersions, the drug was dissolved in chloroform and precipitated in the presence of a carrier, which was dispersed as particles. In this case the drug might have been precipitated in micro particulate size and got coated over the surface of the carrier. This may be responsible for the relatively faster dissolution observed. T_{50}, T_{90} values decreased with increasing carrier ratios. The K values first order rate constants, obtained showed that all the dispersions followed first order kinetics as the K values of solid dispersions were more than that of the pure drug.

The order of increase in dissolution by various carriers was found to be as follows: β-cyclodextrin>methylcellulose>PVP>PEG_{4000}>PEG_{6000}>PEG20000. During formulation as capsules the addition of additives did not hinder the dissolution characteristics of dispersions and complied with USP standards. Solid dispersions of naproxen with different carriers had improved the dissolution rate. The results of interaction studies using tlc and melting point analysis revealed the absence of any chemical interaction between the drugs and carriers indicating their compatibility. Formulation into capsules and release studies showed that these are fast release formulations of naproxen.

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