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Particle engineering of fenofibrate for advanced drug delivery system

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Abstract

Background: The goal of the current investigation was to formulate, evaluate co-crystal, and further design of solid unit dosage form of antihyperlipidemic BCS class II drug fenofibrate (FNO). Co-crystals composed of a structurally homogeneous crystalline material that contains two or more components in a definite stoichiometric amount helps in increasing yield, the capability to regulator polymorph fabrication, enhanced invention crystallinity. Ball milling method is used for co-crystal formulation, optimized via 3^2 full factorial design and characterized by saturation solubility, particle size analysis, Fourier transform infrared spectroscopy (FT-IR) study analysis, powder X-ray diffraction (PXRD) study analysis, surface morphology by scanning electron microscopy (SEM) study, flow properties, and ex vivo intestinal permeation study via non-everted rat intestinal sac model. Furthermore, optimized batch compressed into tablets is evaluated for disintegration time, hardness, friability, in vitro drug release study and stability study.

Results: It demonstrated that co-crystal formulation FNOCC7 shows higher saturation solubility 0.3874 ± 2.82 g/ml with less particle size 221.231 ± 0.456 nm, FT-IR spectra confirmed significant structural alterations in the formulation indicating the hetero-molecular interaction, the presence of hydrogen bonding had occurred in the co-crystals, PXRD spectra of formulation determined by the increase in the crystalline nature. FNO co-crystals show flux (F) and permeability coefficient (P_{app}) 0.322 ± 0.068 μg/min, 5.38 ± 0.093 cm/min respectively increased compared to the pure drug makes in an enhancement of solubility as well as the bioavailability of BCS class II drug.

Conclusions: The solubility and dissolution percentage of FNO can be improved by the utilization of Co-crystal of FNO with PEG 4000. The solubilization impact of PEG 4000 might be contributed because of the decrease of molecule conglomeration of the drug presence of crystallinity, expanded wettability, and dispersibility; pharmaceutical co-crystals speak to a beneficial class of crystal form with regard of pharmaceuticals.

Keywords: Crystallization, Co-crystal, Antihyperlipidemic, Solid dispersion, permeability, BCS class II

Background

Fenofibrate (FNO) stayed in a biopharmaceutics classification system in class II hypolipidemic lipophilic compound by low solubility and great permeability, has high lipophilicity (log P = 5.24) (Fig. 1) [1–3]. The pharmacological activity of fenofibric acid, an active metabolite, produces reductions in total cholesterol concentration in plasma, total triglycerides in patients. The bioavailability of Fenofibrate is exclusively based on the rate of dissolution in the gastrointestinal tract. Hence, modifications should be demanded in dissolution study of fenofibrate dosage forms as it binds its absorption from the gastrointestinal tract [4].

High dose size is required for poorly water-soluble drugs in demand to attain to reach its plasma concentration at a therapeutic level. Oral bioavailability and dose decrease are achieved by the means of improvement in the extent and rate of dissolution. In the field of particle engineering, attempts are undertaken to improve solubility, micrometric, and compression properties, and obtaining suitable polymorphs is one of the key factors for enhancement of the dissolution rate of poorly soluble drugs. Some physical modifications like reduction in particle size and generation of amorphous states enhance the surface area, solubility, and wettability of the powder particles [5–7]. Several studies make sure

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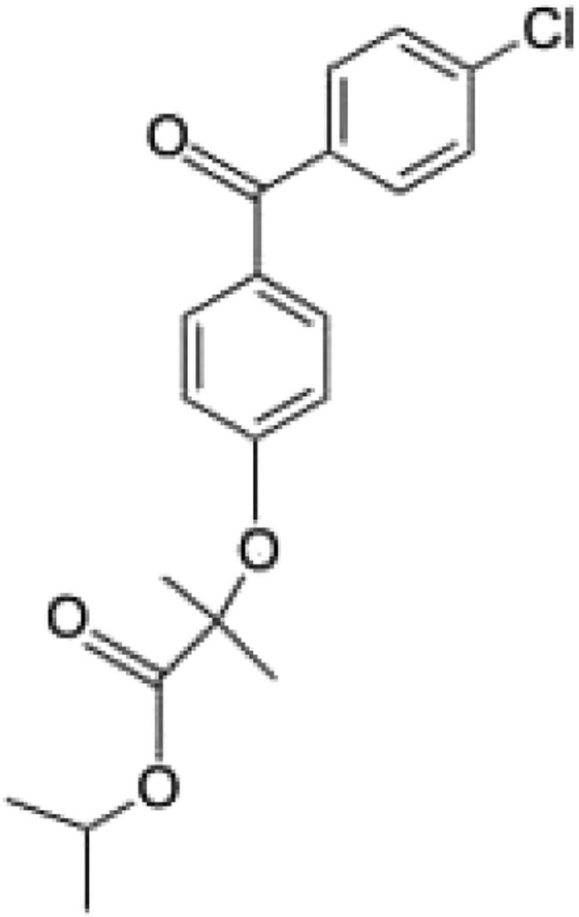

Fig. 1 Compound structure of Fenofibrate

reported to upturn the bioavailability of the fenofibrate orally by using micronization [8], co-grinding and spray-drying [9], the effect of the role of surfactant and pH [10], nanosuspensions, and SLN [11]. Micronization process increased the bioavailability of drugs, e.g., by jet or ball milling has been fine approved, e.g., danazol [7], progesterone [12], and digoxin [13]. Ball mill method is widely used to reduce the particle size up to nanometer [10, 14]. Yet, the use of surfactants is a rational methodology, which if executed properly can approximate the GI fluid condition.

Co-crystal technology by ball milling is another evolving approach for the delivery of insoluble drugs. The modification in the physicochemical properties of a drug substance by complexation is highly required for the rate of dissolution, bioavailability, stability, and processing consideration [12, 13, 15, 16]. The model for the development of the co-crystal formulation here was by co-grinding ball mill technique including polyethylene glycol 4000 (PEG 4000) and subsequently preparing solid dosage form. Further, they were evaluated with respect to their Fourier transform infrared spectroscopy (FT-IR), powder X-ray diffraction (PXRD) study analysis, scanning electron microscopy (SEM) study, and in vitro drug release. In vitro dissolution studies of the fenofibrate co-crystals and solid dosage, formulations were performed and compared with commercial fenofibrate products from the market formulation fenoglide.

Methods

Materials

Fenofibrate (FNO) was procured by way of a gift sample from Abbot Healthcare Ltd. (Goa, India). Polyethylene glycol 4000 (PEG 4000), Lactose was purchased from Merck chemicals, Pvt. Ltd. (Mumbai, India). Sodium starch glycolate, magnesium stearate, polyvinyl pyrrolidone (PVP), and isopropyl alcohol was obtained from Sigma Aldrich (Kolkata, India) and the rest of the chemicals that were used of analytical grade.

Preparation of co-crystal

The co-crystal process was carried out in a ball mill by maintaining 70% of its critical velocity using the various size of balls and different time intervals (RPM). A homogenous powder mixture of a weighed PEG 4000 (400 mg) along with FNO (500 mg) was formed in the vessel (Pan) for 30 min at 100 rpm. A 25 ml of stainless steel milling jar contains an oscillatory ball mill having three 9 mm stainless steel balls are used for FNO with PEG 4000 respectively. At a specified period, i.e., 1 min to 30 min milling was carried out. By changing the number of balls and time period, nine batches of co-crystals were prepared. The details of each are mentioned in Table 4.

Effect of response variables (3^2 factorial designs)

The aim of the factorial design (3^2 = 2 variables at 3 levels) was to decide the stages of the three independent variables (Table 1) of balls and time which yield co-crystal with least particle size and more saturation solubility.

Characterization of co-crystals

Saturation solubility and particle size

The determination of saturation solubility performed by dissolving an identified surplus quantity of drug in distilled water, phosphate buffer, ethanol, methanol, isopropyl alcohol, and acetone. The suspensions were magnetically stirred at 20 rev/min for 48 h temperature ranges 38 ± 0.5 °C. Afterwards, at the end withdrawal of

Table 1 Translation of coded labels into the actual unit

Variable	Coded (level)= +1	level = 0	Uncoded (level) = −1
X_1 (No. of balls)	9	6	3
X_2(Time) (Min)	90	60	30

samples was done and a membrane filter of 0.45 mm is utilized for filtration. The resultant filtrates were properly diluted and analysis is done by employing a UV-visible spectrophotometer (Jasco V-500, Japan) at 263 nm. The find out results are shown in triplicate quantities and also their means were stated.

The laser light diffraction technique is used for particle size determination. The apparatus comprised of a Malvern Mastersizer 2000 (Malvern Instruments, Malvern, UK) through assessment of facts by Malvern software version 5.2.

FT-IR

To explore the potential chemical interfaces amongst the drug and the co-former, FT-IR spectral study analysis was done on the Fourier transform infrared spectroscopy (FT-IR) Spectrophotometer (JASCO FT-IR-8400 Tokyo, Japan); various samples were mixed with KBr and creased to create pellets by means 150 kg/cm^2 pressure. FT-IR spectra of PEG 4000, pure FNO and FNO co-crystal were scanned in the 4000–400 cm^{-1} range.

PXRD

The powder X-ray diffraction (PXRD) arrangements of pure FNO, pure FNO after ball milling and FNO Co-crystal noted down by means of an X-ray diffractometer (PW 1729. Philips, Netherland), using Copper as an anode material and crystal graphite monochromatic worked on 30 kV voltage apply and 30 mA of current. Upon Cu-Kα radiation, samples were exposed over 2θ angles from 2 to 50° range. The range and the graphing speed were 5 × 103 CPS and 10 mm/°2θ, respectively.

SEM

Scanning electron microscopy (SEM) study was done to evaluate co-crystal morphologically. Pure drug FNO and co-crystal were coated with a thin gold-palladium layers by Sputter coater unit (VG-Microtech, UK) and the superficial geography was investigated with a scanning electron microscope (SEM Jeol JSM 6360, Japan) worked at 10 kV of acceleration voltage.

Micromeritic properties

The flow properties were categorized in expressions of the angle of repose (θ), Carr's index and Hausner ratio. The angle of repose (θ) was determined by the procedure in which the handled drug samples were passed from the walls of a funnel that was secure at a place such that hard surface is 2.0 cm below from the lower tip of the funnel. The co-crystal was passed till period the lower tip of the funnel is touched to the upper tip of the pile surface. The standard value for the angle of repose is given (Table 2).

Table 2 The standard value of Angle of repose

Angle of repose	Flow properties
< 25	Excellent
25-30	Good
30-40	passable
>40	poor

The angle of repose (θ) calculated using Eq. (1) [17].

$$\mathrm{Tan}\,\theta = \mathrm{h}/\mathrm{r} \tag{1}$$

Where h = height of pile and r = radius of the pile

In a graduated cylinder, an accurately weighed quantity of powder blend was carefully discharged and initial volume was noted down. Afterwards, this was closed with the cover fixed on tap densitometer for 100 tapping and final volume was noted down. This procedure was followed three times. From these readings bulk density (BD), tapped density (TD) are calculated. The standard value for Carr's index is given (Table 3).

Carr's index and Hausner ratio were calculated using Eqs. (2) and (3) [18].

$$\text{Carr's Index} = [(\mathrm{TD}-\mathrm{BD})/\mathrm{TD}] \times 100 \tag{2}$$

$$Hausnerratio = (TD)/(BD) \tag{3}$$

Ex-vivo intestinal absorption study

Animals

About 210–240 g of weight healthy Wistar male rats, were procured from Shree farm, Neemgaon, Bhandara, Nagpur, Maharashtra, India. The rats were kept in polypropylene cages under controlled environmental conditions (24 ± 1 °C, 50 ± 2% RH), maintained at 12:12-h light/dark cycle with free access to standard laboratory diet and water. The animals fasted, then again delivered free access to water, medium-term earlier at the beginning of the test.

Non-everted rat intestinal sac model

The non-everted rat intestinal sac tests were completely dependent on the strategy depicted. The rats were anesthetized by ether inward breath after medium-term starving. And the pain response lost was checked. A cut is made on rat abdomen in middle ranging 4–5 cm, separate out the small intestine and taken for a wash by

Table 3 The standard value of Carr's Index

Carr's Index	Flow ability
5-10	Excellent
12-16	Good
23-35	Poor
>40	Very poor

Table 4 Effect of No. of balls & time on Saturation solubility and particle size distribution of co-crystal (n = 3, mean ± SD)

Batch No./ Runs	X1 (No. of balls) (….)	X2 (Time) (min.)	Saturation solubility (g/ml) (Y_1)	Particle size(nm)±S.D (Y_2)
FNOCC1	(+1) 9	30 (-1)	0.0603±0.02	1342.0±0.402
FNOCC2	(-1) 3	90 (+1)	0.1034±0.07	721.329±0.41
FNOCC3	(-1) 3	60 (0)	0.1969±0.08	453.459±0.23
FNOCC4	(0) 6	90 (+1)	0.0816±0.02	450.127±0.62
FNOCC5	(+1) 9	60 (0)	0.0703±0.01	443.189±0.603
FNOCC6	(+1) 9	90 (+1)	0.1142±0.05	974.665±0.512
FNOCC7	(-1) 3	30 (-1)	0.3874±0.32	221.231±0.456
FNOCC8	(0) 6	30 (-1)	0.1600±0.04	1371.818±0.510
FNOCC9	(0) 6	60 (0)	0.1206±0.03	1095.870±0.462

super cold regular oxygenated Krebs Ringer PBS solution of pH 7.4 employing a syringe furnished by sharp end. Then, lower end of ileum and the upper end of the duodenum were detached out into 10 ± 0.2 cm long sacs taking a width of 0.5 cm. Every single sac was secured at the individual end, occupied with 1 ml of a suspension of simulated intestinal fluid in which respective drug and processed drug co-crystal is uniformly dispersed (1 mg/ml) via a blunted pointer in the mucosal partition and was fixed by securing another end [19].

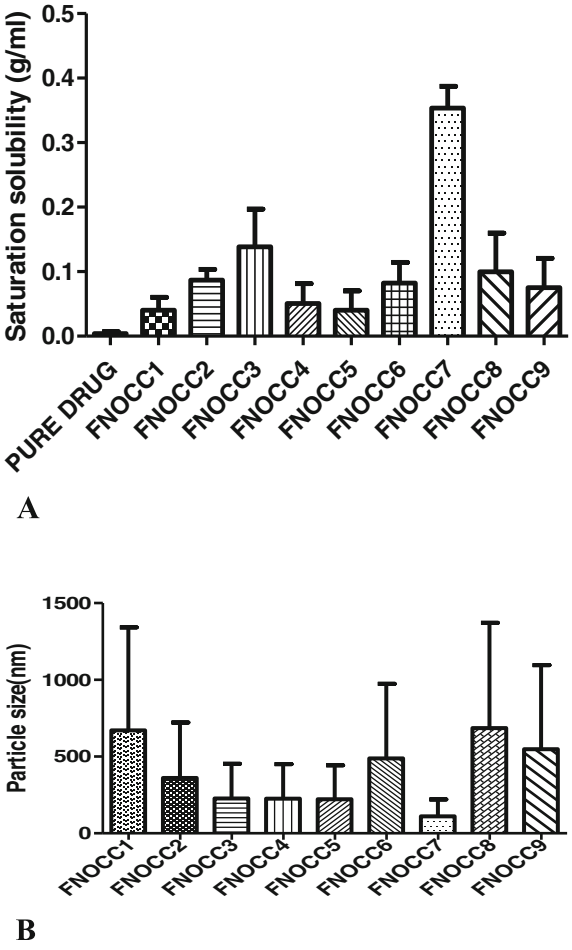

Fig. 2 a Saturation solubility of pure drug and fenofibrate co-crystals. **b** Particle size distribution of fenofibrate co-crystals

Every non-everted rat intestinal sac was set in a 100 ml glass beaker holding 90 ml fusion of Krebs Ringer phosphate buffer saline solution pH 7.4 and isopropyl alcohol (8:3 v/v) preserved at 38 °C in a shaky water bath working at 50 rpm and always circulated air through by oxygen (10–16 bubble/min) by lab aerator. At times interval, test samples were taken from outdoor of sac (serosal partition) meant for 4 h and supplanted through new fresh medium each time. Afterwards, filtration is done by Whatman filter paper No. 41 (Whatman, Middlesex, UK), the concentration of FNO found out using UV-visible spectrophotometer 263 nm.

Preparation of solid unit dosage form

The optimized batch of FNO co-crystal with optimum parameters was prepared in solid unit dosage form using different excipients and co former, sodium starch glycolate, lactose, and magnesium stearate, polyvinyl pyrrolidone. Finishing preparations were delivered from a 16 mesh screen and were directly compressed by 10 punch position tablet machine, via 8 mm and 11 mm diameter across round punches with level countenances. The machine setting was in tune to produce tablets of 500 mg weight with a hardness of about 5.5 ± 0.25 kg/cm^2. Compressed tablets every one comprising of 500 mg of FNO was set up by direct pressure strategy utilizing starch curved in punches as a specifically compressible vehicle. Every one of the ingredients essential according to the formulations was mixed in a sealed polyethylene bag. The mixtures were compressed into tablet pressing machine (Bimix Machinery Co. Pvt. Ltd) to a

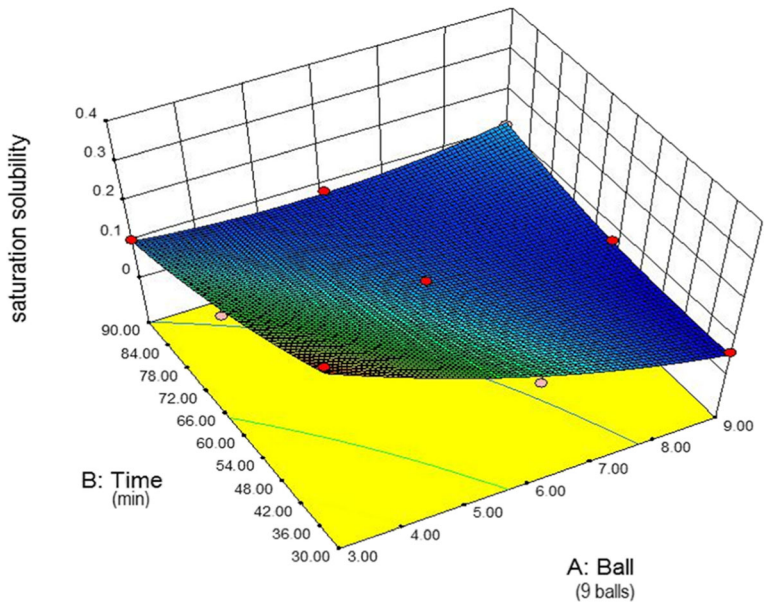

Fig. 3 Response surface curve showing effect of number of balls and time on Saturation Solubility

hardness of 5.5 ± 0.25 kg/cm^2 using 9 mm concave punches.

Assessment of solid unit dosage form

Hardness The hardness of the tablet was dignified using Monsanto hardness tester by placing the tablet between the anvils and measured the force required to break the tablet.

Friability Ten tablets from each batch were correctly weighed and positioned in the friability test apparatus (Roche friabilator). Apparatus was operated at 100 rpm for 4 min. The tablets were taken out after 100 rotations,

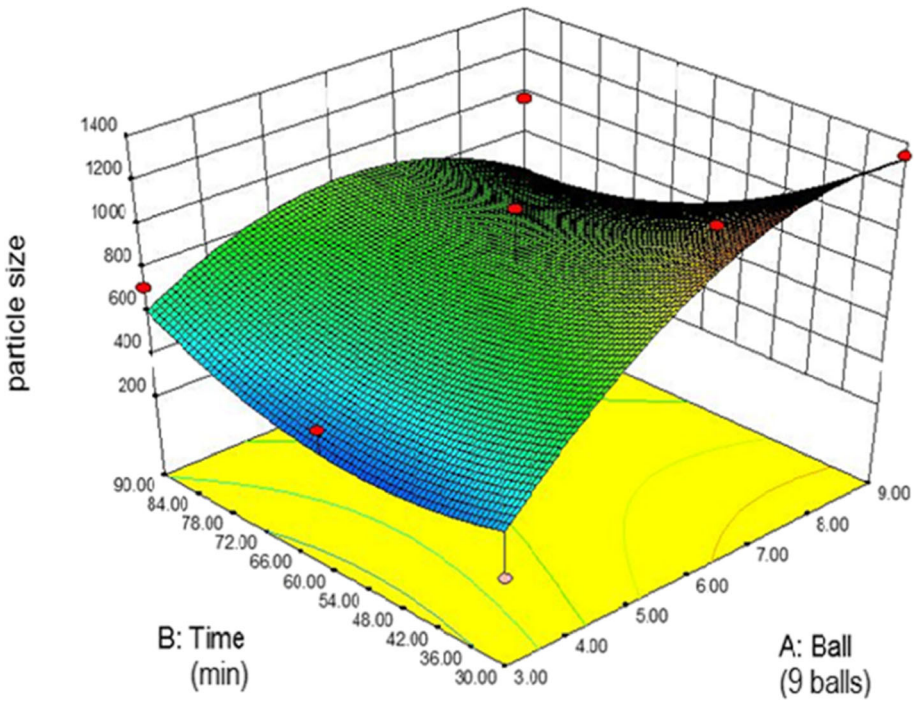

Fig. 4 Response surface curve showing effect of number of balls and time on Particle Size

dedusted, and reweighed. The friability was calculated as the percentage weight loss by following formulae given below. The % friability of formulation is shown (Table 8) [20].

$$\%\text{Friability} = (W_o - W)100/W \quad (4)$$

Where W_o = initial weight of the tablets before testing
W = final weight of the tablets after testing

Disintegration test Disintegration test is performed by the USP method (Lab India tablet disintegration test machine model: DT 1000) in which 6 glass tubes, 3 in. long, top open and hold on the 10 in. the screen at the lowest end of the basket rack assembly. About 900 ml of PBS pH 7.4 at 37 ± 2 °C is taken at basket rack and 1 tablet in every tube is placed. When the tablet is completely disintegrated the disintegration time is noted down.

In vitro dissolution study The paddle type dissolution test apparatus (USP type II) is used for in vitro dissolution study. In that tablet containing 500 mg of FNO and phosphate buffer, pH 7.4 was used as the dissolution media with temperature sustained at 37.0 ± 0.5 °C at 100 rpm. The volume of sample (1 ml) was withdrawn at (0, 5, 15, 30, 45, 60, 120 min) interval, passed through Whatman filter paper (No. 41) diluted properly for cumulative drug release using UV-visible spectrophotometer at 263 nm.

Stability study A stability study for processed crystals was accomplished by storing it in closed glass vials at ambient temperature and under accelerated conditions of 40 ± 2 °C/75 ± 5% relative humidity (RH) for up to 3 months as per ICH guidelines.

Results

Saturation solubility and particle size

The aim of the factorial design (3^2 = 2 variables at 3 levels) was to conclude the levels of the three independent variables (Table 4) of balls and time which yield co-

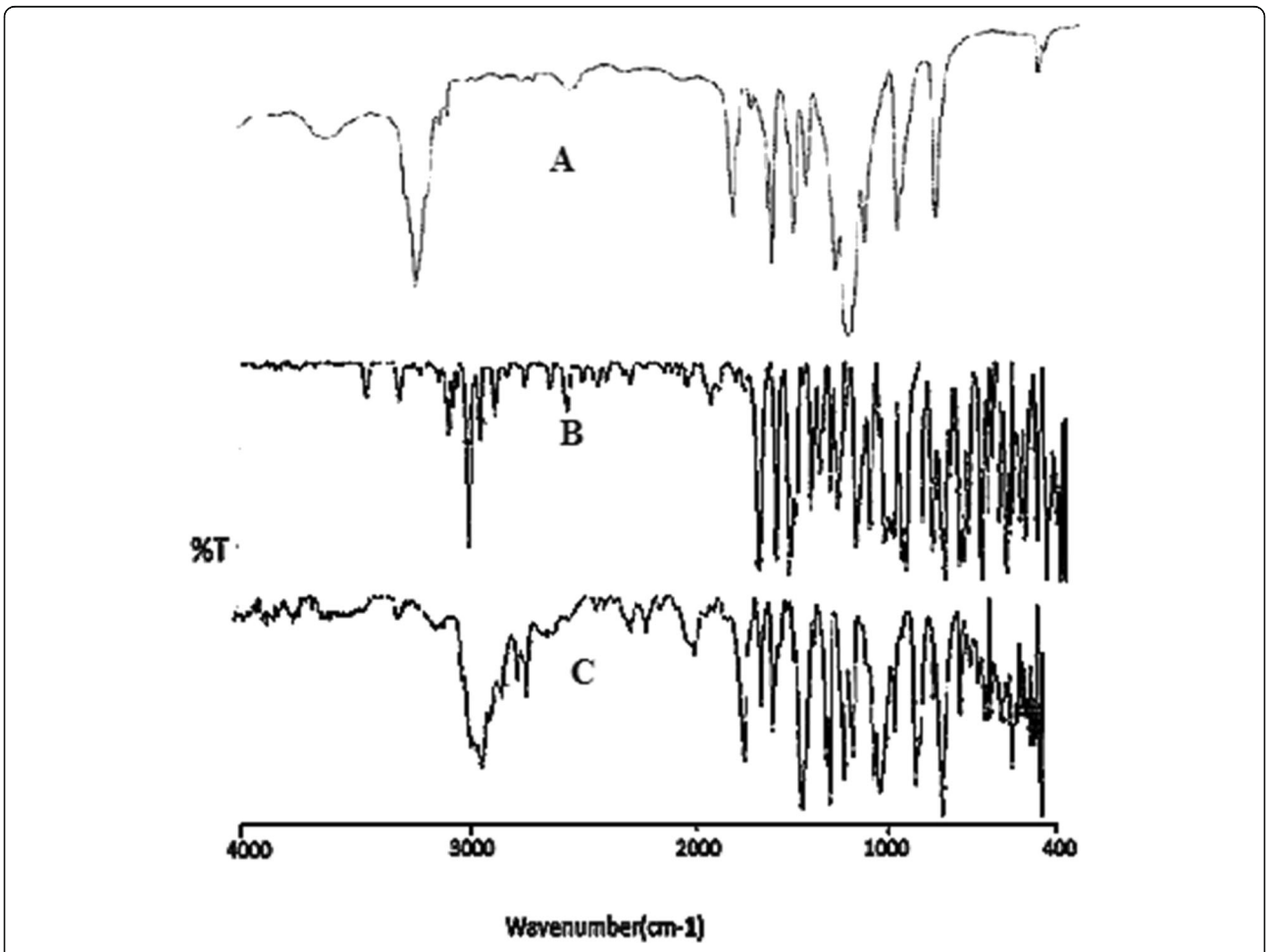

Fig. 5 FT-IR spectra of (**a**) PEG 4000 (**b**) Pure Fenofibrate (**c**) Fenofibrate Co-crystal

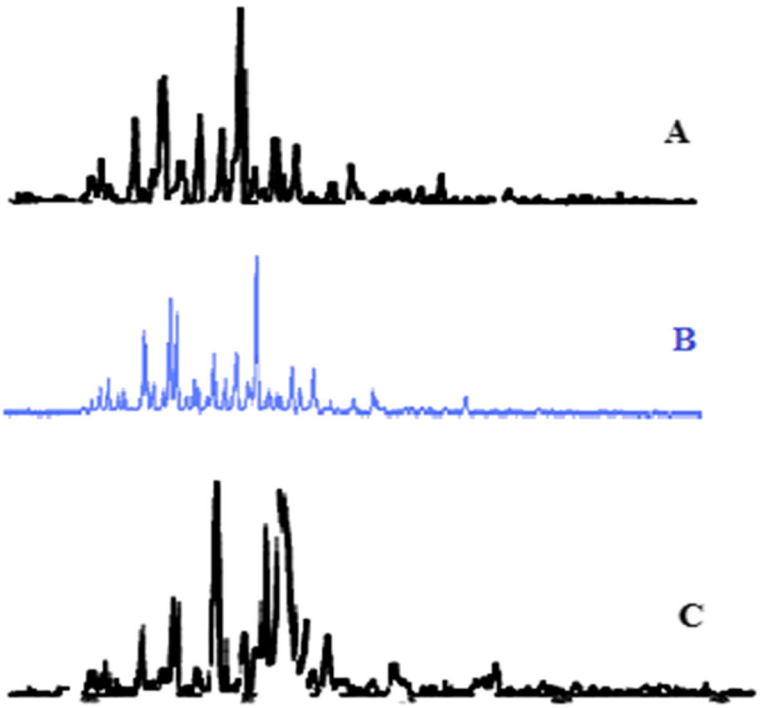

Fig. 6 PXRD spectra of (**a**) Pure Fenofibrate and (**b**) Pure Fenofibrate after Ball milling (**c**) Fenofibrate Co-Crystal

crystal with minimum particle size and maximum saturation solubility (Fig. 2a, b).

Effect on saturation solubility

$$Y_1 = 0.11 - 0.74X_1 - 0.051X_2 + 0.084X_1X_2 + 0.035{X_1}^2 + 0.022{X_2}^2 \quad (5)$$

Values of correlation coefficient indicate a fair fit (R^2 = 0.5701). The impact of process parameters, i.e., a number of balls and time are studied in equation (5). Particle size denotes a negative influence for X_1(no. of balls) and X_2 (time) where a negative influence on saturation solubility was observed that is supported by the response surface plot (Fig. 3).

Effect on particle size

$$Y_2 = 850.8 + 227.4X_1 - 131.5X_2 - 276.9X_1X_2 - 279.9{X_1}^2 + 182.7{X_2}^2 \quad (6)$$

Values of correlation coefficient indicate a fair fit (R^2 = 0.9847). Response surface model graph (Fig. 4) and equation (6) depicts the impact of a number of balls (X_1)

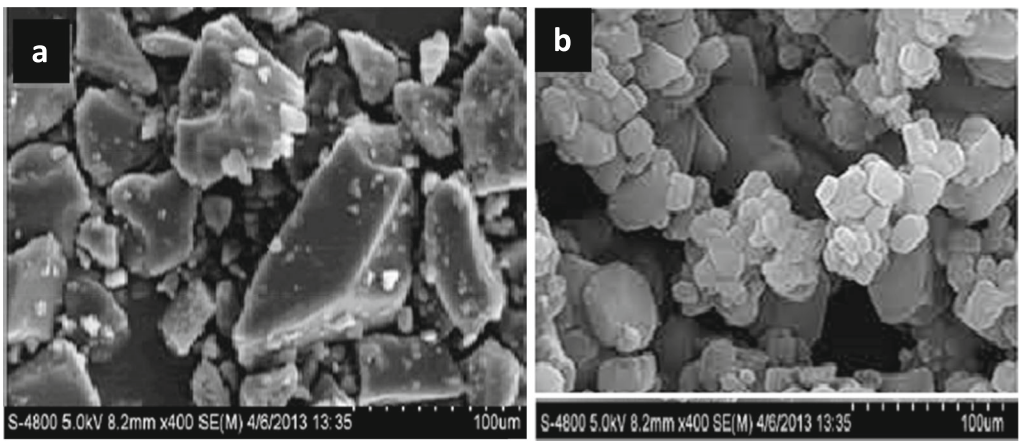

Fig. 7 SEM images of **a** pure fenofibrate and **b** fenofibrate co-crystal

and time (X_2). According to equation (6), X_1 showed predominant positive impact as compared to (X_2) resulting in increased particle size increasing within the X_2; this might be due to the longer amount of time applied results in the re-bonding between the particles and turning to the agglomeration.

Fourier transform infrared spectroscopy

The status of the drug with functional groups peak in co-crystal along with new peaks was examined by FTIR. Figure shows (Fig. 5) FT-IR spectra of PEG 4000, pure drug FNO and prepared co-crystals respectively. The changes in IR peaks of FNO in prepared co-crystals compared to pure FNO drug thereby indicating the hetero-molecular interaction, the presence of hydrogen bonding had occurred in the co-crystals. The peak at 2926.45 cm-1 indicated aromatic C-H stretching, peak at 1674.87 cm-1 indicated C=O stretching whereas, peaks at 1220 and 1033.66 cm-1 indicated aralkyl and dialkyl ether C-O stretching, respectively. In co-crystal spectra there is no peak within range of 2700-3300 cm-1 was observed suggesting the possibility of O-H bridging between C=O of FNO and O-H of PEG 4000.

Powder X-ray diffraction analysis

PXRD was a potent technique for the evaluation of the development of an innovative crystal-like phase in a compact state. If an accurate co-crystal has been molded amongst dual solid phases, then spreading pattern of co-crystal would be clearly different after superimposition of every of the compound. In three-dimensional arrangement, crystal is periodically settled but amorphous substances have not periodicity and atoms are casually dispersed in three-dimensional space. The point at which X-rays are sprinkles by atom is noted down if the periodic organization found the sprinkling is only specific direction when they knock out the designed lattice planes, the high-intensity peaks are formed. Apart from the amorphous phase, the X-rays will be sprinkles in numerous ways prominent to an enormous collision dispersed in a wide array (2Θ) as an alternative of great strength narrower peaks. Thus, we can see the large bumpy pattern distributed in a wide range in Fig. 7. Thus, the saturation solubility of co-crystal is higher than that of pure FNO due to its crystalline nature. As we can see, the change in characteristic peaks of co-crystal as compared with pure FNO may be due to the co-former PEG (Fig. 6).

Scanning electron microscope

In the microphotographs of pure FNO (a), crystal of bigger and regular shape with apparently smooth surface.

Table 5 Micromeritic properties of Fenofibrate Co-crystal (FNOCC7) (n = 3, mean ± SD)

Parameters	Result
Angle of Repose(^{0})	21.4±0.173205
Carr's Index	11.8±0.31
Hausner Ratio	1.133±0.01
Tap Density	1.254±0.05 g/ml
Bulk Density	1.106±0.07 g/ml

The microphotographs (b) shows prepared cocrystals of FNO, from that it was observed that fenofibrate showed large crystals while cocrystals of co-former showed small, uniform crystals. Cocrystals of FNO reduced crystallinity as compared to pure Fenofibrate (Fig. 7). It was also confirmed by PXRD study.

Micromeritic properties

The flow properties characterized showed that angle of repose and Carr's index was brought into being to 21.4 and 11.8 respectively which were within the range for good flow of powder (Table 5).

Permeation study

Standard calibration of FNO was drawn by plotting absorbance v/s concentration using UV-visible spectrophotometer. FNO followed Beer-Lambert's in the concentration series of 10–50 μg/ml at λ_{max} of 263 nm. The calibration curve of FNO was linear (y = 0.0115x + 0.0071) with its correlation coefficients being 0.996. The penetrability of drug applicants over the GI mucosa is a standout amongst the most critical aspects in characterizing their bioavailability and biotic activity. Various in vivo, in situ, and in vitro models are accessible to execute GI absorption of drugs, for example, synthetic membrane, cultured cells, isolated tissues, and body part perfusions. Regularly, these prototypes look for cooperation amongst their amount and prescient perspective.

The plots of the amount of FNO absorbed from the crystal in the intestine (duodenum) at various time intervals. Subsequently executing a linear regression investigation, the slope was taken as the permeation flux (F, μg/min). The apparent permeability coefficient (P_{app} cm/min) was determined according to the Equation (7),

Table 6 Permeation flux and apparent permeability coefficient of FNO and its Co-crystal formulation (FNOCC7) (n = 3, mean ± SD)

Samples		F, flux (μg/min)	P_{app} x10^{-5} (cm/min)
Intestinal non-everted sac	Pure drug	0.014±0.141	3.86±0.167
	FNOCC7	0.322±0.068	5.38±0.093

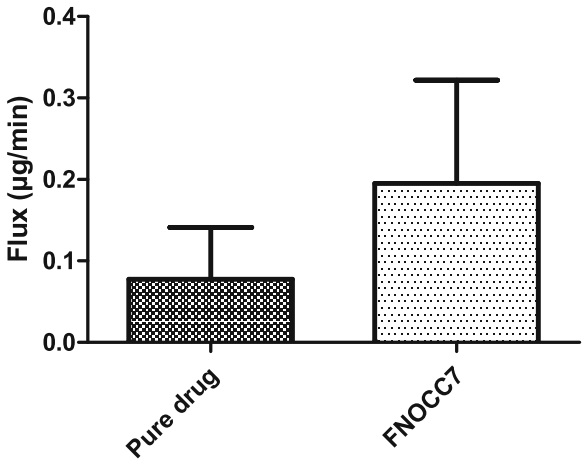

Fig. 8 Permeation flux of fenofibrate pure drug and fenofibrate co-crystal formulation (FNOCC7) in non-everted rat intestinal sac model

$$P_{app} = \frac{F}{SA \times Co} \quad (7)$$

Where, F is flux (slope of linear regression analysis), SA is surface area of intestine (0.75 cm^3), C_0 is an initial concentration of drug (μg/ml).

The rate of permeation (flux, F) of pure fenofibrate and its co-crystal formulation (FNOCC7) was observed to be 0.014, 0.322 μg/min, respectively (Table 6). The apparent permeability coefficient (P_{app}) of pure FNO and co-crystal was observed to be 3.86 × 10^{-5}, 5.38 × 10^{-5} cm/min, respectively (Fig. 8).

Solid unit dosage form

Based upon the above results of saturation solubility, particle size distribution, permeation flux, and apparent permeability coefficient the FNOCC7 formulation of co-crystal are optimized for further solid dosage form preparation (Table 7). Entire tablets formulated were assessed for the content of active components, hardness, friability, and disintegration time and dissolution rate as per authorized (IP) methods. Monsanto hardness tester was utilized for hardness determination, and Roche friabilator is employed for friability calculations. Lab India tablet disintegration test machine (model DT 1000) was used for disintegration time determination (Table 8).

Table 7 The composition of prepared solid unit dosage form

S.No	Drug & Excipients	Composition
1.	Fenofibrate co-crystal (Equivalent to Fenofibrate 500mg)	760mg
2.	Sodium starch glycolate	75mg
3.	Lactose	149mg
5.	Polyvinyl pyrrolidone	75mg
4.	Magnesium stearate	1mg

Table 8 Evaluation parameters of tablet of Formulation containing co-crystal (n = 3, mean ± SD)

Batch	Hardness (kg/cm^2)	Friability (%weight loss)	Disintegration time (min)
CCT	5.12±0.21	0.58±0.08	5.40±1.63

In vitro dissolution study

In vitro dissolution outlines of the tablet of Formulation containing co-crystal (CCT) manufactured by wet granulation. In vitro rate of dissolution of CCT enhanced in comparison to the pure drug. The dissolution percentage of FNO pure drug was precise low; with 2.1% dissolution in 30 min. Dissolution of prepared CCT was significantly enhanced (15.998% release in 30 min). The drug dissolution of above 69.67% was obtained in 120 min, and the marketed formulation is 21.61% release in 120 min (Table 9). The significant increase in the rate of dissolution accredited to the greater hydrophilic appeal of the co-ordination owing to the existence of water-soluble polymer and that portion of the drug dissolution (Fig. 9).

Stability study

The formulation containing co-crystal (CCT) were charged on accelerated stability condition (40 °C, 75%RH) for drug content at 1, 2, and 3 months. The data found shows that there is no significant deviation in appearance, content pure FNO drug and optimized co-crystal up to 3 months (Table 10).

Discussion

In saturation solubility, the negative distinguished impact of X_1 and X_2 indicates that if the number of balls is reduced together with time, enhancement in saturation solubility is observed. This can be supported by the comminution process of the imparting energy, fracture and cleavage of particles occurring when extreme tensions are functional that yield fragments of size 50–80 make the most the size of the preliminary particle size. The positive

Table 9 The drug release profile of Pure FNO, Formulation containing co-crystal (CCT) and Marketed formulation (n = 3, mean ± SD)

Time	% drug release of Pure drug	% drug release of Formulation containing Co-crystal(CCT)	% drug release of Marketed
0	0	0	0
5	0.676±0.555	0.926±0.325	2.786±0.325
15	1.986±0.642	7.364±1.024	4.987±0.554
30	2.109±0.552	15.998±1.554	7.988±0.685
45	2.768±0.578	23.987±2.055	10.766±0.885
60	3.654±0.702	32.986±3.688	14.559±1.525
120	10.39±0.924	69.67±5.326	21.618±3.544

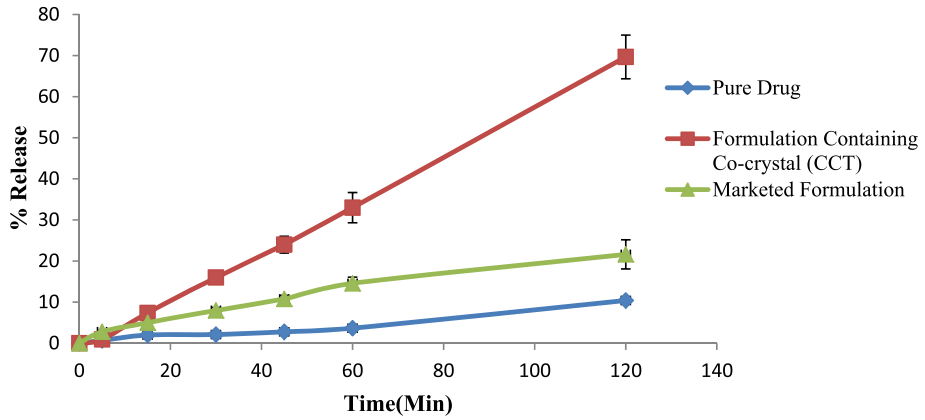

Fig. 9 Dissolution profile of pure drug (blue line), formulation containing co-crystal (CCT) (red line) and marketed formulation (green line) (n = 3, mean ± SD)

value (0.084) of the interaction term X_1X_2 attributes to slight decrease within the saturation solubility. This may be because of low attrition and impaction mechanism of the colliding balls that disrupts their binding force as in (X_2). The rise in a number of balls consequence in a reduction in saturation solubility as an outcome of increasing the number of balls occupies over 50% of the interior volume of the mill leading to fewer voids.

The curvilinear graph explains the increase within the particle size with an increase within the number of balls as shown in X_1 whereas, X_2 shows the relatively opposite relationship as mirrored in equation (6). At the initial time, particle size determined was low because the particles might have occupied 50% of the volume of mill resulting in high friction between the particles however because of increase is the time alongside along with of balls the particle size was found to be increased. The rise in particle size can be owing to excessive aggregation of particles carried out because of the increase within the number of balls. However, the pronounced positive signs of constant b0 could also be because of less contact with the physical mixture throughout the fragmentation method and resulting in the coarser particle size in the incidence of each the method parameters.

Non-everted rat GI sac demonstrates a broadly utilized procedure to anticipate in vivo human absorption kinetics and bioavailability of combinations with reduced water dissolvability, poor stability and could give data almost drug absorption mechanism. The situation favorable circumstances above the everted sac show are the straightforward arrangement, necessities a smaller amount of test sample, permits the progressive accumulation of serosal tests with not as much of GIT morphological variations. Hence, this strategy was utilized to evaluate the absorption of FNO in rat stomach as well as intestine with the end goal to discover the site-subordinate ingestion of FNO beginning the rat abdominal region. The rate of permeation (flux, F) of pure fenofibrate and its co-crystal formulation (FNOCC7) was observed to be 0.014, 0.322 μg/min, respectively. The apparent permeability coefficient (P_{app}) of pure FNO and co-crystal was observed to be 3.86×10^{-5}, 5.38×10^{-5} cm/min, respectively.

The enhanced rate of dissolution of formulated CCT can be accredited to a rise in the superficial extent of FNO subsequently adsorption onto the drug and polymer in the case of Co-crystal comprising Polyethylene glycol, as the meltable binder the dissolution rate, was enhanced as related to the pure drug.

Table 10 Stability study of Formulation tablet contained Co-crystals (n = 3, mean ± SD)

Parameters	Accelerated condition (40°C,75%RH)			
	Formulation containing co-crystal (CCT)			
Sampling Intervals	Initial	1 month	2 month	3 month
%Drug content	98.41±0.19	97.78±0.41	96.89±0.22	96.81±0.71

Conclusions

The solubility and dissolution percentage of FNO can be improved by the utilization of co-crystal of FNO with PEG 4000. The solubilization impact of PEG 4000 might be contributed because of decrease of molecule conglomeration of the presence of the drug crystallinity, expanded wettability, and dispersibility; pharmaceutical co-crystals speak to a beneficial class of crystal form with regard of pharmaceuticals. Co-crystals of drugs and drug aspirants speak to another kind of material for pharmaceutical development. Co-crystals are moderately new to the pharmaceutical industry, and pharmaceutical co-crystals have given another course to manage issues of inadequately with problems of poorly soluble drugs. Co-crystals can possibly be significantly more helpful in pharmaceutical substances

than solvates or hydrates. The importance of co-crystals in API definition incorporates the capacity to adjust physical properties, characterization of API, distinguish and grow novel, exclusive systems of recommended drugs and the coincidental to produce protected innovation.

Abbreviations

BCS: Bio-pharmaceutics classification system; BD: Bulk density; CCT: Formulation containing co-crystal.; CPCSEA: Committee for Purpose of Control and Supervision of Experiments on Animals; FNO: Fenofibrate; FNOCC7: Fenofibrate containing co-crystal formulation; FT-IR: Fourier transform infrared spectroscopy; ICH: International Conference on Harmonization; P_{app}: Permeability coefficient; PEG 4000: Polyethylene glycol 4000; PVP: Polyvinyl pyrrolidone; PXRD: Powder X-ray diffraction; RPM: Rotation per minute; SEM: Scanning electron microscopy; SLN: Solid lipid nanoparticles; TD: Tapped density; USP: United State Pharmacopoeia

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Authors' contributions

SR designed the study and developed the methodology. RJ performed the experiments. WA wrote the manuscript. NG contributed to manuscript revision and provided supervision. All authors reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ex vivo intestinal permeation study work was completed at Guru Ghasidas Vishwavidyalaya, according to the protocols permitted by the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, under the reference no. 73/IAEC/Pharmacy/2014 on the recommendations of the Institutional Animal Ethical Committee of Guru Ghasidas Vishwavidyalaya (Bilaspur, India).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflict of interests.

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