ABSTRACT: Solid dispersions were prepared using polyethylene glycol 6000 (PEG), talc and their combinations as carriers by the combination of melting and solvent approach technique to enhance the solubility of poorly soluble nimesulide as a model drug. The dissolution of nimesulide from these dispersions was studied and it was evaluated by thermal behavior (DSC). It was found that in these carriers the drug dissolution rate was a function of drug loading. Dispersions of PEG and PEG / talc provided dissolution rates faster than those from dispersion of talc. The incorporation of talc in PEG yielded dispersions with proportions of less tackiness and ease of handling.

KEY WORDS: Nimesulide, Polyethylene glycol 6000, Talc.

INTRODUCTION

Many drugs show bioavailability problems due to their low water solubility, slow dissolution rate, and instability in the gastrointestinal tract. Nimesulide is a non-steroidal anti-inflammatory, analgesic and anti-pyretic agent, chemically is N-(4 nitro-2-phenoxy phenyl) methane sulfonamide. It is poorly soluble in water and irregularly absorbed by gastrointestinal tract. Among the various approaches to improve the dissolution of poorly soluble drugs, the preparation of solid dispersions has often to be successful1. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-fusion methods1,3. In solid dispersions, the particle size of the drugs was reduced, wettability and the dispersibility of the drugs were enhanced; therefore, drug dissolution was improved markedly5. Solid dispersion is a promising approach to improve the dissolution and bioavailability of drugs5,6. The methods utilized in the preparation of solid dispersion include melting, use of common solvent and a combination of melting and solvent approach1,6. Various hydrophilic carriers, such as polyethylene glycols, polyvinyl pyrrolidone, and hydroxyl propyl methylcellulose have been investigated as carriers for solid dispersions, improvement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs1,6.

Solid dispersion prepared from soluble carriers such as polyethylene glycol, usually have the disadvantage of being tacky and therefore difficult to subdivide and handle. PEG solid dispersions were formulated using combinations of melting and solvent approach in which the melted drug and carrier mixture were granulated with excipients that result less tacky granulation. In this study, PEG 6000, talc and a combination of talc and PEG were used as dispersion carriers, to investigate the dissolution behavior of nimesulide.
MATERIALS AND METHODS

Materials

Nimesulide – gift sample from Reddy’s Laboratory, Hyderabad, Polyethylene glycol 6000 (Ranbaxy Laboratory Ltd). All other chemicals were analytical grade.

Methods

Preparation of solid dispersion

Solid dispersions were prepared by taking different ratios of nimesulide, PEG 6000 and talc, calculated on the weight basis by the melting and solvent approach method. Nimesulide and solid dispersion carriers were accurately weighed and transferred to a beaker. A sufficient quantity of chloroform was added to dissolve and or disperse the ingredients.

The mixture was then stirred and evaporated to dryness. The samples were dried at 40ºC for 1 hour passed through 60 mesh screen and placed in an oven at 40ºC overnight to complete the drying process.

Nimesulide content in dispersion

An aliquot of dispersion equivalent to 10-20 mg of drug was weighed and transferred to a 50 ml volumetric flask. Isopropanol was added to the flask and sonicated for an hour to assure complete extraction of the drug from the dispersion. The mixture was filtered, diluted with water and assayed spectrophotometrically at 436 nm to determine amount of nimesulide present in dispersion.

Differential Scanning Calorimeter Studies (DSC)

DSC scans of nimesulide and solid dispersions were performed in an atmosphere of nitrogen in the following way, the samples were kept in hermetically sealed aluminum pans and were heated at a scan speed of 10º min⁻¹ over a temperature range of 160- 280ºC in a differential scanning calorimeter – (Perkin Elmer, DSC – 7, calibrated with indium) at a chart speed of 10mm min⁻¹.

In-vitro release studies

In-vitro release study of nimesulide loaded solid dispersion was carried out at 37± 1ºC in 900ml of the dissolution medium ( One volume of phosphate buffer of pH 7.2 and three volumes of distilled water containing 8.0% tween 80 ) in paddle type dissolution apparatus. A sample of solid dispersion equivalent to 100mg of nimesulide was taken in each test. 5 ml aliquots of dissolution fluid were withdrawn at the intervals of 15 minutes upto 2 hours. Each sample was diluted with 0.1N NaOH and analyzed spectrophotometrically at 436 nm for drug content.

Drug loading

The influence of drug loading on the dissolution of nimesulide from the dispersion was studied using dispersion containing 83.3%, 50%, 16.7% and 9.1% nimesulide in talc, PEG and PEG – talc (1/1).

RESULTS AND DISCUSSION

Appearance of solid dispersions

Physically, the talc dispersions were finely powdered, so that easy to mix and screen, on the other hand the PEG dispersions were tacky and difficult to mix and screen during preparation. The partial development of PEG with talc yielded dispersions that were less tacky and easy to handle.

Differential Scanning Calorimetry (DSC) Studies

DSC thermograms of nimesulide showed a sharp endothermic peak at 147ºC which was close to the reported melting point (147º- 151ºC) of nimesulide. In contrast, no endothermic sharp peak corresponding to fusion or interaction of nimesulide was observed in the thermogram.

Effect of drug loading

The weight percentage of nimesulide received from the dispersion was determined. The results indicated that, for all drug dispersion, the recovery was in the range from 87% to 99% of the theoretical amount. Figures 2, 3 &4 show the percentage of nimesulide released versus time from dispersions prepared using talc, PEG, PEG/talc (1/1) respectively. The nimesulide in the dispersion demonstrated a dissolution rate increased with decreasing drug loading. This may be attributed to the finer subdivision of drug particles in dispersion containing higher carrier loading. Nimesulide pure drug showed the slowest dissolution rate.

Effect of carriers

For dispersion containing the same percentage of drug, talc provided the slowest drug dissolution rate in the time interval studied as shown in figure 2, 3 and 4. This became more significant as drug loading increased. However similar results of nimesulide dissolution were obtained from PEG, talc and PEG/talc solid dispersion at 83.3% drug loading.

PEG was found to be better than talc in enhancing the drug dissolution. This superior performance of PEG in
enhancing drug dissolution may be explained in that PEG being water soluble, increases the wettability of nimesulide, whereas talc being insoluble provides no effect on the wettability of nimesulide. Also subdivision of the drug particle in PEG dispersion is finer than in talc dispersion. Further more, PEG may increase a solubility of nimesulide as a result of over lapping the diffusion layers between PEG and drug.

Results of nimesulide dissolution obtained from PEG/talc dispersions were greater than those of talc dispersion or comparable to those of PEG containing the same percentage of drug loading. This suggests that replacing required amount of PEG with talc in the PEG dispersion will alter the drug dissolution, especially at a low percentage of drug loading.

**Effect of PEG /Talc/ ratio on drug dissolution**

Fig 4 illustrates the percentage of drug dissolved versus time for dispersions containing 9.1% drug loading in a carrier composed of PEG/talc in the ratios of 1/9, 1/3, 1/1, 3/1 and 9/1. The drug dissolution rate increased with the increasing PEG/talc until it was equal to or greater than one; then the difference of the dissolution rates became insignificant, indicating that increasing the PEG content does play a role in the enhancement of drug dissolution from PEG/ talc dispersions. It appears that the effect of pH of the medium demonstrated no effect on the drug dissolution from dispersions.

**CONCLUSIONS**

The present study conclude that , solid dispersions of poorly soluble drug nimesulide prepared using PEG 6000,Talc, and PEG 6000/ Talc as carriers by combination of melting and solvent approach technique showed significant increases in drug dissolution. Dispersions of PEG and PEG/Talc provided faster dissolution rate than other dispersions. In other hand the PEG dispersions were tacky and difficult to mix and screen during preparation, but incorporation of Talc in PEG yielded dispersions with proportions of less tackiness and ease of handling. The PEG 6000/Talc a combination was found to be better dispersion carrier for enhancement of dissolution of poorly soluble drugs.

**FIG.1 DIFFERENTIAL SCANNING CALORIMETRY THERMOGRAMS OF NIMESULIDE (A), PEG 6000 (B), TALC (C), PEG 6000/TALC (D)**
FIG. 2 PERCENTAGE RELEASE OF NIMESULIDE FROM TALC COMPLEXES

FIG. 3. PERCENTAGE RELEASE OF NIMESULIDE FROM PEG 6000 COMPLEXES

FIG. 4 PERCENTAGE RELEASE OF NIMESULIDE FROM PEG 6000/TALC COMPLEXES
REFERENCES


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