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Influence of Process Parameters on Compressibility, Solubility and Release Characteristics of Melt Sonocrystallized Fenofibrate

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Authors' contributions

This work was carried out in collaboration between all authors. Authors Sachinkumar Patil and Shitalkumar Patil designed the study, wrote the protocol and wrote the first draft of the manuscript. Author GK managed the literature searches, formulation and evaluation study including the experimental process. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: The aim of the present study was to investigate the suitability of the melt sonocrystallization (MSC) technique to modify the processability properties along with solubility and drug release of anti-hyperlipidemic drug fenofibrate (FNO) as a BCS Class II drug candidate.
Study Design: By 3^2 factorial design.
Place and Duration of Study: The study was performed in Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadagoan, Tal. Hatkanangale, Dist. Kolhapur, Maharashtra, India-416112 and the duration was two years.
Methodology: Melt sonocrystallized fenofibrate agglomerates (MSC-FNO) were prepared by probe ultrasonicator at varying sonication time (1, 2 and 3 min) and level of amplitude (60, 70 and 80%) by 3^2 factorial design. Prepared MSC-FNO agglomerates were further evaluated for various parameters.

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Results: Stable MSC-FNO agglomerates were prepared successfully with 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 increase in solubility and 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 which has indicated decrease in crystallinity of drug. As sonication time and amplitude increased properties of MSC-FNO were proportionally improved. Study of Fourier Transform Infrared Spectroscopy revealed that no chemical transition of FNO has occurred during MSC.

Conclusion: Thus MSC is a promising cost-effective technique that may give powder with improved required processability properties with better improvement in solubility and drug release, much needed for BCS class II drugs.

Keywords: Fenofibrate; melt sonocrystallisation; saturation solubility; dissolution rate.

1. INTRODUCTION

Physicochemical properties of drug crystals have a significant role in processability of drug during formulation and also in the therapeutic efficacy of drug, with the same intention most of the particle engineering techniques are used to prepare drug crystals with desirable micromeritic and biopharmaceutical 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 favor more attention over large crystals for high permeable and poor soluble pharmaceuticals considering better 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 agglomeration occur, including 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 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 have been used to achieve nucleation at moderate super saturation during crystallization process or terminal treatment to achieve deagglomeration and to obtain desired crystal habit. Several attempts have been made on applications of MSC on drugs like ibuprofen [9], celecoxib [10], naproxen [11] and carbamazepine [12]. Fenofibrate (FNO) is an anti-hyperlipidemic drug 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 present study deals with preparation and evaluation of melt sonocrystallized agglomerates of FNO (MSC-FNO) to improve the compressibility along with solubility and drug release and also demonstrate the effect of processing parameters on compressibility, solubility and release characteristics of MSC-FNO.

2. MATERIALS AND METHODS

Fenofibrate (FNO) was obtained as gift sample from Smruti Organics Limited, Solapur (India). Sodium Lauryl Sulphate (SLS) was purchased from Loba Chemicals, Mumbai (India).

2.1 Preparation of MSC-FNO Agglomerates

The FNO (1 gr) was melted using a water bath maintained at 80-85℃.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 1. The product obtained was collected by vacuum filtration, dried at room temperature and stored in a desiccator before use. The process given above was repeated several times to obtain enough materials for characterization and

to observe repeatability. Processing temperature was an important factor in the design of this technique. MSC was carried out at 85ºC, which is well above the glass transition temperature of FNO that is -20ºC, so that ultrasonic energy should be applied to viscous melt or melt liquid for a longer time. During preliminary study, it was observed that as the melt was immersed in water, the fine as well as larger droplets of the melt was formed on the upper side of water layer due to solidification process and ultrasonic treatment.

Table 1. 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)]

2.2 Evaluation of FNO and MSC-FNO Agglomerates

2.2.1 Yield and drug content

After drying agglomerates were weighed and percent yield was calculated as given in equation 1.

$$\text{Percentage yield} = \frac{\text{Actual weight}}{\text{Calculated weight}} \times 100 \quad (1)$$

For determination of drug content, 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 (pore size 25 µm) and drug content was determined spectrophotometrically at 290 nm using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan). Percentage drug content was calculated using equation 2.

$$\text{Percentage drug content} = \frac{\text{Practical drug concentration}}{\text{Theoretical drug concentration}} \times 100 \quad (2)$$

2.2.2 Micromeritic properties and compaction behavior

Mean particle size of pure FNO and all batches of MSC-FNO were determined by randomly counting average diameter of 100 particles using microscopy method [1]. Bulk density, tap density, Carr's index, Hausners ratio and angle of repose were determined as given equation 3, 4 and 5 [1]. The compaction behavior of pure FNO and all batches of MSC-FNO were determined by the Heckel equation given as equation 6.

$$\text{Hausners ratio} = \frac{\text{Tap density}}{\text{Bulk density}} \quad (3)$$

$$Carr'sIndex = \frac{\text{Tap density - Bulk density}}{\text{Tap density}} \times 100 \quad (4)$$

$$\text{Angle of Repose} = \theta = \tan^{-1}(\text{height/radius}) \quad (5)$$

$$\text{Heckel equation} = \text{In}\frac{1}{1-D} = KP + A \quad (6)$$

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. From the value of the intercept, A, the relative density, D_a and the relative density of powder bed at the point when the applied pressure equals to zero, D_o, can be calculated using equation 7, 8 and 9.

$$D_a = 1 - e^{-A} \quad (7)$$

$$D_o = 1 - e^{-Ao} \quad (8)$$

$$D_b = Da - Do \quad (9)$$

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 pressure 20, 30, 40, 60, 80, 100 and 120 kN and thickness, weight and diameter of compacts were determined. Heckel parameters were determined using Heckel equation [16]. For determination of Elastic Recovery (ER) of pure FNO and all batches of MSC-FNO, thickness of the compact was determined at compression pressure 60 kN and at 24 hrs after releasing the tablet and calculated using equation 10 [17].

$$ER = [(t_2 - t_1) / t_1] \quad (10)$$

Where t_1 is the minimal thickness of the powder bed in the die and t_2 is the thickness of the recorded tablet. Crushing strength was measured immediately after compression with a tablet strength tester and Tensile strength Q was calculated in equation 11 [18] (ErwekaTBH 30, Germany).

$$Q = 2H / (\pi d\, t) \quad (11)$$

Where H is the tablet crushing strength, d is the diameter and t is the thickness of the tablet.

2.2.3 Solubility studies

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 hr 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).

2.2.4 Scanning Electron Microscopy (SEM)

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

2.2.5 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 analyzed between 2-60° (2 θ). 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.

2.2.6 Differential Scanning Calorimetry (DSC)

Thermal properties of FNO and MSC-FNO (F5) were analyzed 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 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 aluminum pans. Heat runs for each sample were set from 30 to 220℃ at a heating rate of 10℃/min.

2.2.7 Fourier Transforms Infrared Spectroscopy (FTIR)

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

2.2.8 *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±0.5ºC and with 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41 (pore size 25 µm), concentration of FNO was determined spectrophotometrically at 290 nm on UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan).

2.2.9 Stability studies

All MSC-FNO agglomerates were charged for the accelerated stability studies as per ICH guidelines (40±2℃ 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 aluminum caps. The samples were withdrawn at 30, 60, 90 and 180 days and evaluated for the drug content.

2.2.10 Statistical significance

Results are expressed as mean ± S.D for triplicate samples. The results were statistically analyzed 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).

3. RESULTS AND DISCUSSION

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

Yield, drug content and all micromeritic properties of all batches MSC-FNO are given in Table 2. The percent yield and drug content of all of MSC-FNO formulations were satisfactory between 92 to 97 w/w % and 91 to 93% respectively. As drug might have lost due to sticking to the instrument or during processing, the Yield, drug content was less than 100%.

The data obtained from the experiments were subjected to multiple-regression analysis using Design Expert, statistic version 3. The data were fitted in the equation 12.

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

Multiple-regression analysis and F statistics were used to identify statistically significant term. β_0 is the arithmetic mean response, β_1 is the coefficient of factor X_1 and β_2 is the coefficient of factor X_2 β_{11} , X_{11} . β_{22}, X_{22}, β_{12} and X_{12} represents the magnitude and direction of each of these second-order effects, indicated by the respective coefficients. The results of multiple-regression analysis are summarized in Table 3. The influence of variables on evaluation parameters is discussed subsequently. SEM images of Pure FNO and MSC-FNO (F5) are as shown in Fig. 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].

As sonication time increased, particle size was found to be reduced. This may be due to reason that application of ultrasonic energy to the melted FNO leads to formation of smaller crystals due to super saturation and crystal growth that forms many nuclei, this was resulted in reduction in particle size and surface roughness [9]. The flow properties of all MSC-FNO were improved than FNO as indicated by low angle of repose (<40º), low compressibility index (<25) and low Hausner's ratio (<1.12). It has been observed that as 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 Fig. 2. The Heckel parameters D_b and MYP with ER are as given in Table 4.

It was observed that D_b values of MSC-FNO are higher than pure FNO indicated that fragmentation may be the dominant mechanism of compression although fragmentation 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 [19]. 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 Fig. 3. It was found that the tensile strength of tablets with MSC-FNO were dramatically increased indicating enhanced fragmentation during compression [20]. The elastic recoveries of the compacts of MSC-FNO were smaller than that of 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.

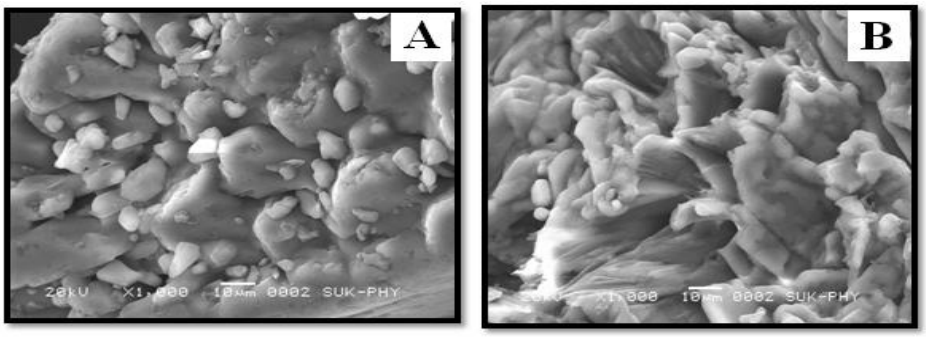

Fig. 1. SEM image of A: Pure FNO and B: MSC-FNO (F5)

Table 2. 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)	Tap density (g/cc)	Carr's index (%)	Hausners ratio
FNO	---	---	23.7±1.05	52.23±0.75	0.322±0.007	0.362±0.006	11.11±1.9 **	1.12±0.04
F1	95±2	92±2	21.3±1.13	23.14±0.65	0.281±0.006	0.298 ±0.007	5.62±2.4 **	1.06±0.05
F2	94±2	93±1	18.5±0.81	22.23±0.75	0.279±0.006	0.295 ±0.005	5.55±0.1.8 **	1.05±0.04
F3	97±1	91±3	15.7±1.19	23.23±0.29	0.275±0.008	0.293 ±0.007	6.23±2.1 **	1.06±0.05
F4	95±2	92±2	19.5±0.70	24.13±0.34	0.271±0.004	0.289 ±0.005	6.16±2.1 **	1.06±0.06
F5	94±2	93±1	17.5±0.83	26.12±1.10	0.276±0.008	0.293 ±0.007	5.88±2.2 **	1.06±0.09
F6	97±1	91±2	16.5±0.53	21.21±0.98	0.269±0.012	0.285 ±0.009	5.87±1.6 **	1.05±0.03
F7	92±3	90±2	18.4±0.65	22.23±0.43	0.332±0.003	0.373 ±0.004	11.10±1.7 **	1.12±0.03
F8	95±2	92±2	17.6±0.86	22.23±0.33	0.342±0.003	0.363 ±0.006	5.89±1.5 **	1.06±0.03
F9	94±2	93±1	16.7±0.72	23.23±0.13	0.4012±0.002	0.42 5±0.008	5.55±1.4 **	1.06±0.03

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

Table 3. 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

Table 4. 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±0.0 8 **
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 (*)

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 Fig. 4. It may be due to reason that with increasing amplitude particle size has decreased. Solubility of FNO was improved considerably up to 1.5 folds than native drug as given in Table 4.

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

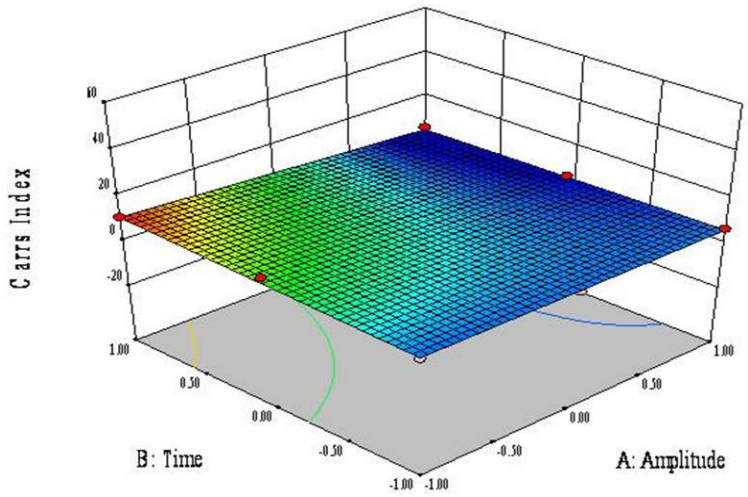

Fig. 2. Effect of sonication time and amplitude on carr's index of MSC-FNO batches

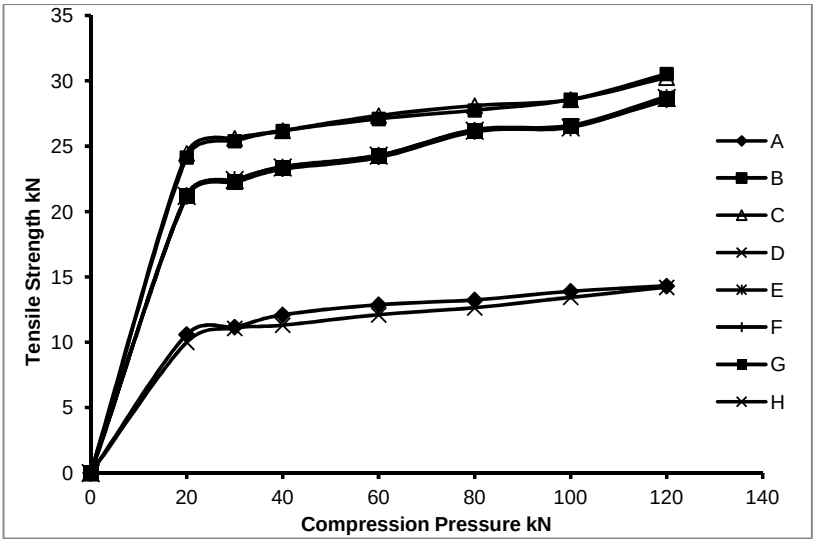

Fig. 3. Tensile strength of tablets prepared with MSC-FNO and raw crystals of FNO

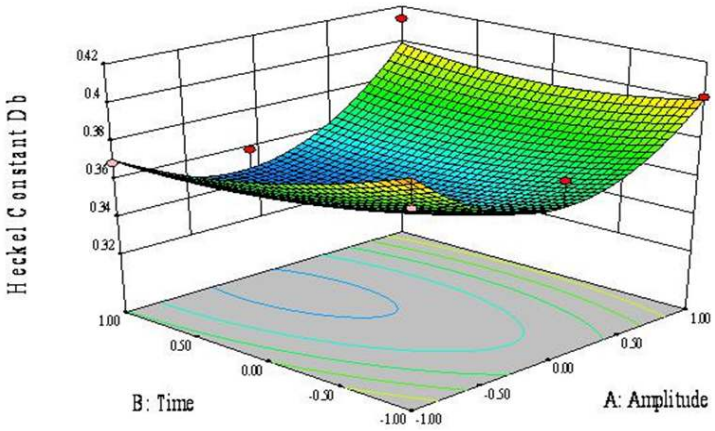

Fig. 4. Effect of sonication time and amplitude on heckel constant D_b of MSC-FNO batches

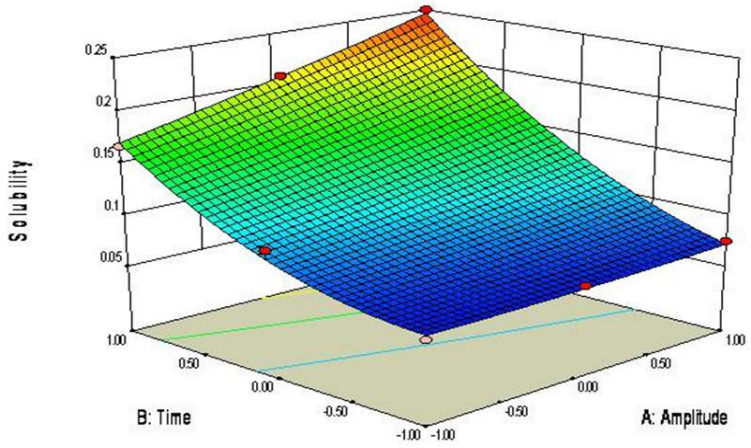

Fig. 5. Effect of sonication time and amplitude on solubility of MSC-FNO batches

XRPD patterns of FNO and MSC FNO agglomerates (F5) are as shown in Fig. 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 decrease in crystallinity of drug.

DSC thermograms of FNO and MSC FNO agglomerates (F5) are as sown in Fig. 7. Pure drug has shown melting endotherm at 82.01℃ with an enthalpy 51.80 (J/g) whereas MSC-FNO has shown slight broad endothermic peak with decrease in enthalpy 47.77 (J/g).

Thus DSC data have well supported the XRPD results indicating decrease in crystallinity of drug.

The FTIR Spectrum of pure FNO and MSC-FNO (F5) is as shown in Fig. 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 763.01 cm^{-1}. So it has indicated that the drug remains in its pure form with no prominent change in its characteristics even in the formulation.

Dissolution profile of FNO and MSC –FNO was as shown in Fig. 9. The study revealed that drug release has increased with increase in ultrasonic treatment as shown in Fig. 10.

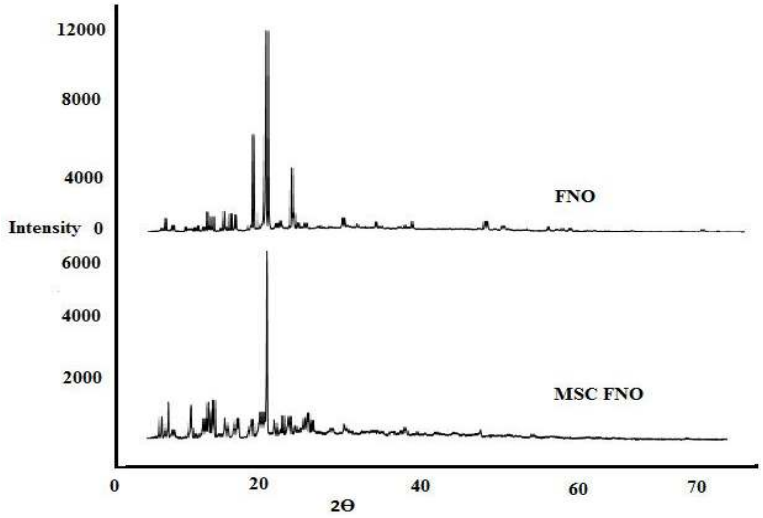

Fig. 6. XRPD spectra of FNO and MSC-FNO (F5)

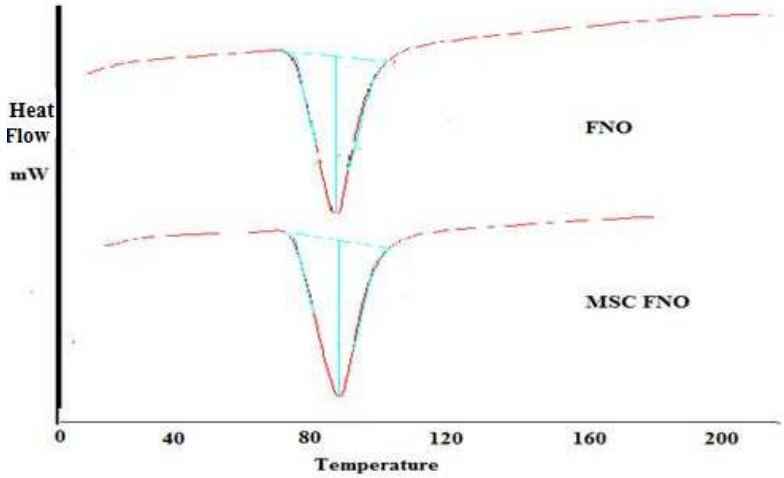

Fig. 7. DSC thermogram of FNO and MSC-FNO (F5)

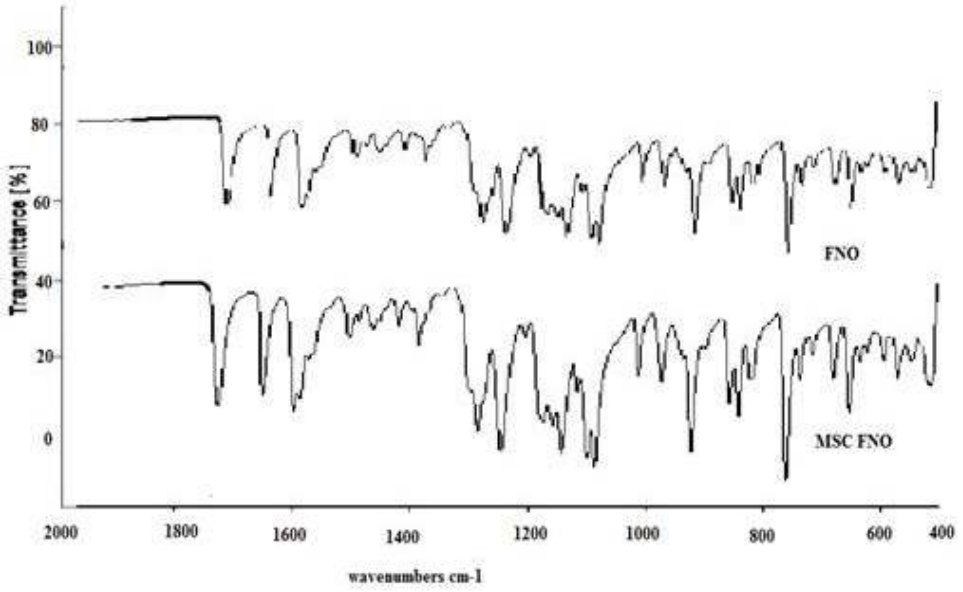

Fig. 8. FTIR spectra of FNO and MSC-FNO (F5)

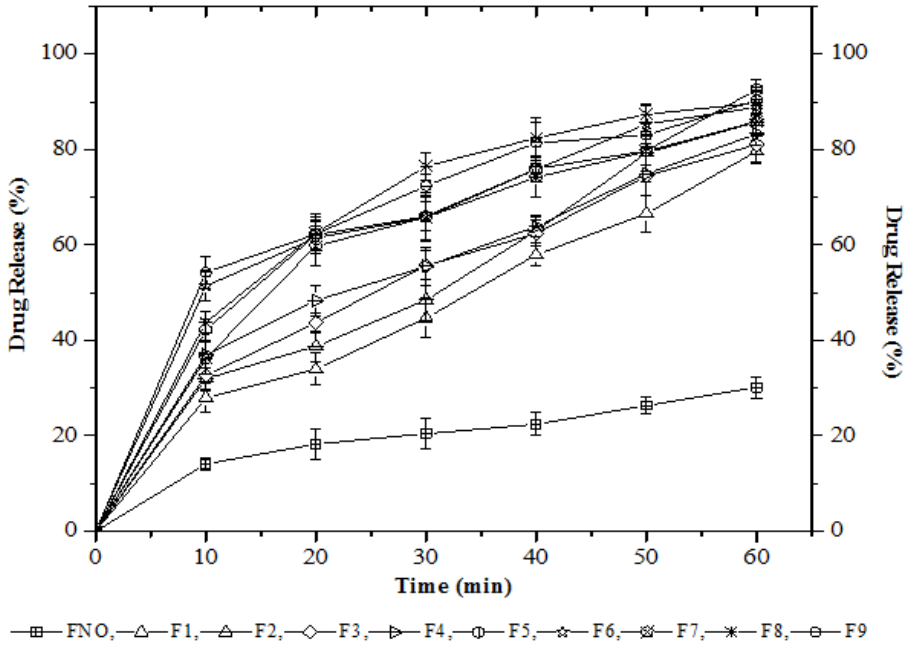

Fig. 9. *In –vitro* drug release of FNO and MSC –FNO batches

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 native drug may be due to increase in surface area of drug in agglomerated form as well as porous and amorphous nature of drug. The agglomerates did not show any significant change in drug content during stability study as given in Table 5. It has indicated that the prepared agglomerates were adequately stable as per regulatory requirements [21].

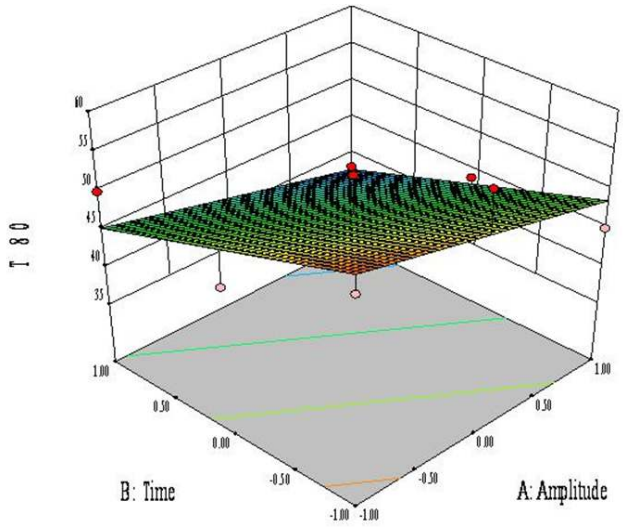

Fig. 10. Effect of sonication time and amplitude on T 80% of MSC-FNO batches

Table 5. Drug content of MSC-FNO agglomerates after stability study 40 ± 2℃ and 75±5% RH after different time

FC	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

4. CONCLUSION

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

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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