PREPARATION AND EVALUATION OF NAPROXEN BY SOLID DISPERSION TECHNIQUE
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ABSTRACT
Naproxen, an anti-inflammatory drug, exhibits poor water solubility and flow properties. Naproxen is poor water soluble and may show dissolution limited absorption. The solid dispersion of naproxen by physical triturating method, and fusion method were prepared using 1:1, 1:4 and 1:5 ratios of drug and polymers (PEG 4000, PEG 6000 and urea). The solid dispersion (SD) was characterized for physical appearance, solubility, IR, and in vitro dissolution studies. FTIR study revealed that drug was stable in SDs. Solubility of naproxen from SDs increased in distilled water. The drug content was found to be high and uniformly distributed in all the formulation. The in vitro dissolution studies were carried using USP type XXVII (paddle) type dissolution apparatus. The prepared dispersion showed marked increase in the dissolution rate of naproxen than that of pure drug. The dispersion with PEG 6000 (1:5) by fusion method showed faster dissolution rate (107.26%) as compared to other dispersions with PEG 4000 and urea (1:4 and 1:5) whichever prepared by physical mixture (PM) and fusion method). Of the three carriers used, dissolution of the drug was more in PEG 6000 based SDs. It is concluded that dissolution of the Naproxen could be improved by the solid dispersion and PEG6000 based solid dispersions were more effective in enhancing the dissolution.

Keywords: Naproxen, Solid dispersion, PEG 4000, PEG 6000, Urea, In vitro release

INTRODUCTION:
The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development1. Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. The formulation of poorly soluble compounds for oral delivery is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs 2,3 there are practical limitation of these techniques. In 1961, Sekiguchi and Obi4 developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures.

MATERIALS AND METHODS
Naproxen was obtained from Apex Laboratories, Chennai, as a gift sample. PEG 4000, PEG 6000, Urea, Sodium hydroxide (NaOH), Potassium di-hydrogen phosphate were purchased from S.D.fine chemicals limited, Mumbai. All the carriers used were of analytical grade.

Preparation of solid dispersion
Solid dispersions were prepared by melting the accurately weighed amounts of carriers (PEG 4000, PEG 6000 and urea) in a water bath and the drug was dispersed in the molten solution. Fusion method was used for the preparation of solid dispersions. Briefly appropriate amount of naproxen was taken in china dish and required amount of carriers (PEG 4000, PEG 6000 and urea) were added to prepare required drug to carrier ratio for formulations as shown in table 1. Then the mixture was heated under controlled temperature to melt drug and carrier with continuous stirring. The melted preparation was transferred to porcelain tile to solidify and cooled in an ice bath. The solid dispersions prepared were pulverized and sifted (80#) and stored in a desiccators.

Preparation of physical mixture and drug content uniformity
Drug and carriers physical mixture were prepared by slightly grinding drug naproxen and carriers (PEG 4000, PEG 6000 and urea) in mortar for 2 min at the required drug/carriers ratio (as shown in table 1). Then the powder was passed through the sieve no - 80. The resulted product was stored in a desiccator to carry out further analysis. The drug content uniformity was estimated using solid dispersion of 100 mg equivalent of naproxen in pH 5.8 phosphate buffer as solvent. The estimation was done in a UV/Visible spectrophotometer at 243nm.

Evaluation of solid dispersions
Physical characterization and saturation solubility study
The excess amount of the formulations (PMs and SDs) was added to conical flasks containing 10 ml of distilled water and subjected to shaking on a rotary shaker for 48 hours at 37°C. Then the flasks were removed and filtered. Suitable aliquots were withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with distilled water and compared with pure drug solubility.

FTIR study of pure drug and all preparations
For all the formulations and naproxen the pellets have been prepared using potassium bromide (KBr) for FT-IR study. The pellets were subjected to FT-IR instrument ‘Perkin Elmer FTIR spectrometer, spectrum 1000 Germany’ for the collection of IR spectra which are illustrated in figures 4 and 5.

Drug content analysis
Preparations equivalent to 20 mg was weighed accurately and transferred to 100 ml volumetric flask and dissolved in phosphate buffer pH 5.8. The volume was made up with phosphate buffer pH 5.8 up to the mark. After suitable dilution absorbance of the resulting solution was measured at
**In vitro release studies**

Accurately weighed amount of sample was taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the medium. The volume withdrawn at each time intervals were replaced with same quantity of fresh medium.

**Physical characterization and saturation solubility study**

Naproxen is practically insoluble in water as the intrinsic solubility of naproxen in pure water at room temperature is found to be 0.084mg/ml. Among PMs and SDs (1:5) the carrier PEG 6000 containing PM and SD showed highest saturation solubility. This may be due to the inherent differences between the carriers in terms of hydration, dissolution and possible complexation of drug with different carriers.

These significant changes indicate the possibility of intermolecular hydrogen bonding between the carboxylic group of naproxen and –OH group of PEG 6000. Comparison spectra of PMPEG6000 and SDPEG 6000 with drug and carrier showed significant changes. However, although little shifts in the stretching vibration due to C=O groups (of PEG 6000) appeared at wave numbers 1724 cm$^{-1}$ suggesting possible difference in the degree of interaction between drug and carrier in PM and SD. Peaks at wave numbers 1174 cm$^{-1}$, 1155 cm$^{-1}$ and 1223 cm$^{-1}$ may be due to -OH group bending vibrations and at 1190 cm$^{-1}$, 1681 cm$^{-1}$ and 1500 cm$^{-1}$ may be due to -C=C- of aromatic ring bending vibrations of Naproxen. A decrease in the intensity of peak of carboxylate group of naproxen at (1600 cm$^{-1}$) may support intermolecular hydrogen bonding between drug and carrier in both physical mixture and solid dispersion. A decrease in the intensity of bands may also be due to the amount of compounds. Thus it can be concluded with some reservation, the absences of interaction between two compounds by FTIR.

**Drug content analysis**

Drug content is found to be between 95.72 % and 107.63 %. All the PMs and SDs showed presence of high drug content and low standard deviations of results. It is indicated that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for the preparation of SDs.

**In vitro dissolution study**

The formulation of solid dispersion of naproxen with various carriers like PEG 4000, PEG 6000 and Urea were screened for the selection of suitable carriers. These carriers were found to be encouraging since they did not undergo any chemical change during the preparation of solid dispersion. The solid dispersion of naproxen with carriers PEG 4000, PEG 6000, and Urea showed a marked increase in the dissolution rate in pH 5.8 phosphate buffer. Dissolution of the naproxen increased with increasing proportions of carriers and T50% and T80% values were least with the SDs of urea (i.e.:1:1-1:5). Above all the formulations the ratio of naproxen: PEG 6000 (SD6) showed (1:5) maximum proving that higher concentration of matrix formed with PEG 6000 of ratio 1:5 increased the dissolution rate. These observations indicate the enhanced dissolution of SDs with increase in the concentration of carriers possibly due to the increased wet-ability of the drug by the carrier, drug particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier.

**Stability studies**

Formulations (SDPEG4000, SDPEG6000 and urea) which showed promising results were subjected to stability studies at ambient room conditions for 3 months. After 3 months, SDs did not show any change in physical appearance or drug content. It indicates that the drug was stable in SDs even after three months of short term storage. Initially solubility studies were conducted to analyze the solubility of Naproxen in different solvents/buffers. Formulation studies included the preparation of physical mixtures (PMs) and solid dispersion (SDs) of Naproxen with different carrier (PEG 4000, PEG 6000 and urea) with solvent method and their physicochemical characterization using FT-IR spectroscopy, solubility studies, drug content analysis, dissolution studies and stability studies. All PMs and SDs shows high drug content (~95 %). The dissolution of naproxen from the PMs was higher than pure drug. The formulations of naproxen in SDs significantly improved the dissolution of naproxen. SDs of naproxen with the same proportion of PEG 6000 as a carrier was superior in dissolving Naproxen compared with PEG 4000 and urea. The dissolution of naproxen from SDs of PEG 6000 increased with increasing proportion of carrier from 1:1 to 1:5. Three months stability studies of selected formulations at ambient room conditions showed no change in the physical character and drug content. It is concluded that dissolution of the naproxen could be improved by solid dispersions and PEG 6000 based solid dispersions are more effective in the enhancing the dissolution. The dissolution of a poorly/sparingly soluble drug is based on the bioavailability and method employed for the particle size reduction of different methods used for the preparation of solid dispersion was briefly reviewed in the introduction. The spectrophotometric method was most suitable for estimation of the drug content and dissolution study of various solid dispersion of naproxen. It was adopted throughout the investigation. The formulation of solid dispersion of naproxen with various carriers like PEG 4000, PEG 6000 and Urea were screened for the selection of suitable carriers. These carriers were found to be encouraging since they did not undergo any chemical change during the preparation of solid dispersion. Solid dispersions of naproxen in pH 5.8 phosphate buffer were prepared using the dissolution apparatus described in the USP Paddle-II. The results obtained in the dissolution study were found to be satisfactory. This revealed that the solid dispersion of naproxen with carriers PEG 4000, PEG 6000, and Urea showed a marked increase in the dissolution rate in pH 5.8 phosphate buffer. Above all the formulations the ratio of Naproxen: PEG 6000 (SD4) showed (1:5) maximum proving that higher concentration of matrix formed with PEG 6000 of ratio 1:5 increased the dissolution rate. The increase in the in vitro characteristics can be attributed due to the formation of solid dispersion of naproxen with carriers, with resulting size reduction. In addition to the size reduction of the crystalline substance, the faster dissolution rate of the drug may be due to excellent wettability and dispersability of drug from a solid dispersion system prepared with water soluble carriers.
comparative study of in-vitro dissolution profile of different ratios of naproxen and its various carriers were studied.

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REFERENCES:

Table 1: Physical characteristics and solubility studies of solid dispersions

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Nature of formulation</th>
<th>Carrier</th>
<th>Drug carrier ratio</th>
<th>Method</th>
<th>Drug solubility in water mg/ml(±SD, n=3)</th>
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<tbody>
<tr>
<td>Pure drug</td>
<td>White crystalline powder</td>
<td></td>
<td></td>
<td>Physical mixture</td>
<td>0.084±0.015</td>
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<tr>
<td>PM1</td>
<td>Off-white sticky particles</td>
<td>PEG 4000</td>
<td>1:1</td>
<td>Physical mixture</td>
<td>0.149±0.012</td>
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<td>SD1</td>
<td>Off-white sticky particles</td>
<td></td>
<td>1:1</td>
<td>Solid dispersion (fusion method)</td>
<td>0.215±0.013</td>
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<tr>
<td>SD2</td>
<td>Solid sticky lumps</td>
<td></td>
<td>1:4</td>
<td>Solid dispersion (fusion method)</td>
<td>0.224±0.018</td>
</tr>
<tr>
<td>SD3</td>
<td>Solid sticky lumps</td>
<td></td>
<td>1:5</td>
<td>Solid dispersion (fusion method)</td>
<td>0.152±0.011</td>
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<tr>
<td>PM2</td>
<td>Off-white sticky particles</td>
<td>PEG 6000</td>
<td>1:1</td>
<td>Physical mixture</td>
<td>0.298±0.019</td>
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<td>SD4</td>
<td>Off-white soft particles</td>
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<td>1:1</td>
<td>Solid dispersion (fusion method)</td>
<td>0.319±0.014</td>
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<tr>
<td>SD5</td>
<td>Solid sticky lumps</td>
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<td>1:4</td>
<td>Solid dispersion (fusion method)</td>
<td>0.339±0.017</td>
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<td>SD6</td>
<td>Solid sticky lumps</td>
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<td>1:5</td>
<td>Solid dispersion (fusion method)</td>
<td>0.142±0.016</td>
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<td>PM3</td>
<td>White free flowing powder</td>
<td>Urea</td>
<td>1:1</td>
<td>Physical mixture</td>
<td>0.175±0.013</td>
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<td>SD7</td>
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<td>1:4</td>
<td>Solid dispersion</td>
<td>0.196±0.014</td>
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<td>SD8</td>
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<td>1:5</td>
<td>Solid dispersion (fusion method)</td>
<td>0.202±0.014</td>
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<tr>
<td>SD9</td>
<td>White free flowing powder</td>
<td></td>
<td>1:5</td>
<td>Solid dispersion (fusion method)</td>
<td>0.202±0.014</td>
</tr>
</tbody>
</table>

Table 2: In-vitro dissolution data for pure drug and solid dispersions

| Time (min) | Pure drug | PM1 | SD1 | SD2 | SD3 | PM2 | SD4 | SD5 | PM3 | SD6 | PM1 | SD1 | SD2 | SD3 | PM2 | SD4 | SD5 | PM3 | SD6 | PM1 | SD1 | SD2 | SD3 | PM2 | SD4 | SD5 | PM3 | SD6 |
|------------|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 10         | 29.22 (±2.3) | 39.31 (±3.5) | 41.24 (±2.7) | 49.83 (±1.4) | 52.22 (±2.8) | 32.35 (±2.4) | 42.52 (±2.1) | 42.56 (±2.1) | 53.26 (±2.0) | 67.28 (±5.3) | 70.12 (±1.9) | 70.26 (±1.3) | 81.65 (±2.7) |
| 20         | 47.42 (±3.2) | 60.84 (±4.2) | 65.72 (±3.9) | 72.12 (±4.3) | 87.33 (±5.4) | 55.44 (±2.5) | 65.97 (±2.9) | 70.51 (±2.3) | 82.62 (±2.8) | 77.27 (±1.9) | 79.64 (±3.9) | 80.32 (±1.8) | 98.44 (±1.2) |
| 30         | 55.45 (±2.4) | 80.66 (±4.5) | 91.27 (±3.4) | 97.45 (±1.3) | 100.0 (±3.4) | 88.65 (±2.9) | 98.47 (±1.2) | 100.0 (±2.3) | 107.2 (±2.4) | 82.49 (±2.2) | 81.65 (±2.2) | 85.30 (±2.3) | 100.8 (±3.3) |

Figure 1: Dissolution profile of Paracetamol: PEG 4000 formulations in phosphate buffer pH 5.8
Figure 2: Dissolution profile of Paracetamol: PEG 6000 formulations in phosphate buffer pH 5.8

Figure 3: Dissolution profile of Paracetamol: Urea formulations in phosphate buffer pH 5.8

Figure 4: FT-IR spectrum of pure Paracetamol and Solid dispersion.

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