ABSTRACT

The study was carried out with a view to enhance dissolution rate of poorly water soluble drug by preparing tablets of solid dispersion of Diflunisal. The solid dispersion was prepared by using carriers like Crosspovidone, PEG and Urea. The solid dispersion was prepared by Physical mixture, Fusion, Kneading and Solvent evaporation methods using different ratio of Diflunisal and carrier. The optimized solid dispersion batch F8 and F9 were incorporated into tablets for faster release of Diflunisal. *In-vitro* dissolution rate of both batches of Diflunisal from solid dispersion was found to be 99.49 % and 98.90 % drug release after 2 hr compared to 46.27% release shown by pure drug after 2 hr.

KEYWORDS

Diflunisal, Urea, Physical mixture, Solvent evaporation method

INTRODUCTION

Drugs that undergo dissolution rate limited Gastrointestinal absorption generally show improved dissolution and bioavailability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in pure wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have reduced the incidence of these problems and enhanced dissolution\(^1\). The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion has great potential for both increasing the bioavailability of drug and developing controlled release preparations. Thus to solve bioavailability issues with respect to poorly water soluble drugs solid dispersion technology has grown rapidly. The dosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process the system might have an advantage over such other commonly used bioavailability enhancement technique as micronization of drugs and soft gelatin encapsulation. Aim of the present work is to enhance the solubility of Diflunisal by Solid dispersion techniques and to formulate a dosage form containing Diflunisal which is stable and has improved dissolution rate.

Advantages

a. Reduced particle size.
b. Improved wettability.

c. Improved porosity of drug.

Conversion crystalline structure of drug in to amorphous form.3

**MATERIAL & METHODS**

**Materials**

Diflunisal were obtained from Arti Industries Ltd, Thane, India. Tris (hydroxymethyl) aminometh, Urea, Lactose was obtained from Ozone International Mumbai, India. Citric acid was obtained from Vijay Chemical Industry, Solapur, Maharashtra, India. Crosspovidone, PEG, Methanol, Polyvinyl pyrrolidone, Mannitol were obtained from Research lab fine chemical Industry, Mumbai, Maharashtra, India. Talc, Magnesium stearate were obtained from Vikash Pharma, Mumbai, Maharashtra, India.

**Methods**

Different formulations of solid dispersions of Diflunisal were prepared with four different polymers as carrier by four methods, viz. Physical mixture, Melt fusion (MF) method and Solvent evaporation (SE). The compositions of the formulations are shown in Table 1.

**Physical Mixture**

Physical mixture was prepared by mixing the Diflunisal : Crosspovidone in 1:1, 1:2, 1:3 ratios in mortar and pestle and passed through sieve #60 and the tablets were formulated using direct compression method.

**Fusion Method**

Accurately weighed amount of carrier was placed on a hot plate and molten, with constant stirring, maintaining the critical temperature just below 70°C. An accurately weighed amount of Diflunisal was incorporated into the molten carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. It was cooled in an ice-bath, allowed to solidify and sieved through sieve #60 and the tablets were formulated using direct compression method.

**Solvent Evaporation Method**

The Diflunisal : Urea in 1:1, 1:2, 1:3 ratio was dissolved in sufficient volume of methanol with continuous stirring. The resulting mixture was transferred into petridish and evaporation of the solvents was carried out by keeping the petridish at room temperature. The mass obtained was crushed and passed through sieve 44# and the tablets were formulated using direct compression method.

**Formulation of Solid Dispersion**

Table 1: Formulation of Solid Dispersion

| Method                  | Carrier       | Batch | Ratio (Drug:Carrier) mg |
|-------------------------|---------------|-------|-------------------------|
| Physical Mixture        | Crosspovidone| F1    | 250:250                 |
|                         |               | F2    | 250:500                 |
|                         |               | F3    | 250:750                 |
| Fusion method           | PEG           | F4    | 250:250                 |
|                         |               | F5    | 250:500                 |
|                         |               | F6    | 250:750                 |
| Solvent evaporation     | Urea          | F7    | 250:250                 |
| method                  |               | F8    | 250:500                 |
|                         |               | F9    | 250:750                 |

**Characteristics of Solid Dispersion Complex**

**Bulk Density (Db)**

Accurate weighed amount of solid dispersion preparation of different ratios were poured in to 25 ml of measuring cylinder and bulk volume was noted and then calculated by the following equation

\[ Db = \frac{\text{Mass}}{\text{Bulk volume}} \]

**Tapped Density (Dt)**

Accurate weighed amount of solid dispersion preparation of different ratios were poured in to
25 ml of measuring cylinder and then tapped for 750 times and the tapped volume was noted and calculated by the following equation.

\[ D_t = \frac{\text{Mass of powder}}{\text{Tapped volume}} \]

Compressibility Index

\[ I = \frac{(V_b - V_t)}{V_b} \times 100 \]

Where, \( I \) is the Compressibility index, \( V_b \) is the bulk volume of powder, \( V_t \) is the tapped volume of the powder.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

\[ \text{Hausner ratio} = \frac{D_t}{D_b} \]

Where, \( D_t \) is the tapped density, \( D_b \) is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose

Angle of repose was determined using fixed funnel method. The solid dispersion was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of heap (r) was measured and angle of repose was calculated by using the following equation.

\[ \theta = \tan^{-1} \frac{h}{r} \]

Table 2: Characteristics of Solid dispersion complex

| Batch | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr’s index | Hausner Ratio (%) | Angle of Repose (θ) |
|-------|----------------------|------------------------|--------------|-------------------|-------------------|
| F1    | 0.3154±0.0050        | 0.3751±0.0103          | 15±0.0108    | 1.1889±0.0214     | 27.77±0.2598      |
| F2    | 0.3100±0.0062        | 0.3693±0.0090          | 14±0.0152    | 1.1800±0.0176     | 29.10±0.5022      |
| F3    | 0.3077±0.0039        | 0.3077±0.0039          | 15±0.0100    | 1.1912±0.0292     | 29.38±0.2540      |
| F4    | 0.3051±0.0103        | 0.3554±0.0050          | 13±0.0108    | 1.1689±0.0214     | 27.57±0.2598      |
| F5    | 0.3193±0.0090        | 0.3400±0.0062          | 14±0.0152    | 1.1080±0.0176     | 29.20±0.5022      |
| F6    | 0.3265±0.0056        | 0.3577±0.0039          | 12±0.0100    | 1.1712±0.0292     | 29.48±0.2540      |
| F7    | 0.3091±0.0103        | 0.3554±0.0050          | 13±0.0108    | 1.1689±0.0214     | 27.57±0.2598      |
| F8    | 0.3139±0.0090        | 0.3300±0.0062          | 14±0.0152    | 1.1580±0.0176     | 26.20±0.5022      |
| F9    | 0.3065±0.0056        | 0.3677±0.0039          | 12±0.0100    | 1.1712±0.0292     | 29.48±0.2540      |
Formulation of Optimized Batch

Table 3: Formulation Of the Optimize Batch F8 and F9 of Tablet

| Sr.no. | Ingredients               | Quantity given in (mg) | F8  | F9  |
|--------|---------------------------|------------------------|-----|-----|
| 1.     | Solid Dispersion Complex  | 750                    | 800 |     |
| 2.     | PVP                       | 10                     | 10  |     |
| 3.     | Lactose                   | 10                     | 10  |     |
| 4.     | Talc                      | 10                     | 10  |     |
| 5.     | Magnesium stearate        | 10                     | 10  |     |
| 6.     | Mannitol                  | 5                      | 5   |     |
| 7.     | Sodium starch glycolate   | 5                      | 5   |     |

RESULTS AND DISCUSSION

Calibration curve of Diflunisal

Calibration curve of Diflunisal was found to be linear in concentrations between 10 to 60 μg/ml with equation \( y = 0.0191x + 0.0002 \) and coefficient \( R^2 = 0.9999 \).

Figure 1: Standard curve of Diflunisal

In-vitro Dissolution Study of Solid Dispersion

Figure 2: Dissolution profile of Solid dispersion pure drug F1, F2, F3

Figure 3: Dissolution profile of Solid dispersion pure drug F4, F5, F6

Figure 4: Dissolution profile of Solid dispersion pure drug F7, F8, F9
Table 4: *In-vitro* Dissolution study of Solid dispersion batches F1 to F6

| Time (min) | Pure drug | F1 | F2 | F3 | F4 | F5 | F6 |
|------------|-----------|----|----|----|----|----|----|
| 12         | 7.7       | 25.04 | 17.84 | 23.06 | 15.54 | 22.95 | 18.57 |
| 30         | 19.87     | 33.17 | 28.80 | 36.76 | 39.75 | 35.40 | 30.47 |
| 45         | 27.29     | 42.46 | 36.06 | 41.77 | 54.58 | 52.41 | 42.12 |
| 60         | 34.33     | 58.48 | 54.53 | 61.00 | 68.67 | 64.18 | 70.76 |
| 90         | 37.60     | 78.19 | 66.52 | 70.42 | 75.21 | 76.13 | 79.29 |
| 120        | 46.27     | 88.48 | 82.65 | 92.53 | 92.53 | 84.69 | 88.81 |

Table 5: *In-vitro* dissolution study of Solid dispersion batches F7 to F9

| Time (min) | Pure drug | F7 | F8 | F9 |
|------------|-----------|----|----|----|
| 15         | 7.7       | 16.69 | 24.00 | 40.81 |
| 30         | 19.87     | 26.81 | 34.99 | 44.18 |
| 45         | 27.29     | 40.11 | 51.05 | 60.83 |
| 60         | 34.33     | 42.84 | 54.05 | 70.32 |
| 90         | 37.60     | 57.06 | 71.48 | 81.52 |
| 120        | 46.27     | 73.04 | 79.80 | 96.61 |

**Evaluation of Solid Dispersion Tablet**

Table 6: Post compression parameters of prepared Tablet

| Batch | Weight Variation(mg) | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | (% Drug Content) |
|-------|----------------------|----------------|-------------------|---------------|-----------------|
| F1    | 802±0.25             | 12.00±0.11     | 7.0±0.10          | 0.12±0.3      | 98.00           |
| F2    | 798±0.20             | 13.00±0.25     | 7.0±0.12          | 0.28±0.2      | 97.32           |
| F3    | 799±0.60             | 12.50±0.50     | 7.5±0.25          | 0.29±0.6      | 96.22           |
| F4    | 803±0.45             | 11.80±0.01     | 7.0±0.29          | 0.36±0.8      | 99.01           |
| F5    | 801±0.12             | 12.00±0.05     | 6.5±0.28          | 0.35±0.4      | 98.67           |
| F6    | 800±0.19             | 12.25±0.15     | 7.0±0.35          | 0.62±0.4      | 97.45           |
| F7    | 803±0.25             | 13.25±0.28     | 7.5±0.50          | 0.29±0.1      | 97.89           |
| F8    | 795±0.12             | 12.50±0.30     | 7.0±0.20          | 0.11±0.2      | 99.49           |
| F9    | 803±0.85             | 12.00±0.27     | 7.0±0.00          | 0.12±0.5      | 98.90           |
Uniformity of Weight
Uniformity of weight revealed that the tablets of all formulations were within the range of Pharmacopoeial specification. F8 and F9 formulations pass uniformity of weight.

Tablet Hardness
The tablet hardness are shown in table 6.

Tablet Thickness
The thickness was found to be in between 11 mm to 12 mm for both formulations. The thickness of the tablet depends upon the diameter of die, the amount of fill permitted to enter the die, the compaction characteristic of the fill material and the force applied during compression.

Drug Content Uniformity
The drug content uniformity was performed for F8 and F9 prepared solid dispersion tablet by direct compression method. The % drug content were found 99.49% and 98.90% of Diflunisal. The % drug content data estimated for the prepared tablets were in the prescribed limits.

Tablet Friability
Friability is related to tablet ability to withstand both shock and abrasion without physical damage during the handling of manufacturing, packaging, shipment and consumer use. Friability of formulations shows 0.112 and 0.125 respectively for F8 and F12 batch. All value of friability lie between the prescribed limits (0.1-0.9%).

In-vitro Dissolution Study
Dissolution study of tablets was performed in USP type-II (paddle) dissolution test apparatus using 900 ml of 0.1M Tris buffer pH 7.2 as dissolution media. The tablets were loaded into each basket of dissolution apparatus; the temperature of dissolution media was maintained at 37.5±0.5°C with stirring speed of 50 rpm throughout the study. The 5ml samples were withdrawn at a suitable interval of time and analysed by UV- Visible spectrophotometer at 228 nm.

Dissolution Parameter
- Medium: ph 7.2 0.1M tris buffer.
- Apparatus: USP type II (paddle).
- Speed: 50 rpm.
- Time points: 15, 30, 45, 60, 90, 120 min.
- Temperature: 37± 0.5°C

Stability Study
Stability studies revealed that there was no significant change found in color, hardness, drug content and in-vitro drug release of Diflunisan tablets even after stored at 25±2°C/60±5% RH and 40±2°C/75±5% RH for 45 days. The results proved that there was no significant effect of storage temperature on the drug release.

CONCLUSION
The objective of presence study was to improve the solubility and dissolution rate of poorly soluble drug Diflunisal by using Crosspovidone, PEG, and Urea as carriers. The formulation of F8 and F9 batch shows good % drug release (99.49 and 98.90% respectively) from solid dispersion techniques after 2 hr compared to 46.27% release shown by pure drug after 2 hr.. The tablets were prepared by using sodium starch glycolate as super disintegrant by direct compression method. The optimized F8 and F9 batch shows excellent solubility, dissolution rate and drug content than the other batches. Thus it can be concluded the solubility of the poorly soluble drug Diflunisal can be improved by using solid dispersion technique and the carrier urea has increased the dissolution rate of the drug without any drug interaction.

ACKNOWLEDGEMENT
The authors are thankful to Principal Mr. R. Y. Patil sir and, R. Kanade, A. Patil, S. Sadaphule, B. Gaikwad, V. Jamkhandi, K. Kulkarni, and D.S.T.S Mandal’s College of Pharmacy, Solapur for providing necessary facilities to carry out the work.
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