ORIGINAL ARTICLE

INFLUENCE OF PROCESS PARAMETERS ON COMPRESSIBILITY, SOLUBILITY AND RELEASE CHARACTERISTICS OF MELT SONOCRYSTALLIZED FENOFIBRATE

SACHINKUMAR PATIL*, SHITALKUMAR PATIL, GEETA KAVATHEKAR

Department of Pharmaceutics Ashokrao Mane College of Pharmacy, Peth-Vadagoan, Maharashtra, India-416112

**corresponding author: sachinpatil79@rediffmail.com*

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Abstract

The aim of the present study was to investigate the suitability of the melt sonocrystallization (MSC) technique in order to modify the processability properties along with solubility and drug release of anti-hyperlipidemic drug fenofibrate (FNO) as a Biopharmaceutical Classification System (BCS) Class II drug candidate. Melted sonocrystallized fenofibrate agglomerates (MSC-FNO) were prepared by probe ultrasonicator by varying the sonication time (1, 2 and 3 min) and the level of amplitude (60, 70 and 80%) by 3^2 factorial design. Stable MSC-FNO agglomerates were successfully prepared with an adequate percentage yield and drug content, having porous surface and different crystal habits such as needles, plates, and some hollow tubes. MSC-FNO has shown improved micrometric properties consequently compressibility and flowability than FNO. Also MSC-FNO has shown an increase in the solubility and the drug release may be due to formation of porous agglomerates witnessed in Scanning Electron Microscopic photographs. These results were well supported by Differential Scanning Calorimetry and X-ray Powder Diffraction (XRPD), which has indicated the decrease in drug crystallinity. As sonication time and amplitude increased, MSC-FNO properties were proportionally improved. Study of Fourier Transform Infrared Spectroscopy revealed that no chemical transition of FNO has occurred during MSC. Thus MSC is a promising cost-effective technique that may give a powder with improved required processability properties with better improvement in solubility and drug release much needed for BCS class II drugs.

Rezumat

Scopul acestui studiu a fost de a investiga tehnica sonocristalizării de topire (CSM) ca o metodă adecvată pentru a modifica proprietățile de prelucrare, împreună cu solubilitatea și eliberarea de fenofibrat medicament anti-hiperlipemiant (FNO), substanță ce face parte din clasa a doua *BCS (Biopharmaceutical Classification System*). Au fost topite aglomerate de fenofibrat sonocristalizat (MSC-FNO), după ce au fost preparate în prealabil într-un ultrasonicator cu sondă la diferite moment de sonicare (1, 2 și 3 min) și având nivelul de amplitudine (60, 70 și 80 %) cu model factorial de 3^2. Aglomeratele stabile MSC-FNO s-au preparat cu un randament procentual adecvat și având un conținut de substanță activă cu suprafața poroasă și diferite tipuri de cristale, cum ar fi ace, plăci, și unele tuburi goale. MSC-FNO a demonstrat proprietăți mult îmbunătățite micrometrice, de compresibilitate și de curgere față de FNO. De asemenea, MSC-FNO a demonstrat că modificarea solubilității și eliberarea medicamentului se poate datora formării de aglomerate poroase, evidențiate prin microscopie electronică de baleiaj. Aceste rezultate au fost evidențiate prin calorimetrie diferențială de baleiaj și de raze X cu pulbere de difracție (XRPD), care a indicat modificări în structura de cristal a medicamentului. Pe măsură ce timpul de sonicare și amplitudinea au crescut, proprietățile MSC-FNO s-au îmbunătățit în mod proporțional. Studiul spectroscopiei în infraroșu prin transformată Fourier a arătat că tranziția chimică a FNO nu a avut loc în timpul MSC. Astfel, MSC este o tehnică promițătoare din punct de vedere al costurilor, care poate da pulberi cu proprietăți îmbunătățite de prelucrare necesare îmbunătățirii solubilității și eliberării substanței medicamentoase, atât de necesare pentru clasa II *BCS* de medicamente.

Keywords: Fenofibrate, Melt Sonocrystallisation Technique, Saturation solubility, dissolution rate

Introduction

Physicochemical properties of drug crystals have a significant role in the processability of drug during formulation and also in the therapeutic efficacy of a drug. With the same intention, most of the particle engineering techniques are used to prepare drug crystals with desirable micrometric and bio-pharmaceutical properties [1]. Remarkable latest technologies are emerging in the field of pharmaceuticals for particle engineering focusing on simple standard formulations as economical as possible. In general, fine crystals favour more attention over large crystals for high permeable and poor soluble pharmaceuticals, considering a large bioavailability. However, fine crystals often hamper powder processability parameters in formulation of solid oral dosage forms. Some of the prior technologies, where simultaneous crystallization and particle agglomeration occur, include spherical crystallization [2], extrusion spheronization [3], melt solidification [4], spray drying [5], pastillation

[6], solution atomization and crystallization by sonication [7]. These technologies add positive approach in the development of BCS class II drugs as it contemplate on solubility enhancement, equally on powder processing parameters in the development of solid oral dosage forms. MSC is a novel particle processing technique, involves application of ultrasonic energy to the soft viscous or molten mass, dispersed in suitable dispersion media maintained at suitable temperature, with or without agitation during crystallization [8]. MSC has been used to achieve nucleation at moderate super saturation during crystallization process or terminal treatment, in order to achieve de-agglomeration and to obtain desired crystal habit. Several attempts have been made by applying the MSC on drugs like ibuprofen [9], celecoxib [10], naproxen [11] and carbamazepine [12]. Fenofibrate (FNO) is an anti-hyperlipidemic drug that shows poor flowability and compaction properties along with poor dissolution. Various works were reported concerning the issues for solubility enhancement of FNO using melt granulation [13] and melt solidification [14] technique and also for compressibility improvement using spherical crystallization techniques [15].

The aim of the present study was the preparation and evaluation of melt sonocrystallized agglomerates of FNO (MSC-FNO), in order to improve the compressibility along with solubility and drug release. It also aimed to demonstrate the effect of processing parameters on compressibility, solubility and release characteristics of MSC-FNO.

Materials and Methods

Fenofibrate (FNO) was obtained as a gift sample from Smruti Organics Limited, Solapur (India). Sodium Lauryl Sulphate (SLS) was purchased from Loba Chemicals, Mumbai (India). All other chemicals used were of analytical grade.

Preparation of MSC-FNO Agglomerates:

The FNO (1 mg) was melted using a water bath maintained at 80-85°C. The obtained molten mass was poured in a vessel containing 40 mL of deionized water at room temperature and sonicated for different time and amplitude, using probe ultrasonicator (Lab Quip Biologics, India) and applying 3^2 factorial design, as given in Table I. The obtained product was collected by vacuum filtration, dried at room temperature and stored in a desiccator before use. The described process was repeated several times for obtaining enough material for characterization and for determining the repeatability. The processing temperature was an important factor in the design of this technique. MSC was carried out at 85ºC, which is above the glass transition temperature of FNO of -20ºC, so that ultrasonic energy should be applied to viscous melt or liquid melt, for a longer time.

Table I

Different batches with their experimental coded level of variables for 3^2 factorial design

Batch code	X_1 = Amplitude[a]	X_2 = Time[b]
F1	−1	−1
F2	−1	0
F3	−1	1
F4	0	−1
F5	0	0
F6	0	1
F7	1	−1
F8	1	0
F9	1	1

[a]X_1 = levels [60% (−1), 70 % (0), 80 % (+1)], [b]X_2 = [1 min (−1), 2 min (0), 3 min (+1)]

Evaluation of MSC-FNO Agglomerates:

Yield and drug content

Agglomerates were weighed after drying and the percentage yield was calculated as given in the following formula:

$$\text{Percentage yield} = \frac{\text{Practical weight}}{\text{Theoretical weight}} \times 100$$

For the drug content determination, MSC-FNO agglomerates equivalent to 100 mg of FNO were triturated and dissolved in 0.05 M SLS. Appropriately diluted samples were filtered through Whatman filter paper 41 (25 µm pore size) and drug content was determined spectrophotometrically, at 290 nm, using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan). The percentage of drug content was calculated using the following formula:

$$\text{Percentage drug content} = \frac{\text{Practical drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Micrometric properties and Compaction behaviour

Mean particle size of pure FNO and all batches of MSC-FNO were determined by randomly counting average diameter of 100 particles, with an optical microscope. Bulk density, tap density, Carr's index, Hausners ratio and angle of repose were determined [1]. The compaction behaviour of pure FNO and all batches of MSC-FNO were determined by the Heckel study.

$$\text{Hausners ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

$$Carr's Index = \frac{\text{Tap density}}{\text{Bulk density}} \text{Tap density} \times 100$$

Heckle equation: $\ln (1/1\text{-}D) = KP + A$,

where, D is the relative density of powder for applied pressure P. A is the intercept. The slope of the straight-line portion K is the reciprocal of the mean yield pressure (MYP) of the material.

The study was performed by compressing 500 mg of pure FNO and all batches of MSC-FNO on hydraulic press (Samrudhi Enterprises, Mumbai, India) using 13 mm flat faced punch and die set, at

a pressure of 20, 30, 40, 60, 80, 100 and 120 kN. The thickness, the weight and the diameter of compacts were determined. Heckel parameters were determined using Heckle equation [16]. For determination of Elastic Recovery (ER) of pure FNO and all batches of MSC-FNO, thickness of the compact was determined at 60 kN compression pressure and at 24 hours after releasing the tablet [17].

$$ER= [(t_2 – t_1) /t_1],$$

where t_1 is the minimal thickness of the powder bed in the die and t_2 is the thickness of the recorded tablet.

The crushing strength was measured immediately after compression with a tablet strength tester (ErwekaTBH 30, Germany) [18].

Solubility studies

Saturation solubility studies of FNO and all batches of MSC-FNO were performed in distilled water. Excess amount of sample was added to 25 mL distilled water and shaken for 24 hours using orbital shaker (Remi Instrument Ltd., Mumbai). Appropriately diluted samples were filtered through Whatman filter paper 41 (pore size 25 µm) and solubility was determined spectrophotometrically at 290 nm using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan).

Scanning Electron Microscopy (SEM)

The samples of pure FNO and MSC-FNO (F5) were coated with a thin gold-palladium layer by sputter coater unit (VG- Microtech, United Kingdom) and the surface topography was analysed with a Cambridge Stereoscan S120 scanning electron microscope (SEM, Cambridge, United Kingdom), operated at an acceleration voltage of 10 kV.

X-ray powder diffraction (XRPD)

X-ray powder diffraction of FNO and MSC-FNO (F5) were analyzed by Philips PW 1729 X-ray diffractometer. Samples were irradiated with monochromatized Cu K_α –radiations (1.542 Å) and analysed between 2-60° (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5 x 10^3 cycles/s and the chart speed was kept at 100 mm/2θ.

Differential Scanning Calorimetry (DSC)

Thermal properties of FNO and MSC-FNO (F5) were analysed by DSC (TA Instruments, USA, model SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at a flow rate of 50 mL per min and 100 mL per min through the cooling unit. The sample (5-10 mg) was heated in a hermetically sealed aluminium pans. Heat runs for each sample were set from 30 to 300°C at a heating rate of 10°C/min.

Fourier transforms Infrared spectroscopy (FTIR)

Fourier transforms Infrared spectroscopy of FNO and MSC-FNO (F5) was recorded using a Jasco V5300 (Jasco, Japan) FTIR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 400 to 2000 cm^{-1}.

In-vitro Dissolution studies

The rate of dissolution of drug and MSC-FNO agglomerates was studied using USP 26 Type I dissolution test apparatus (VDA-8DR, USP, Veego, India). Sample equivalent to 100 mg FNO was placed separately in the dissolution vessel containing 900 mL 0.05 M SLS in distilled water maintained at 37 ± 0.5°C and with 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41 (25 µm pore size), concentration of FNO was determined spectro-photometrically at 290 nm on a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan).

Stability studies

All MSC-FNO agglomerates were charged for the accelerated stability studies as required by the ICH guidelines (40 ± 2°C and 75 ± 5% RH), for a period of 6 months in a stability chamber (Thermolab, Mumbai, India). The samples were placed in vials with bromobutyl rubber plugs and sealed with aluminium caps. The samples were withdrawn at 30, 60, 90 and 180 days and evaluated for the drug content.

Statistical significance

Results are expressed as mean ± S.D for triplicate samples. The results were statistically analysed and significant differences among formulation parameters were determined by One-way analysis of variance, using Graph Pad Instate®, Version 3.05 (USA), statistical analysis program. Statistical significant was considered at $p < 0.05$. The factorial design was performed using software Design Expert®, v8 (USA).

Results and Discussion

The MSC method here described appeared to be a suitable and simple technique to prepare agglomerates of FNO.

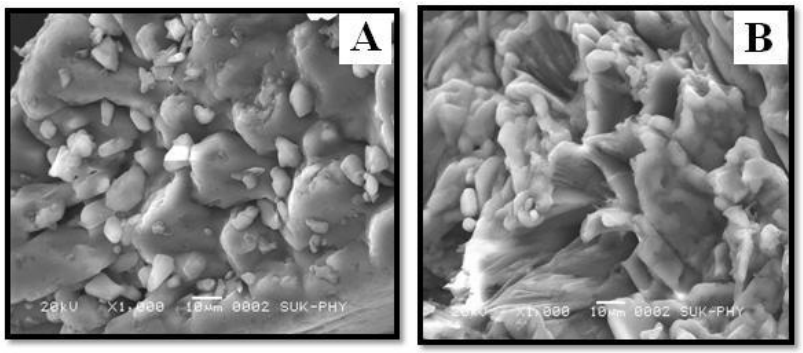

Figure 1.
SEM image of A: Pure FNO and B: MSC-FNO (F5)

Yield, drug content and all micrometric properties of all batches MSC-FNO are given in Table II. The percent yield and drug content of all MSC-FNO formulations were satisfactory between 92 to 97 % w/w and 91 to 93 % respectively.

The data obtained from the experiments were subjected to multiple-regression analysis using Design Expert, statistic version 3. The data were fitted in the following equation:

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_{11} + \beta_{22} X_{22} + \beta_{12} X_{12}$

Multiple-regression analysis and F statistics were used to identify statistically significant term. β_0 is the arithmetic mean response, and β_1 is the coefficient of factor X_1. The results of multiple-regression analysis are summarized in Table III. The influence of variables on evaluation parameters is discussed subsequently. SEM image of pure FNO and MSC-FNO (F5) is shown in Figure 1. It has been observed that, as compared with FNO, MSC-FNO agglomerates were irregular in shape having rough surface with pores, some plates like structure and fines. This may be due to the micronization of the agglomerates by cavitation force of ultrasonication treatment [8].

Table II
Micrometric properties of pure FNO and MSC-FNO (n = 3)

Batch Codes	Yield (%)	Drug content (%)	Diameter (μm) n = 100	Angle of repose (°)	Bulk density (g/cc)	Carr's Index (%)	Hausners ratio
FNO	---	---	23.7 ± 1.05	52.23 ± 0.75	0.322 ± 0.007	11.11 ± 1.9**	1.42 ± 0.04
F1	95 ± 2	92 ± 2	21.3 ± 1.13	23.14 ± 0.65	0.281 ± 0.006	5.62 ± 2.4**	1.18 ± 0.05
F2	94 ± 2	93 ± 1	18.5 ± 0.81	22.23 ± 0.75	0.279 ± 0.006	5.55 ± 0.1.8**	1.16 ± 0.04
F3	97 ± 1	91 ± 3	15.7 ± 1.19	23.23 ± 0.29	0.275 ± 0.008	6.23 ± 2.1**	1.16 ± 0.05
F4	95 ± 2	92 ± 2	19.5 ± 0.70	24.13 ± 0.34	0.271 ± 0.004	6.16 ± 2.1**	1.17 ± 0.06
F5	94 ± 2	93 ± 1	17.5 ± 0.83	26.12 ± 1.10	0.276 ± 0.008	5.88 ± 2.2**	1.16 ± 0.09
F6	97 ± 1	91 ± 2	16.5 ± 0.53	21.21 ± 0.98	0.269 ± 0.012	5.87 ± 1.6**	1.23 ± 0.03
F7	92 ± 3	90 ± 2	18.4 ± 0.65	22.23 ± 0.43	0.332 ± 0.003	11.10 ± 1.7**	1.25 ± 0.03
F8	95 ± 2	92 ± 2	17.6 ± 0.86	22.23 ± 0.33	0.342 ± 0.003	5.89 ± 1.5**	1.25 ± 0.03
F9	94 ± 2	93 ± 1	16.7 ± 0.72	23.23 ± 0.13	0.4012 ± 0.002	5.55 ± 1.4**	1.25 ± 0.03

Significantly different from the value for FNO at $p < 0.001$ (**) and $p < 0.01$

Table III
Regression Analysis of Different Evaluation Parameters

Coefficient	Carr's Index	Heckel Constant D_b	Solubility	T 90%
β_0	+7.03	+0.35	+0.11	+47.00
β_1	-1.63	+7.000	+0.020	-3.83
β_2	+0.78	-003	+0.070	-5.50
β_{12}	1.65	8.000	+0.018	+3.67
R^2	0.8113	0.8932	0.9969	0.9268
F	10.13	07.36	36.92	24.23
P	0.0010	0.0012	0.0004	0.0008

As sonication time increased, particle size was found to be reduced. This may be due to the application of ultrasonic energy to the melted FNO, that leads to formation of smaller crystals due to super saturation and crystal growth that forms many nuclei, as resulted in reduction in particle size and surface roughness [9]. The flow properties of all MSC-FNO was improved compared to FNO, as indicated by the low angle of repose (< 40º), low compressibility index (< 25) and low Hausner's ratio (< 1.25). It has been observed that the amplitude has increased from 60 to 70%, Carr's

index has drastically decreased but no significant difference was observed for 70 and 80% as shown in Figure 2. The Heckel parameters D_b and MYP with ER are as given in Table IV. It was observed that D_b values of MSC-FNO are higher than pure FNO indicated. Fragmentation may be the dominant mechanism of compression although it was followed by plastic deformation. MYP for pure FNO was higher than MSC-FNO, which suggested that plastic deformation started earlier for MSC-FNO at lower compression pressure compared with pure FNO. Compactibility of samples was evaluated based on the tensile strengths of the compacts compressed at different compaction pressures. The tensile strength of tablets prepared with MSC-FNO and raw crystals of FNO were plotted as a function of compression pressure shown in Figure 3. It was found that the tensile strength of tablets with MSC-FNO were dramatically increased indicating enhanced fragmentation during compression resulting in increased D_b. The elastic recoveries of the MSC-FNO compacts were smaller than the original drug crystals. These findings suggested that the MSC-FNO crystals were easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression.

The result has indicated that, as sonication time increased D_b value has increased for 60 % amplitude, but for 70 and 80 % amplitude the relation was not uniform as shown in Figure 4. The explanation is that the particle size decreased by increasing amplitude. Solubility of FNO was improved considerably up to 1.5 folds than native drug, as given in Table IV.

Table IV

Heckel parameters, Elastic recovery and solubility of FNO and MSC-FNO (n = 3)

Batch Codes	Heckel Constant D_b	Mean Yield Pressure (kN)	Elastic Recovery (%)	Solubility (mg/mL)
FNO	0.201 ± 0.007	22.54 ± 2.1	8.1 ± 1.2	0.0032 ± 0.03**
F1	0.387± 0.005**	26.62 ± 2.4**	4.8 ± 0.4***	0.0625 ± 0.03**
F2	0.379± 0.004**	28.55 ± 0.1.8**	5.1 ± 0.6***	0.0699 ± 0.04**
F3	0.402± 0.006**	32.66 ± 2.1**	5.0 ± 0.5***	0.0745 ± 0.06**
F4	0.395± 0.007**	29.11 ± 1.9**	5.8 ± 0.7***	0.103 ± 0.08**
F5	0.349± 0.003**	30.88 ± 2.2**	6.1 ± 0.8***	0.111 ± 0.024**
F6	0.378± 0.004**	5.87 ± 1.6**	5.5 ± 0.4***	0.130 ± 0.08**
F7	0.369± 0.005**	31.10 ± 1.7**	6.2 ± 0.8*	0.167 ± 0.07**
F8	0.338± 0.006**	29.89 ± 1.5**	5.2 ± 0.6***	0.207 ± 0.09**
F9	0.413± 0.003**	31.55 ± 1.4**	5.3 ± 0.5***	0.250 ± 0.07**

Significantly different from the value for raw crystals of PGH at $p < 0.001$ (***), $p < 0.01$ (**) and $p < 0.05$ (*)

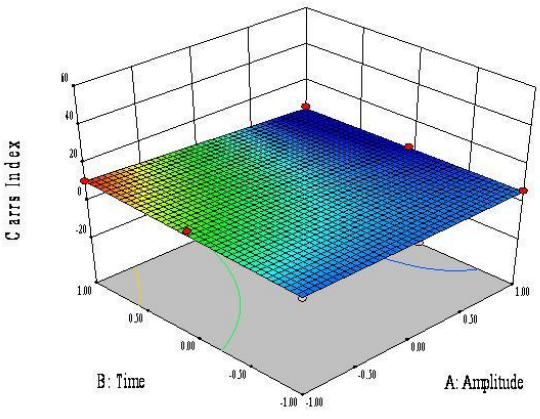

Figure 2.
Effect of sonication time and amplitude on Carr's index of MSC-FNO batches

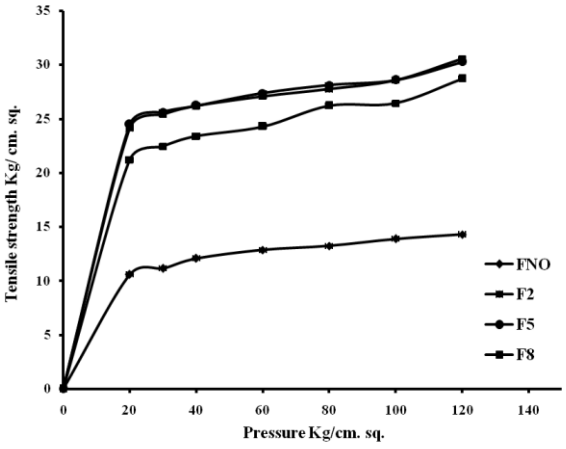

Figure 3.
Tensile strength of tablets with MSC-FNO and raw crystals of FNO

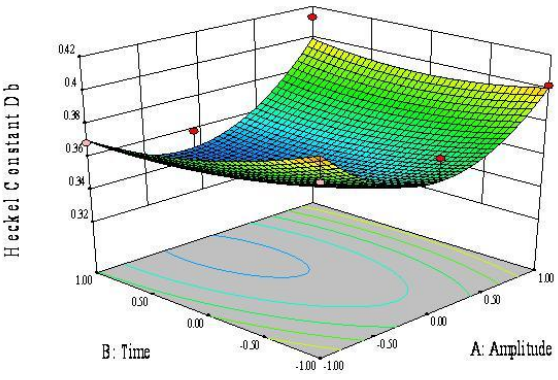

Figure 4.
Effect of sonication time and amplitude on Heckel constant D_b of MSC-FNO batches

The study revealed that agglomerates were natively porous in nature as compared with the pure drug. It can be confirmed from SEM image of MSC-FNO that has shown tube like hollow structure, as shown in Figure 1. The results have indicated that as sonication time and amplitude increased, saturation solubility also increased, as shown in Figure 5. It may be due to formation of porous nature of the MSC-FNO.

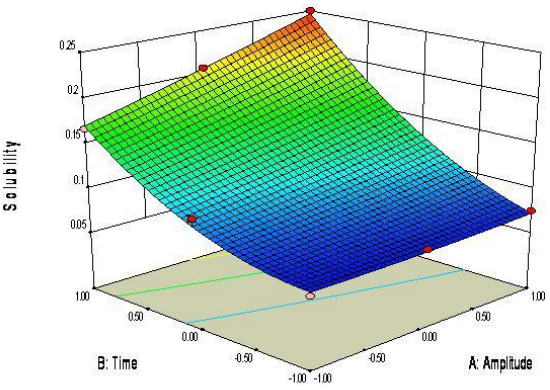

Figure 5.
Effect of sonication time and amplitude on solubility of MSC-FNO batches

XRPD patterns of FNO and MSC FNO agglomerates (F5) are as shown in Figure 6. The pure drug has shown sharp peaks at 2θ: 21.83°, 21.85° and 21.88° while MSC-FNO has shown less intensive peak at the same 2θ values indicated the crystallinity drug decrease.

DSC thermograms of FNO and MSC FNO agglomerates (F5) are as shown in Figure 7. The pure drug has shown an endotherm melt at 82.01ºC with a 51.80 J/g enthalpy whereas MSC-FNO has shown a slight broad endothermic peak with a decrease in enthalpy 47.77 J/g.

Thus, DSC data has well supported to XRPD indicating a decrease in the drug crystallinity.

The FTIR Spectrum of pure FNO and MSC-FNO (F5) are shown in Figure 8. The spectrum of FNO displayed characteristic peaks at 1384.14 cm^{-1} and 1285.01 cm^{-1}, due to C-O stretching, at 1724.42 cm^{-1}, due to C=O stretching, at 654.12 cm^{-1} and 762.82 cm^{-1}, due to C-Cl Stretching. Whereas, the spectrum of MSC-FNO (F5) displayed characteristic peaks at 1384.83, 1246.14, 1725.55, 654.91 and 763.01cm^{-1}. So it has been indicated that the drug remains in its pure form, with no prominent change in its characteristics even in the formulation.

Dissolution profiles of FNO and MSC –FNO were as shown in Figure 9. The study revealed that drug release has increased with the increase of ultrasonic treatment, as shown in Figure 10.

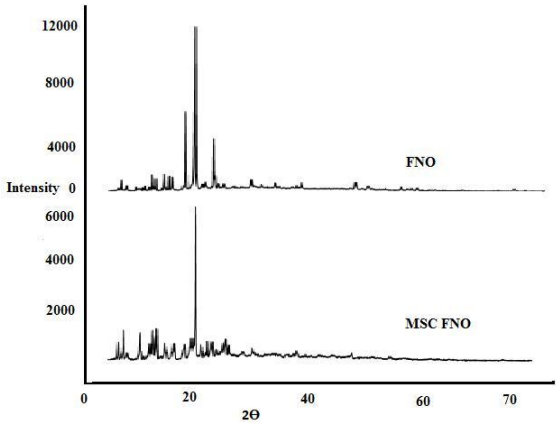

Figure 6.
XRPD spectra of FNO and MSC-FNO (F5)

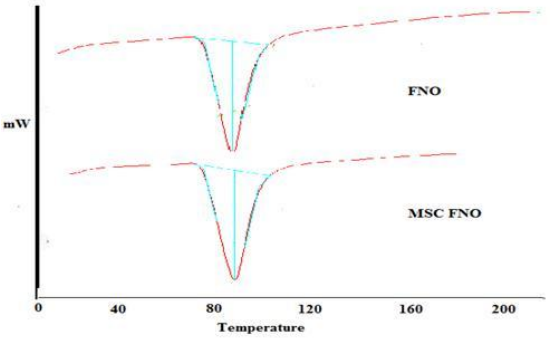

Figure 7.
DSC thermogram of FNO and MSC-FNO (F5)

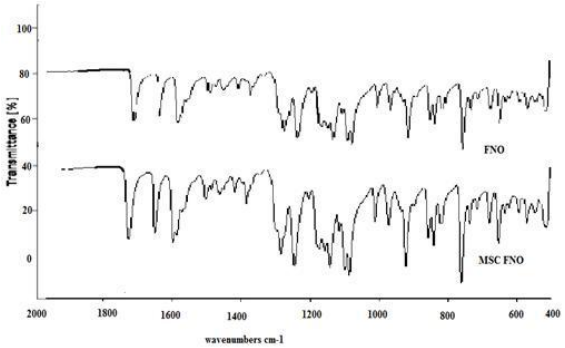

Figure 8.
FTIR spectra of FNO and MSC-FNO (F5)

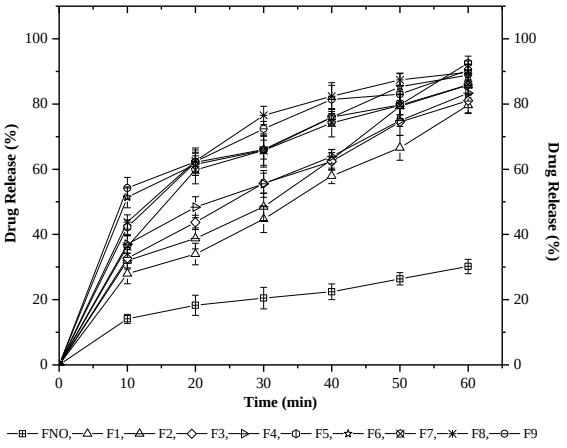

Figure 9.
In vitro drug release of FNO and MSC-FNO batches

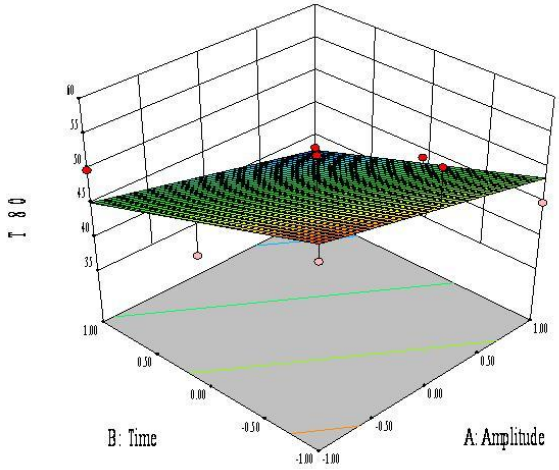

Figure 10.
Effect of sonication time and amplitude on T 80 % of MSC-FNO batches

It has been observed that up to 50 to 90 % drug was released within half an hour for MSC-FNO, whereas pure drug has shown only 30 % release within the same time. The MSC-FNO showed faster drug release than the native drug, that may be due to the increased drug surface area in agglomerated form as well as porous and amorphous nature of drug.

The agglomerates did not show any significant change in the drug content during stability study, as given in Table V. It has been indicated that the prepared agglomerates were adequately stable as established by the regulatory requirements [19].

Table V

Drug content of MSC-FNO agglomerates after stability study 40 ± 2°C and 75 ± 5% RH after different times

Batch Codes	0 Days	30 Days	60 Days	90 Days	180 Days
F1	92 ± 2	91 ± 2	90 ± 2	91 ± 1	90 ± 1
F2	90 ± 1	90 ± 1	88 ± 2	89 ± 1	88 ± 2
F3	91 ± 3	90 ± 2	89 ± 3	90 ± 1	88 ± 1
F4	94 ± 2	92 ± 2	91 ± 2	91 ± 1	90 ± 2
F5	91 ± 1	90 ± 1	90 ± 2	88 ± 1	89 ± 1
F6	92 ± 2	90 ± 2	89 ± 1	66 ± 2	89 ± 2
F7	93 ± 2	92 ± 3	91 ± 1	89 ± 2	88 ± 1
F8	92 ± 2	91 ± 3	91 ± 1	90 ± 2	90 ± 1
F9	93 ± 2	92 ± 3	91 ± 1	90 ± 2	90 ± 1

Not significantly different from the values of 0 days as $p > 0.1$ for 30, 60, 90 and 120 days

Conclusions

Agglomerates of fenofibrate were successfully prepared by melted sonocrystallization method. The prepared agglomerates were irregular, with a rough surface, porous and showed improved micrometric properties and compressibility. Agglomerates showed improved solubility and dissolution rate, as compared with the native drug. Thus, it can be concluded that the prepared agglomerates of FNO by melted sonocrystallization technique may be a potential, reliable and effective tool for not only improved processability parameters, but also enhanced solubility and dissolution of drug.

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