STUDIES ON SOLID DISPERSIONS OF LEFLUNOMIDE

MAHAPARALE PR1*, THORAT VP2

1Department of Pharmaceutics, Government College of Pharmacy, Aurangabad, Maharashtra, India. 2Department of Pharmaceutics, Siddhi College of Pharmacy, Chikhali, Pune, Maharashtra, India. Email: paresmahaparale@gmail.com

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INTRODUCTION

The recent advent of high throughput screening of potential therapeutic agents has given rise to number of poorly soluble drug candidates. The formulation of poorly soluble compounds in oral delivery presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. Drugs with low aqueous solubility have low dissolution rates and suffer from oral bioavailability problems. Many methods such as solubilization in surfactant systems, formation of watersoluble complexes, use of prodrug, and salt formation approach have been reported for increasing solubility, dissolution, and, in turn, bioavailability of drugs. The solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by the melting (fusion), solvent evaporation, or melting-solvent method [1-3]. Leflunomide is a nonsteroidal anti-inflammatory drug, which is poorly water soluble.

MATERIALS AND METHODS

Materials

Leflunomide (Alembic Pharmaceuticals Ltd., Baroda) and various carriers such as polyethylene glycol (PEG) 4000, PEG 6000 (Qualigens Fine Chemicals, Mumbai), Poloxamer 188, and Poloxamer 407 (BASF, Germany) were used. All other chemicals and reagents were of analytical grade.

Methods

Preparation of solid dispersions

Solid dispersions of leflunomide were prepared by the following two methods.

Solvent evaporation method

Leflunomide and each of water-soluble carriers such as PEG 4000, PEG-6000, Poloxamer-188, and Poloxamer-407 were accurately weighed separately, transferred into a beaker, and dissolved in a sufficient quantity of methanol. Subsequently, methanol was evaporated in vacuum evaporator and resulting solid dispersions were stored for 24 h in a desiccator to remove traces of solvent. Finally, the resultant mass was triturated in glass mortar and passed through sieve no. 44. The resulting solid dispersions were stored in tightly-closed containers until further use [4,11].

Melt evaporation method

Leflunomide and each of water-soluble carriers such as PEG 4000, PEG-6000, Poloxamer-188, and Poloxamer-407 were accurately weighed separately in porcelain dish and heated to melt. The drug was added to a molten mass of polymers with vigorous stirring. Resulting solid dispersions were stored in a desiccator for 24 h. The resultant mass was triturated in a glass mortar and passed through sieve no. 44. The resulting solid dispersions were stored in tight-closed containers until further use [4,5].

Evaluation of solid dispersions

Drug content estimation

The percentage drug content in solid dispersions was estimated by dissolving quantities of solid dispersions equivalent to 10 mg of leflunomide in 100 ml of methanol. These solutions were further diluted with distilled water and UV absorbance was recorded at 259.5 nm [6,7].

Saturation solubility study

Solubility study was performed according to the method reported by Higuchi and Connors [3].

X-ray diffraction (XRD) study of solid dispersions

XRD patterns of the selected solid dispersions were compared with that of the plain leflunomide. This was done by measuring the 2θ in the range of 4–50° with reproducibility of ±0.01° on X-ray diffractometer (Philips). The XRD patterns were recorded automatically using rate meter with time constant of 2 × 10⁵ pulse/s and with the scanning speed of 2° (2θ)/min.

ABSTRACT

Objective: Leflunomide is a nonsteroidal anti-inflammatory drug, which is poorly water soluble. In the present study, attempt has been made to prepare and characterize solid dispersions of leflunomide to increase the solubility of drug.

Methods: In preparation of solid dispersion of leflunomide, different polymers such as polyethylene glycol (PEG) 4000, PEG 6000, Poloxamer 188, and Poloxamer 407 were used. The effects of several variables such as type of carrier used, drug: carrier ratios, and method of preparation were studied. The evaluation of solid dispersions was done by solubility study, dissolution study, and X-ray diffractometry.

Results: Improvement in dissolution of the drug was observed in all solid dispersions as compared to pure drug alone. Solid dispersions prepared using Poloxamer 188 showed fastest in vitro drug release. Solid dispersions prepared using solvent evaporation method showed relatively faster drug release than melt evaporation method. X-ray diffraction patterns indicated reduced crystallinity of drug particles, which suggest a mechanism of enhanced solubility and dissolution of drug in solid dispersion systems.

Conclusions: The study indicated that solid dispersion by solvent evaporation can successfully be further explored and employed to improve solubility and dissolution characteristics of poorly soluble drugs.

Keywords: Leflunomide, Solid dispersion, Carrier.
**Table 1: Comparison of various parameters for leflunomide solid dispersion systems**

| System                  | % drug content | Solubility (gm/100 ml) | T<sub>90</sub> (min) |
|-------------------------|----------------|------------------------|----------------------|
|                         | SE | ME | SE | ME | SE | ME |
| LF (alone)              |   |    | 0.0024 | 0.0098 | >90 | >90 |
| LF:PEG 4000 (1:3)       | 98.80±0.91 | 99.86±0.79 | 0.016 | 0.015 | >90 | >90 |
| LF:PEG 4000 (1:5)       | 98.01±0.46 | 96.96±0.46 | 0.016 | 0.015 | >90 | >90 |
| LF:PEG 6000 (1:3)       | 96.38±0.65 | 97.73±0.72 | 0.023 | 0.023 | >90 | >90 |
| LF:PEG 6000 (1:5)       | 98.32±1.12 | 96.89±0.64 | 0.052 | 0.046 | 29 | 54 |
| LF:P188 (1:3)           | 96.2±1.65 | 98.69±1.21 | 0.024 | 0.021 | >90 | >90 |
| LF:P188 (1:5)           | 96.28±2.09 | 96.8±1.21 | 0.038 | 0.032 | 7 | 7 |
| LF:P407 (1:3)           | 96.6±2.09 | 98.54±0.46 | 0.0072 | 0.0065 | >90 | >90 |
| LF:P407 (1:5)           | 97.57±1.65 | 98.12±1.21 | 0.038 | 0.032 | 72 | 72 |
| LF:PEG 4000 (1:5) PM    | 96.52±1.88 | 97.82±0.96 | 0.01 | 0.0093 | >90 | >90 |
| LF:PEG 6000 (1:5) PM    | 98.32±1.92 | 98.22±1.12 | 0.018 | 0.018 | >90 | >90 |
| LF:P407 (1:5) PM        | 97.52±1.25 | 96.95±1.40 | 0.028±1.62 | 0.025±1.08 | 68 | 68 |

*LF: Leflunomide, P188: Poloxamer 188, P407: Poloxamer 407, SE: Solvent evaporation method, ME: Melt evaporation method, PM: Physical mixture

**RESULTS AND DISCUSSION**

**Evaluation of solid dispersions**

**Drug content estimation**

The percentage drug content of all solid dispersions of leflunomide was between 95.52% and 99.86% (Table 1). Standard deviation “<3” indicates the uniform distribution of drugs in various solid dispersions.

**Saturation solubility study**

All solid dispersions showed enhancement in the solubility as compared to pure drug alone (Table 1). The drug: carrier ratio (1:5) showed higher solubility in all solid dispersions. This may be due to the higher proportion of hydrophilic carriers present in solid dispersions. The drug gets uniformly dispersed in water-soluble carriers. Hence, as soluble carrier dissolves, the dispersed drug also gets exposed to an aqueous environment as very fine particles and solubility gets increased. Enhancement in solubility was observed in the following order; Poloxamer 188>Poloxamer 407>PEG 6000>PEG 4000.

**XRD study of solid dispersions**

Dissolution properties of drug particles are greatly affected by the extent of crystallinity present in solid dispersion. An amorphous or the
metastable form dissolves faster because of associated higher levels of internal energy and greater molecular mobility. These together enhance the thermodynamic properties of these forms as compared to crystalline state. XRD studies were performed to reveal the crystallinity of pure leflunomide, its dispersion with Poloxamer 188 (1:5) and pure Poloxamer 188 (Fig. 1). Many broad peaks of low intensity were observed in diffraction patterns, which indicate microcrystalline nature of the drug. The XRD pattern of Poloxamer 188 showed diffraction peaks of very low intensity, which confirmed the amorphous nature. The XRD pattern for solid dispersions prepared with Poloxamer 188 (1:5), however, was characterized by the absence of diffraction peaks of the drug, suggesting conversion of microcrystalline form of the drug to an amorphous state [17-20].

**Dissolution study of solid dispersions**

Solid dispersions of drugs showed better dissolution performance as compared to pure drug alone. After 1.5 h, release of the drug was found to be 25.01%. All solid dispersions of drug showed 68–100% release of drug in <1.5 h. This may be attributed to improved wettability of the drug particles, significant reduction in particle size of the drug during formation of solid dispersions, and higher intrinsic dissolution rate of selected soluble carriers, which can pull insoluble but finely mixed drug particles into the bulk of the dissolution medium [14-16,21].

**Effect of carrier ratio on dissolution rate of leflunomide from different solid dispersions**

Two different drug: carrier ratios (1:3 and 1:5) were selected to assess the effect of the weight fraction of carrier on the release profile of drug from solid dispersions (Fig. 2). The dissolution of drug from solid dispersions prepared using a higher weight fraction of carrier was found to be more; this may be attributed to the molecular and colloidal dispersion of the drug in those carrier matrices.

**Effect of carrier type on dissolution rate of leflunomide from different solid dispersions**

Solid dispersions prepared by both solvent evaporation and melt evaporation method showed improved dissolution profiles of a drug (Fig. 3). Enhancement in the dissolution profile of the drug was found to be of Poloxamer 188>Poloxamer 407>PEG 6000>PEG 4000. The increase in dissolution of solid dispersion with Poloxamer 188 may be due to high HLB value (HLB 29). Poloxamer 407 HLB value is 21.

**Effect of preparation method on dissolution profiles of leflunomide from different solid dispersions**

Solid dispersions prepared by solvent evaporation method showed slightly faster drug release as compared to solid dispersions obtained with the melt evaporation method (Fig. 4). In solvent evaporation method, both drug and polymer are dissolved in a common solvent because of that both may be present in molecular state. When solvent is evaporated, drug may get molecularly dispersed in hydrophilic carrier matrix. In melt evaporation method, solution of drug is added with stirring to melt mass of polymer, which is at a higher temperature than drug solution. At that temperature, solvent gets evaporated out and some of the drug may precipitate out, and hence, total molecular dispersion may not be achieved as that of solvent evaporation method.

**Effect of carrier type on dissolution rate of leflunomide from physical mixture**

Dissolution of drugs from all physical mixtures was found to be more as compared to pure drug (Fig. 5). This may be due to hydrophilicity of carriers. Dissolution of drug from solid dispersion was found to be more than from physical mixture (Fig. 6). This may be due to molecular dispersion of the drug in hydrophilic carriers in solid dispersion than physical dispersion only.

**CONCLUSIONS**

From the study on solid dispersions of leflunomide, it was found that,
- Enhancement in solubility and dissolution of solid dispersions is in the following order: Poloxamer 188>Poloxamer 407>PEG 6000>PEG 4000
- Solid dispersions prepared by both solvent evaporation and melt evaporation method showed significant improvement in dissolution profiles
- The dissolution rate for all solid dispersions increased with increasing concentration of carriers
- Method of preparation of solid dispersions affected the dissolution profile of leflunomide. For the same carrier employed, solid dispersions prepared by solvent evaporation showed more dissolution than those prepared by melt evaporation method.
The enhanced dissolution rate with Poloxamer may be attributed to surfactant activity, which facilitates wetting and subsequent solubilization of the drug. Poloxamer 188 has high HLB value (HLB 29). Hence, it has a greater tendency to solubilize in water.

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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