



RESEARCH ARTICLE

EFFECT OF DISINTEGRANTS ON *IN VITRO* RELEASE OF FENOFIBRATE ORO-DISSOLVING TABLETS

Ramadevi Bhimavarapu, Karuna Priya Chitra, Dhavani Kanikanti*, Manasa Anne, Haritha Meda and N. Gowthami

Department of Pharmaceutics, Sri Siddhartha Pharmacy College, Nuzvid-521 201, Andhra Pradesh, India

*E-mails: kannikantidhavani@gmail.com, kpcpharma@gmail.com

Tel.: +91-9704070229, +91-9949118283

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Fenofibrate is a widely used hypolipidemic drug of the fibrate class. The poor aqueous solubility of the drug leads to variable dissolution rates. The present investigation reports development and characterization of fenofibrate oro-dispersible tablets using direct compression technique. Oro-dispersible tablets of fenofibrate were prepared using different concentrations of super disintegrating agents like crospovidone and sodium starch glycolate by direct compression method. The formulation blends were examined for angle of repose, bulk density and tapped density. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, wetting time, *in vitro* disintegration time, and *in vitro* dissolution studies. The formulation CP-3 was found to be the best as it exhibited least wetting time (43 sec) and disintegration time (26.40 sec) and best *in vitro* drug release (96.402%) as compared to other tablet formulations.

Key words: Fenofibrate, Oro-dissolving tablet, Direct compression, Superdisintegrants.

INTRODUCTION

Fenofibrate is a drug of the fibrate class. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Like other fibrates, it reduces low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and reducing triglycerides level. It also appears to have a beneficial effect on the insulin resistance featured by the metabolic syndrome (Wysocki *et al* 2004). Paediatric and geriatric patients may have difficulties in swallowing or chewing pharmaceutical dosage forms for oral administration. Tablets that rapidly dissolve upon contact with saliva in the buccal cavity could present a solution to those problems and so there is an increased interest in fast dissolving dosage forms for buccal, sublingual and oral administration. Fast dissolving/disintegrating tablet are perfect fit for these patients as they immediately release active drug when placed on tongue by rapid disintegration/

dispersion (Keny *et al* 2010; Dahiya *et al* 2011; Basu *et al* 2011; Solanki and Dahima, 2011). Keeping in view above facts, investigation was directed toward formulation development of oro-dissolving tablets of fenofibrate.

MATERIALS AND METHODS

Fenofibrate was supplied as gift sample from Glukem pharmaceuticals Hyderabad. Sodium starch glycolate, starch, magnesium stearate, lactose, microcrystalline cellulose, carboxy methyl cellulose used were of analytical grade.

Preparation of formulation blends

Mouth dissolving tablet blends containing 100 mg of fenofibrate were prepared by direct compression method and the various formulae used in the study are shown in **Table 1**. The prepared powder blends were evaluated for various parameters like bulk density, tapped density, porosity, angle of repose, void volume etc. After evaluation, each powder blend was subjected to direct compression using a tablet

Table 1. Composition of formulation blends

| Ingredients (mg) | CP-1 | CP-2 | CP-3 | SSG-1 | SSG-2 | SSG-3 |
|-------------------------|------|------|------|-------|-------|-------|
| Fenofibrate | 100 | 100 | 100 | 100 | 100 | 100 |
| Sodium Starch Glycolate | - | - | - | 6 | 10 | 18 |
| MCC | 50 | 50 | 50 | 50 | 50 | 50 |
| Magnesium Stearate | 2 | 2 | 2 | 2 | 2 | 2 |
| Crospovidone | 6 | 10 | 18 | - | - | - |
| D-Mannitol | 28 | 24 | 16 | 28 | 24 | 16 |
| Aspartame | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 |

punching machine (Shu *et al* 2002).

Evaluation of formulation blends

Prior to compression into tablets, the blend was evaluated (Smith and Web, 2007) for following properties:

Angle of repose (Θ)

Angle of repose was determined using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap D was measured. The angle of repose Θ , was calculated by formula:

$$\tan \Theta = h/r$$

$$\Theta = \tan^{-1} (h/r)$$

where Θ is the angle of repose, h is the height in cm and r is the radius.

Bulk density (Db)

Apparent bulk density was determined by pouring pre-sieved drug-excipient blend into graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by:

$$Db = M / V_0$$

where M is the mass of powder and V_0 is the bulk volume of the powder.

Tapped density (DT)

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by:

$$DT = M / VT$$

where M is the mass of powder and VT is the tapped volume of the powder.

Preparation of tablets

Each formulation blend was subjected to direct compression using a hand operated single punch tablet machine.

Evaluation of tablets (BP, 2005; USP, 1995; Rawas-Qalaji *et al* 2006)

All the tablets were evaluated for following different parameters:

General appearance

Five tablets from different batches were randomly selected and organoleptic properties such as colour, odour, taste, shape, were evaluated.

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier callipers. Five tablets from each batch were used and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester.

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch, individually weighed, the average

weight and standard deviation of 20 tablets was calculated.

Disintegration test (Shah and Kohli, 2000)

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (Mesh no. 10) was immersed in water bath at $37\pm 2^\circ\text{C}$. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To comply with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.

Wetting time

A piece of tissue paper (12 cm \times 10.75 cm) folded twice was placed in a petri dish (Internal diameter = 9 cm) containing 6 ml of 0.1 M sodium lauryl sulphate. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red colour on the upper surface of tablet was recorded as wetting time. Three tablets from each formulation were randomly selected and the average wetting time was noted. Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a petri dish. This method will duplicate

the *in vivo* disintegration as the tablet is motionless on tongue.

Dissolution studies (Granero et al 2005)

The release rate of fenofibrate from fast dissolving tablets was determined using USP dissolution rate test apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 M SLS, at $37\pm 0.5^\circ\text{C}$ and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus every 5 min. for a period of 30 min and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatmann filter paper no. 41 and analyzed spectrophotometrically at 290 nm (Elico UV-VIS spectrophotometer).

RESULTS AND DISCUSSION

Evaluation of preformulation properties

For each designed formulation blend, evaluation parameters are summarized in **Table 2**. Bulk density was found to be between 0.41 ± 0.04 to 0.53 ± 0.01 g/cm³ and tapped density between 0.37 ± 0.01 to 0.61 ± 0.03 g/cm³ for all formulations. From density data, void volume was calculated and was found to be 0.5-0.9. Angle of repose was found to be in the range of 23.36 ± 0.03 to 28.91 ± 0.02 . Porosity was found to be 24-34%. All the formulation showed fair to good flow properties.

Table 2. Evaluation parameters of fenofibrate mouth dissolving tablet blends

| S. No. | Formulation blend | Angle of repose (°) | Bulk density (g/cm ³) | Tapped density (g/cm ³) | Void volume | Porosity (%) |
|--------|-------------------|---------------------|-----------------------------------|-------------------------------------|-------------|--------------|
| 1. | CP-1 | 26.78 \pm 0.01 | 0.41 \pm 0.04 | 0.46 \pm 0.03 | 0.9 | 29 |
| 2. | CP-2 | 23.36 \pm 0.03 | 0.51 \pm 0.02 | 0.52 \pm 0.01 | 0.6 | 30 |
| 3. | CP-3 | 24.27 \pm 0.02 | 0.53 \pm 0.01 | 0.53 \pm 0.01 | 0.8 | 27 |
| 4. | SSG-1 | 26.00 \pm 0.02 | 0.5 \pm 0.01 | 0.37 \pm 0.01 | 0.5 | 24 |
| 5. | SSG-2 | 27.15 \pm 0.01 | 0.51 \pm 0.03 | 0.61 \pm 0.03 | 0.7 | 34 |
| 6. | SSG-3 | 29.12 \pm 0.02 | 0.5 \pm 0.01 | 0.480 \pm 0.03 | 0.5 | 24 |

Evaluation of mouth dissolving tablets

Fenofibrate mouth dissolving tablets were formulated successfully using super disintegrants such as sodium starch glycolate (SSG-1, SSG-2 and SSG-3) and cross povidone (CP-1, CP-2, CP-3). Tablets obtained were of uniform weight due to uniform die fill; tablets complied with weight variations test as per pharmacopoeial specifications. All the tablets appeared white in color, odorless, convex in shape with smooth surface and zero defects. The drug content was found in the range of 98.22-99.36% (acceptable limit) and the hardness of

the tablets between 3.21-3.60 kg/cm². Friability of the tablets was found below 1% indicating a good mechanical resistance of tablets. Thickness of the formulations varied from 3.71 ± 0.02 to 3.94 ± 0.02 mm. Wetting time of tablets found in the range of 45-68 sec (**Figure 1**) and disintegration time for all the formulations were found to be 26.40-54.30 sec (**Figure 2**). All the parameters were found well within the specified limits (**Table 3**). The percentage drug release was (92.6, 90.2, 96.4, 58.5, 59.1 and 78.1) for CP-1, CP-2, CP-3, SSG-1, SSG-2 and SSG-3, respectively at 30 min. The formulation CP-3

was found to be the best as it exhibited least wetting time (43 sec) and disintegration time (26.40 sec) and the best

in vitro drug release (96.402%) as compared to other tablet formulations (Table 4, Figure 3).

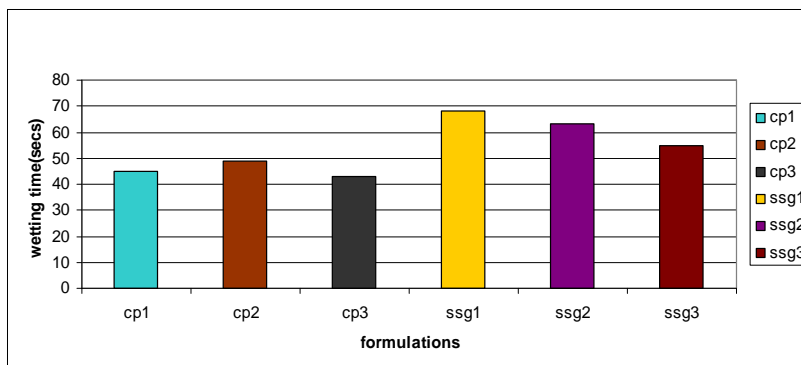


Fig. 1. Wetting time of different compositions of fenofibrate mouth dissolving tablets

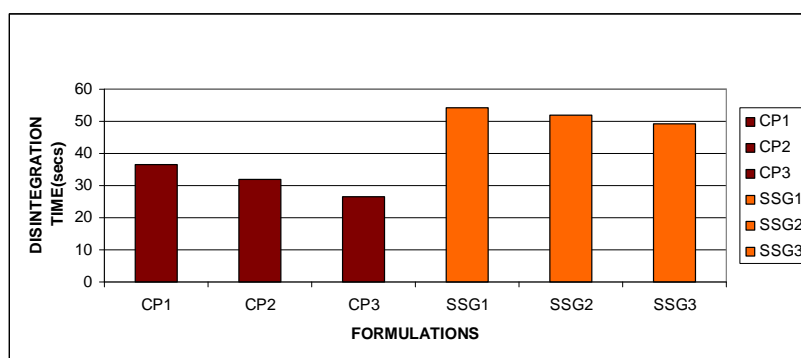


Fig. 2. Disintegration time of prepared mouth dissolving tablets

Table 3. Evaluation parameters of fenofibrate mouth dissolving tablets

| Formulation code | Thickness (mm) | Hardness (kg/cm ²) | Friability (%) | Weight variation (%) | Drug content (%) | Wetting time (sec) | Disintegration time (sec) |
|------------------|----------------|--------------------------------|----------------|----------------------|------------------|--------------------|---------------------------|
| CP-1 | 3.92±0.02 | 3.40 | 0.65 | 2.0 | 99.18 | 45 | 36.70 |
| CP-2 | 3.90±0.02 | 3.31 | 0.81 | 1.8 | 98.21 | 49 | 32.10 |
| CP-3 | 3.71±0.02 | 3.60 | 0.30 | 2.7 | 99.17 | 43 | 26.40 |
| SSG-1 | 3.94±0.02 | 3.40 | 0.72 | 2.4 | 98.24 | 68 | 54.30 |
| SSG-2 | 3.87±0.04 | 3.21 | 0.91 | 2.6 | 99.35 | 63 | 52.10 |
| SSG-3 | 3.80±0.06 | 3.40 | 0.94 | 2.7 | 98.90 | 55 | 49.15 |

Table 4. Percentage drug release data of fenofibrate oro-dissolving tablets

| Time (min) | CP-1 | CP-2 | CP-3 | SSG-1 | SSG-2 | SSG-3 |
|------------|--------|--------|--------|--------|--------|--------|
| 5 | 69.424 | 62.234 | 74.341 | 45.397 | 47.587 | 53.569 |
| 10 | 73.066 | 67.840 | 77.381 | 47.363 | 49.70 | 57.130 |
| 15 | 76.511 | 72.570 | 78.874 | 49.530 | 51.589 | 61.940 |
| 20 | 78.874 | 75.321 | 83.404 | 53.569 | 57.210 | 71.193 |
| 25 | 81.828 | 79.850 | 89.312 | 54.443 | 58.088 | 75.321 |
| 30 | 92.650 | 90.200 | 96.402 | 58.589 | 59.128 | 78.186 |

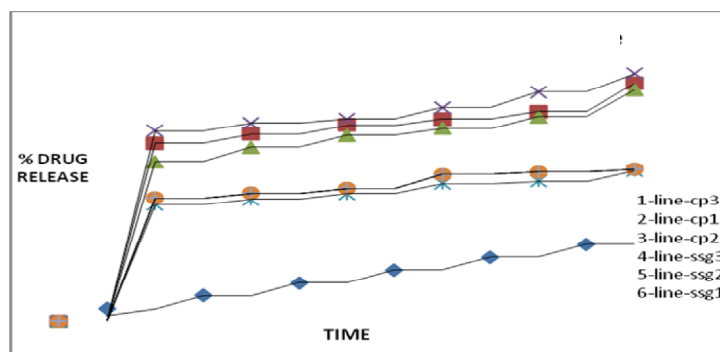


Fig. 3. Comparative *in vitro* drug release profiles of fenofibrate mouth dissolving tablets

CONCLUSION

The present study indicated that crospovidone was a better superdisintegrant as compared to sodium starch glycolate for fenofibrate mouth dissolve tablets since the

tablets containing the former exhibited least wetting and disintegration time and highest drug release as compared to formulations prepared with sodium starch glycolate at same concentration.

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