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# USE OF MELT SOLIDIFICATION TECHNIQUE FOR PREPARATION OF FENOFIBRATE BEADS: A TECHNICAL NOTE

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The purpose of present study is to develop a new, simple, single step melt solidification technique for hypolipidemic agent fenofibrate. The melt solidified beads were prepared by two techniques. The first method involves melting the drug and cooling the melt. In second method, the drug melt was poured in the water stirred at optimum speed to obtain beads. The beads were evaluated by Differential Scanning Calorimetry, Thin Layer Chromatography, Fourier Transform –Infrared Spectroscopy, X-ray powder diffraction, and stereomicroscopic analysis. Flow properties such as angle of repose, Carr's index and Hausner's ratio were also determined. The melt solidified beads were excipient free, non-disintegrating and of irregular shape. DSC, FTIR spectra showed no changes in drug properties. Flow properties of the beads were found to be acceptable. In vitro dissolution studies of melt solidified beads showed slower dissolution rate which might be due to compactness and higher bond strength of the beads. The present technique of melt solidification of Fenofibrate serves to effective as it takes low processing time, convenient methodology, as compared to conventional particle size enlargement techniques.

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*Keywords*: Particle size enlargement, Fenofibrate, Melt solidification.

## 1. Introduction

Fenofibrate (FB), Isopropyl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropionate, is fibric acid derivative, reduces elevated plasma concentrations of triglycerides. It also decreases elevated plasma concentrations of LDL and total cholesterol. [1-3]

Particle size enlargement of drugs is widely used technique in industrial processing. It can be carried out by techniques such melt extrusion, [4] melt granulation, [5] crystal coagglomeration [6]. These techniques serve to be alternative way for granulation by conventional method. Low melting point substances such as waxes were used for preparation of microcapsules by solidification. [7].

Fenofibrate like drugs show amorphous nature and hence have poor flow properties. It also has low melting point of about 79-82$^0$ C. Hideji et al. [8] reported a method for particle size enlargement of ibuprofen. The same method was used here for fenofibrate which involves melting Fenofibrate powder and cooling the melt. The solidified mass of Fenofibrate was then crushed into granules. The multi-step process of particle size enlargement has been made to single step process to get Fenofibrate beads of desired flow properties.

## 2. Materials and methods

Materials

Fenofibrate was kindly supplied by Lupin Laboratories (India). Sodium lauryl sulphate was purchased from Merck (India). All other chemicals were of analytical grade.

Melt solidification technique 1 (MSB1)

Fenofibrate beads were prepared by same melt solidification technique proposed by Hideji et al. [8] for ibuprofen. Fenofibrate (4 g) was melted at 80 $^0$C on a water bath and solidified by cooling at room temperature in a desiccator for 24 h. The solidified mass was crushed to -14/+16 mesh size by grinding in a mortar. The granular product was evaluated.

Melt solidification technique 2 (MSB2)

Fenofibrate powder (4 g) was melted on water bath at 80 $^0$C and poured into 150 ml deionised water in a jacketed crystallization vessel. The system was stirred at 1000 rpm using a constant speed stirrer (Remi) with propeller blade to obtain beads. Temperature was maintained at 30 $^0$C. The beads were separated by filtration and dried at room temperature.

Evaluation of beads

*Yield and drug content*

Beads were weighed after drying and percent yield was calculated considering complete agglomeration of melted Fenofibrate. Drug content was determined by triturating beads (160 mg) and dissolving them in 100 ml 0.05M sodium lauryl sulphate aqueous solution and analyzed at 289.2 nm spectrophotometrically (Shimadzu 1700 UV-Vis Spectrophotometer). All the studies were done in triplicate. (n = 3)

*Thin layer chromatography (TLC)*

The chemical stability of the solidified melts was studied using TLC. The powdered samples were dissolved in methanol and spotted on 12 cm × 3 cm glass plate coated with silica gel which were developed with solvent system; methanol and water (7:3) and were detected by placing the plates in a chamber containing iodine vapor. All the studies were done in triplicate. (n=3)

*Stereomicroscopic analysis*

Stereomicroscopy was used to determine morphological characters of prepared melt solidified beads using Nikon SMZ800 Stereomicroscope.

*Differential scanning Calorimetry (DSC)*

Differential scanning Calorimetry SDT2960 (TA Instruments Inc., USA) was performed to assess thermotropic properties and thermal behaviors of Fenofibrate, MSB1, MSB2. Samples (3-5mg) were placed in aluminum pans and at constant heating range of 15$^0$C/min, covering temperature range to 250$^0$C. Nitrogen was used as purge gas through DSC cell.

*Fourier transform infrared spectroscopy (FT-IR)*

FT-IR spectra were obtained on Shimadzu 8400S FTIR. Spectra were recorded over the wave number range of 4000 to 450 cm$^{-1}$

*X-ray diffraction (XRD)*

Pulverized mass of Fenofibrate beads was used for XRD studies. The samples were studied by using Philips PW3710 X-ray diffractometer. Samples (Fenofibrate, MSB1, MSB2) were irradiated by Cu Kα radiation (1.54 Å) and analyzed between 5 to 40$^0$. The current and voltage applied were 30mA and 40kV, respectively.

*Flow properties*

Flow properties of melt solidified beads were studied by angle of repose, Carr's index and Hausner's ratios [9]. Each analysis was carried out in triplicate. Bulk density measurements were carried by placing fixed weight of powder in graduated cylinder and volume occupied was measured and initial bulk density was calculated. Cylinder is then tapped at a constant velocity till a constant volume was obtained. Then tapped density was calculated. Angle of repose was calculated by fixed height cone method.

*In vitro drug release studies*

The dissolution studies were performed using USP 30 type II dissolution apparatus (LabIndia Dissolution Tester 2000). Fenofibrate beads (-14/+16 fraction) equivalent to 160mg were placed at bottom of dissolution vessel containing 1000 ml of 0.05M aqueous sodium lauryl sulphate solution maintained at 37± 0.5 $^0$C and stirred with paddle at 50 rpm. Samples were collected at fixed time intervals and same volume was replaced with dissolution medium. Samples were filtered and concentration of Fenofibrate was estimated spectrophotometrically at 289.2 nm using Shimadzu 1700 UV-Vis Spectrophotometer. All the studies were done in triplicate. (n=3)

## 3. Results

The *yield and drug content* of beads obtained by both techniques is presented in Table 1.

Both MSB1 and MSB 2 show percentage yield in the range of 94 to 96%. Drug content in both beads was found to be 98 to 99%. Both the batches of beads showed $R_f$ *values* of 0.86.

*Table1. Results of evaluation parameters such as yield, drug content and $R_f$ values.*

| **Batch** | **Yield (%± SD)** | **Drug content (%± SD)** | **$R_f$ value ± SD** |
|---|---|---|---|
| MSB1 | 95.16 ± 0.65 | 99.07 ± 0.83 | 0.861 ± 0.002 |
| MSB2 | 95.87 ± 0.23 | 99.56 ± 0.19 | 0.862 ± 0.004 |

*Stereomicroscopic analysis* (Fig. 1) reveals irregular shaped beads with rough surface.

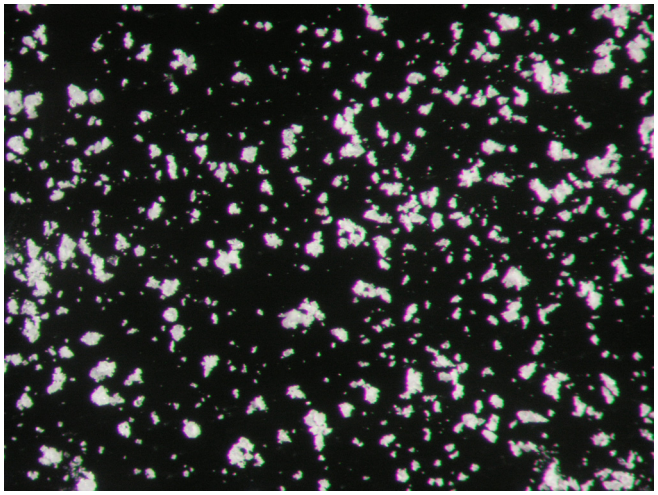

*Fig 1. Stereomicroscopic image of Melt solidified product obtained by MSB2.*

Fenofibrate peak was clearly seen in its *DSC thermograms* (Fig. 2) indicating a sharp characteristic peak at temperature range 79-82$^0$C corresponding to its melting temperature ($T_m$).

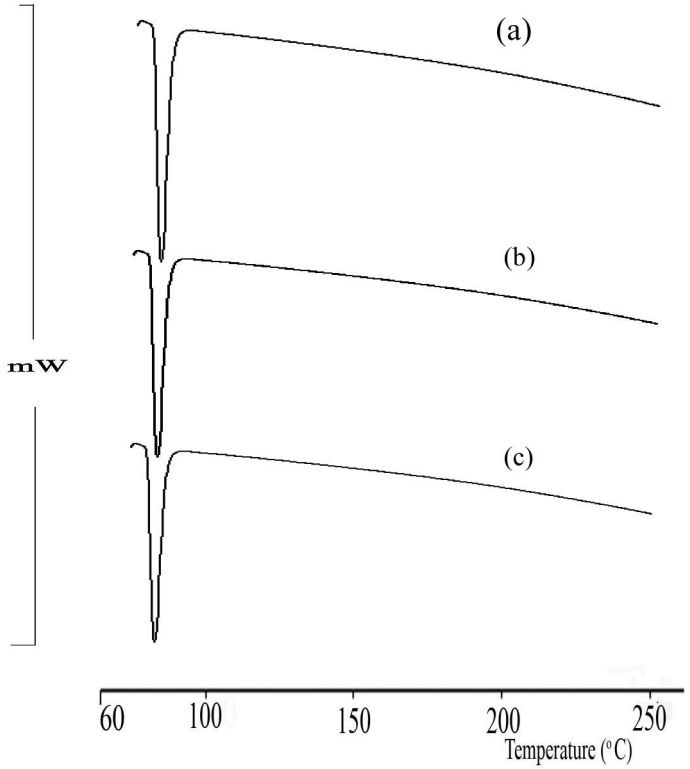


*Fig. 2. DSC thermograms of (a) Fenofibrate (b) MSB1 and (c) MSB2.*

*FTIR spectra* of pure Fenofibrate and both MSB1, MSB2 were shown in Fig. 3. The characteristic peaks of Fenofibrate such as 1728.10 $cm^{-1}$, 1647.10 $cm^{-1}$.

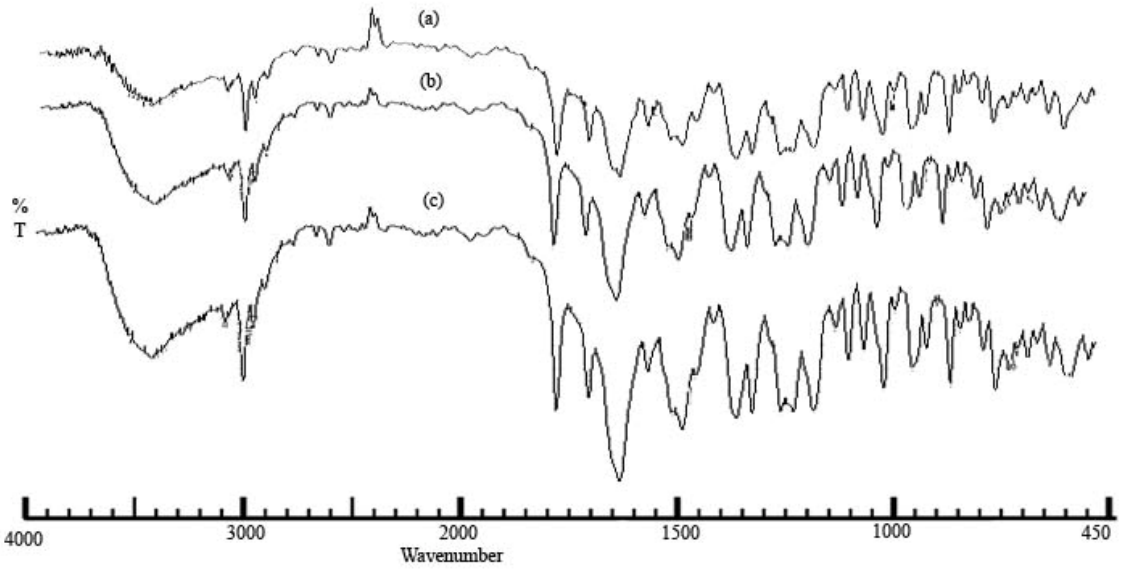


*Fig. 3 FTIR spectra of (a) Fenofibrate (b) MSB1 and (c) MSB2*

Fig. 4 shows XRD patterns of pure Fenofibrate, MSB 1 and MSB2. Sharp distinct characteristic peaks at 2θ diffraction angles for Fenofibrate at $14.285^0$. $16.105^0$and $22.190^0$ indicated its crystalline state.

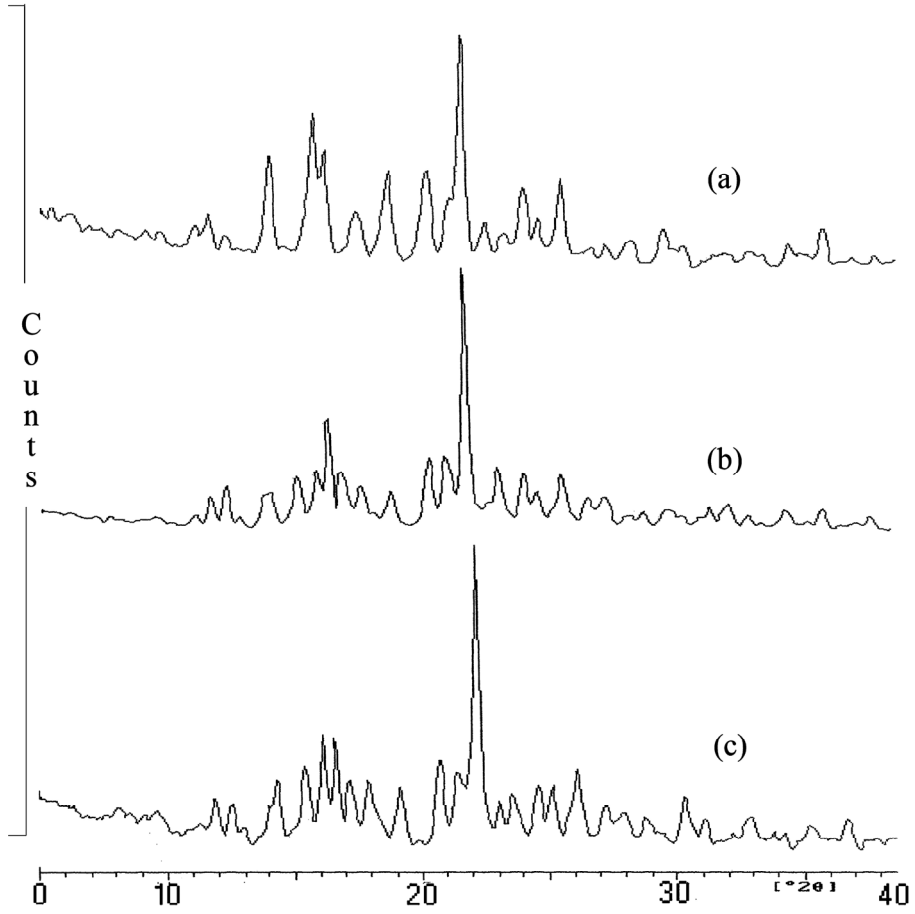


*Fig. 4. X-Ray Diffraction patterns of (a) Fenofibrate (b) MSB1 (c) MSB2*

Results of measurements such as *angle of repose, Carr's index, and Hausner's ratio* are represented in the Table 2.

*Table 2 Results of flowability parameters of melt solidified beads of Fenofibrate*

| **Batch** | **Average Angle of Repose (θ) ± SD** | **Average Carr's index (%) ± SD** | **Average Hausner's Ratio ± SD** |
|---|---|---|---|
| MSB1 | 38.64 ± 0.035 | 22.31± 0.085 | 1.28 ± 0.01 |
| MSB2 | 38.21 ± 0.285 | 22.82 ± 0.340 | 1.29 ± 0.01 |

*In vitro drug release* of melt solidified beads is shown in Fig. 5. Dissolution rates when subjected to statistical analysis by One Way ANOVA showed no significant difference (F=0.0074, P=0.9324). Similarity factor (f2) for the MSB 1 and 2 was found to be 83.10 indicating similarity in dissolution rates.

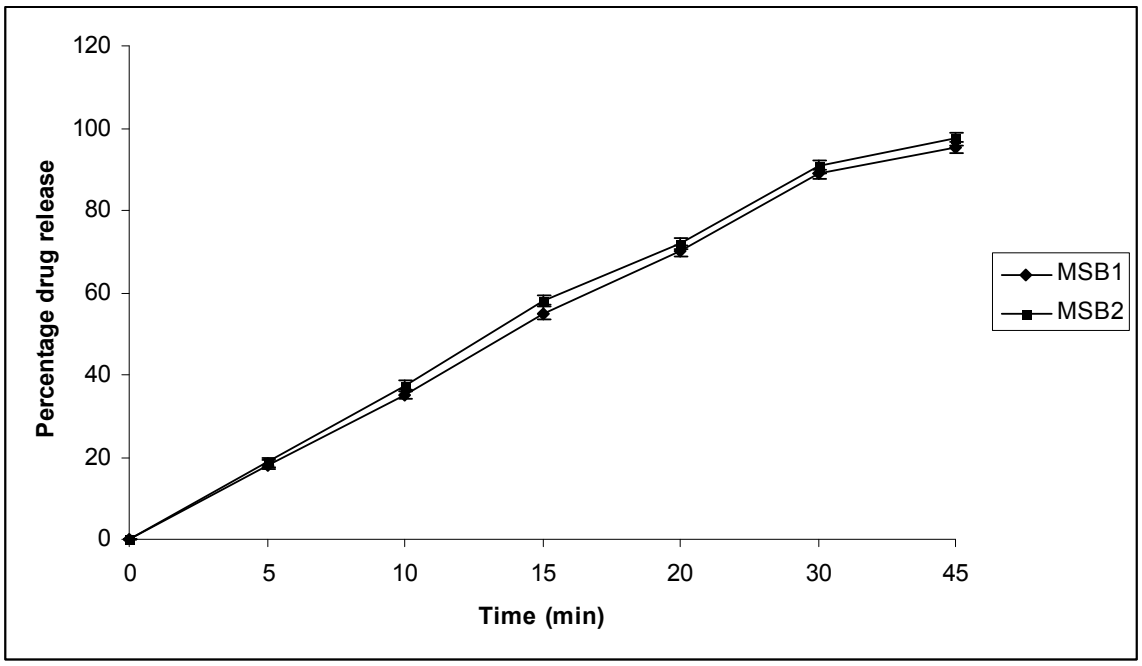


*Fig. 5 Dissolution profile of melt solidified beads of Fenofibrate (MSB1 and MSB2)*

The dissolution data when subjected to Korsmeyer-Peppas equation fitting, n and K values were obtained (Table3). n values are greater than 0.5.

*Table 3 Parameters for Korsmeyer - Peppas equation.*

| **Batch** | **n** | **K** |
|---|---|---|
| **MSB1** | 0.7889 | 5.7408 |
| **MSB2** | 0.7745 | 6.2018 |

## 4. Discussion

Fenofibrate beads were prepared by MSB1 method requires much time in the cooling stage and requires further crushing to obtain desired particle size. As agitation does not involve in MSB1; it needs longer crystallization time (10-20 min). The solidification resulted in formation of solidified mass that crushed into granular mass. As Fenofibrate is insoluble in water and remains pourable, it can be easily dispersed into droplets by agitating in water (for MSB2). 1000 rpm speed was sufficient to form beads in 1-2 min. Results of yield, drug content studies indicate the efficiency of the process. Also $R_f$ values represent the chemical stability of the method. Surface topography was observed from stereomicroscopy which reveals that beads were dense, irregular shaped and with rough surface. *Differential scanning Calorimetry (DSC)* studies were carried out to assess thermotropic properties of beads [10]. Fenofibrate peak was clearly seen in its DSC thermogram (Fig. 2) indicating a sharp characteristic peak at temperature range 79-82$^0$C corresponding to its melting temperature ($T_m$). This shows that Fenofibrate used was in pure form. Also the DSC thermograms for MSB1 and MSB 2 showed characteristic peak in the same temperature range. *Fourier transform infrared spectroscopy (FT-IR)* results (Fig.3) are in accordance with DSC studies. The characteristic peaks of Fenofibrate are retained in MSB1 and 2. No difference was observed in the 2θ diffraction angles for MSB 1and 2 in *XRD studies*. This

indicates that there is no transition during processing. *Flow properties* are the important concern in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose $\geq 40^0$ indicate powders with poor flowability [11]. The results are according to this statement. Also results of Carr's index and Hausner's ratio show good flow behavior. *In vitro drug release studies* of melt solidified beads did not showed much difference as both techniques involve formation of melt solidified bonds. Slower dissolution rates might be due to compactness of beads. The dissolution profile follows Hixon-Crowell model. The 'n' values (Table 3) are more than 0.5 indicate non-Fickian release.

## 5. Conclusion

The developed melt solidification technique is simple, single step. The beads obtained were non disintegrating, excipient free and show acceptable flow properties. The beads obtained by MSB2 method take 1-2 min crystallization time which might be due to low melting point and its poor aqueous solubility of fenofibrate (which results in insolubility of melt in water). Thus the present technique of melt solidification of fenofibrate serves to effective as it takes low processing time, convenient methodology, as compared to conventional particle size enlargement techniques. There is need of improvement of this technique further for extending release with use of proper additives and process variables.

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