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Enhancement of solubility and dissolution rate of Fenofibrate by melt granulation technique

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ABSTRACT: This work describes a melt granulation technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug Fenofibrate (FNO). Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable polymers and surfactants. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because of bypassing drying step, the process is less time consuming and uses less energy than wet granulation. Granules were prepared by using hydrophilic polymer PEG (polyethylene glycol-6000) and surfactant (poloxomers-407). The prepared granules were characterized using powder XRD, DSC and FTIR techniques. A significant enhancement in the solubility and vitro dissolution profiles of the melt granules was observed compared to the pure drug and drug excipient physical mixtures. DSC results indicated change in internal energy of FNO with polymer and surfactant in the melted granules. In conclusion, the results of this work suggest that melt granulation is a useful technique to enhance the solubility and dissolution rate of poorly water-soluble drug like, FNO.

KEY WORDS: Fenofibrate, surfactants, melts granulation, Dissolution, polyethylene glycol, wettability.

INTRODUCTION:

Combinatorial chemistry and high throughput screening are modern techniques in drug research. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to the Biopharmaceutics Classification System [1] . These drugs are poorly water soluble, but once they are dissolved they are easily absorbed through the gastro-intestinal membrane[2,3] Therefore, the bioavailability after oral administration can be improved by enhancement of the dissolution rate [4].One of the approaches to enhance the dissolution rate is the use of fully amorphous solid dispersions[5,6]. A solid dispersion for such application is a system composed of a hydrophilic matrix in which a poorly soluble drug is dispersed. The enhanced dissolution rate of drugs from these solid dispersions is mainly based on four different mechanisms [7,8,9,] :

1. Wetting of the drug is improved by direct contact of the drug with the hydrophilic matrix,
2. The saturation concentration around small particles is higher than around large particles [10] ,
3. The surface area is increased.
4. The drug has higher energy in the amorphous state than in the crystalline state, through which the saturation concentration is increased[11,12] .

In recent years, the interest in melt granulation has increased due to the advantage of this technique over traditional wet granulation method. The water or organic solvents required for granulation are elimination in the melt granulation process. The used solvents in granulation may originating risk of residual solvents; moreover, in melt granulation the drying step is not necessary, thus the process is less consuming in terms of time and energy as compared to wet granulation[13] .The apparatus of choice for melt granulation are the high shear mixers, where the product temperature is raised above the melting point of the binder either by using a heating jacket or via the heat of friction generated by the impeller blades, when the impeller speed is high enough.

Now days, melt granulation technique has been successfully employed to improve the solubility and dissolution rate of poorly soluble compounds and the technique has proved that melt granulation can be used to enhance the in vitro dissolution rate of different pharmaceuticals, employing poloxamer-188 as a melting binder which is mostly used surfactant. The objective of this work was to evaluate the feasibility of the melt granulation technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug Fenofibrate.

Fenofibrate (FNO) (isopropyl ester of 2-[4-(4-chloro-benzoyl) phenoxy]-2-methylpropanoic acid) is a widely used hypolipidemic drug. Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma. Solubility and permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to the Biopharmaceutics Classification System (BCS), FNO is a Class II having low solubility and high permeability. Bioavailability of FNO solely depends on dissolution rate in the gastrointestinal tract. This drug is used mostly in lipid regulation as it

decreases low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) levels, and increases high-density lipoprotein (HDL) level[14].

In the present work, the feasibility of fast-release rate granules by melt granulation has been considered. FNO was chosen as a water-insoluble model drug and PEG, poloxamer as a hydrophilic polymer and surfactant. Polyethylene glycol (PEG) and poloxamer were employed as a melting binder, in consideration of its favourable solution properties, low melting point, rapid solidification rate, low toxicity and low cost. In-vitro release of the drug from the granules was investigated and compared with the pure drug and drug excipient physical mixtures. Differential scanning calorimetry, X-ray powder diffraction and Fourier transform infra red spectroscopy (FTIR) were utilized to investigate the chemistry and crystallinity of the system.

MATERIALS AND METHODS:

Materials:

Fenofibrate was supplied as a gift sample from Alembic Research Ltd (Vadodara, India). Poloxamer 127 (Pluronic F-68) and Polyethylene glycol (PEG-6000) were procured from Lupin Research Park (Pune, India). Sodium Laurel Sulphate (SLS) and other raw materials were procured from S. D. Fine (Mumbai, India).

Preparation of the granules,Physical Mixtures:

Melted granules were prepared in a porcelain dish. Firstly, the mixture of FNO with hydrophilic polymer (Polyethylene glycol) or surfactant (poloxamer-127) mentioned in Table:1 was dry blended for 10 min .Then, this mixture was placed in hot porcelain dish and supply the heat around 60^0C on temperature controlled water bath so as to melt the polymers or surfactant in which the drug was dispersed .The formed molted mass is then cooled to room temperature and at the end of the granulation process the granules were allowed to solidify at room temperature by spreading them in thin layers on glass plates. Pass the melted dried granules through sieve no # 20 so as to form uniform granules. The cooled granules were stored in sealed bags for their evaluation. Prepared the physical mixtures of the same formulation and compared the solubility and dissolution rate with the melt granules.

Yield and Drug Content:

The prepared melt granules were weighed after drying, and process yield was calculated.

Melted granules (200mg) were powdered, from which powder equivalent to 20 mg FNO was weighed and extracted using three portions of 100mL 0.1M SLS. Each portion was filtered through a G-4 sintered glass filter and volume was adjusted to 100 mL.After sufficient dilutions with 0.1N SLS, samples were analyzed spectrophotometrically at 290nm and FNO content was calculated.

Saturation Solubility Studies:

Saturation solubility studies were carried out using deionized water as a solvent. Each excessive quantity (50 mg) of FNO and equivalent prepared melt granules were taken in screws capped test tubes with fixed volume (10 ml) of deionized water. The resultant suspension was treated at 37^o C with 100 rpm in incubator shaker. After 24 hr samples were withdrawn and filtered through 0.2µ filters (Ultipor®N_{66}, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with deionized water and analyzed at 290 nm by UV-visible spectrophotometer (Pharma spec 1700, Shimadzu Corporation, Kyoto, Japan).

In-vitro Dissolution Studies:

A LABINDIA Disso 2000 (Mumbai) dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and samples was carried out on an equivalent of 50 mg of the FNO in 0.1 M SLS as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2 ^{0}C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and replace the same fresh dissolution media so as to maintain sink condition. These samples were assayed through ultraviolet absorbance measurement at 290nm using UV-Visible Spectrophotometer (Shimadzu UV-1700, Japan) by an analytically validated method (r^2 = 0.9992). To increase the reliability of the observations, the dissolution studies were performed in triplicate[14] .

Fourier transform infra red spectroscopy (FTIR):

FT-IR spectra of prepared melt granules were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Powder X-Ray Diffraction (PXRD):

Crystallinity of the drug and the samples was determined using the Philips Analytical XRD

(Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the difffractometer and scanned over a range of 2 values form 10 to 80 ^{0} at a scan rate of 0.05 ^{0}/min.

Differential Scanning Calorimentry (DSC):

Thermal properties of the untreated drug and the prepared agglomerates were analyzed by DSC (TA Instruments, USA, and Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 ^{0}C at a heating rate of 10 ^{0}C/ min, using nitrogen as blanket gas

Flow Properties: Flow properties of the drug and prepared melt granules were studied by determining the bulk density ($_b$), tap density ($_t$), Carr's Index and Hausner ratio. A weighed quantity of the samples was taken to determine the bulk and tap density. The properties were determined using following equations.

Bulk density ($_b$) = Mass / Poured volume (1)

Tap density ($_t$) = Mass / Tapped volume (2)

Carr's Index = [($_t$ – $_b$) / $_t$] x 100 (3)

Hausner ratio = ($_t$ / ($_b$) (4)

Wettability/ Powder Bed Hydrophilicity Study:

The untreated drug and prepared melted granules were placed on a sintered glass disk forming the bottom of glass tube on which methylene blue crystals were placed. The whole device was brought into contact with water. Measure the time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals was noted. Minimum is the time required to reach the water to surface maximum is its wettability.

Stability Studies:

Stability studies for the samples were carried out as per ICH guidelines. The samples (each 10mg, n=3) were kept for stability studies at 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months in environmental test chamber (HMG INDIA, Mumbai). The samples were kept in glass vials sealed with rubber plugs. After 30, 60 and 90 days, the samples were taken out and analyzed for appearance, drug content and dissolution study.

Table: 1 Product coding and solubility of melt granules and their dispersions with polymer and surfactant.

Sr.No:	Composition	Drug:Excipients ratio	Coding	Solubility* (mg/ml)
1	Fenofibrate (API)	------	FNO	0.087±0.001
2	**Melt granules**			
2A	Fenofibrate:PEG	1:1	FNO-PEG1	0.376±0.035
2B	Fenofibrate:PEG	1:2	FNO-PEG2	0.456±0.026
2C	Fenofibrate:Poloxamer	1:1	FNO-POL1	0.415±0.019
2D	Fenofibrate: Poloxamer	1:2	FNO-POL2	0.523±0.032
3	**Physical mixture**			
3A	Fenofibrate:PEG	1:1	FNO-PEG1(PM)	0.092±0.001
3B	Fenofibrate:PEG	1:2	FNO-PEG 2(PM)	0.112±0.001
3C	Fenofibrate:Poloxamer	1:1	FNO-POL1(PM)	0.098±0.001
3D	Fenofibrate: Poloxamer	1:2	FNO-POL2(PM)	0.125±0.010

* Each value represents mean ± S.D. (n = 3)

Table: 2 Technological characterizations of FNO and prepared melt granules.

Characteristics	**FNO**	**FNO-PEG2**	**FNO-POL2**
Production yield (%)*	-------	98±0.085	97 ±0.045
Content (%)*	98±0.060	94±0.075	95±0.098
Bulk density (gm/ml)*	0.525±0.056	0.575±1.023	0.585±0.028
Tap density (gm/ml)*	0.655±0.085	0.655±0.026	0.665±0.065
Compressibility Index(CI)*	19.85±0.023	12.21±0.076	14.16±0.057
Hausner ratio*	1.25±0.045	1.14±0.089	1.14±0.089
Flow time 100 ml/s*	28.56±0.057	21.54±0.019	20.88±0.049

Table: 3 Stability study data of TEL and prepared granules at accelerated conditions.

Parameters	**Accelerated condition (40^0C,75%RH)**											
	FNO				**FNO-PEG2**				**FNO-POL2**			
Duration	**Initial**	**1M**	**2M**	**3M**	**Initial**	**1M**	**2M**	**3M**	**Initial**	**1M**	**2M**	**3M**
Content %)	98.0	97.0	96.0	96.0	96.0	96.0	95.0	95.0	97.0	96.0	96.0	95.0
Dissolution	**%Cumulative Drug Release (%CDR)**											
10 min.	12	12	10	11	42	40	38	37	55	53	52	54
20 min.	19	20	18	17	55	58	58	54	67	65	63	66
30 min.	27	25	22	23	64	63	65	63	75	76	75	74
45 min.	35	33	30	29	75	74	77	73	87	84	83	85
60 min.	40	38	35	34	92	90	92	88	95	93	92	92

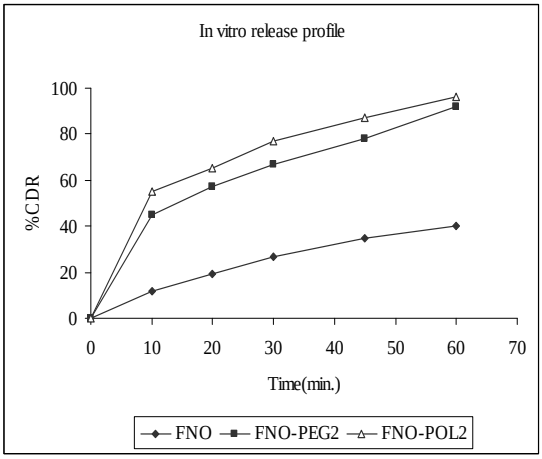

Figure: 1 In vitro release profile of FNO and its optimized melt granules

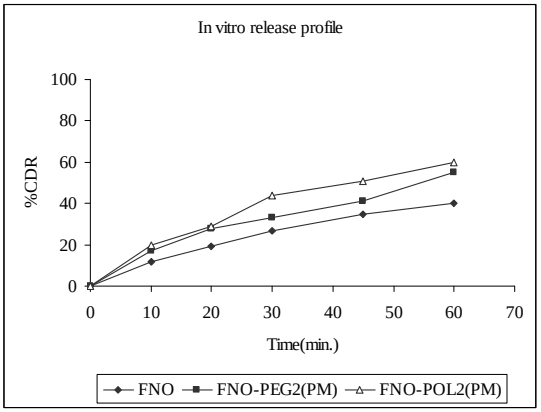

Figure: 2 In vitro release profiles of FNO and its physical mixtures

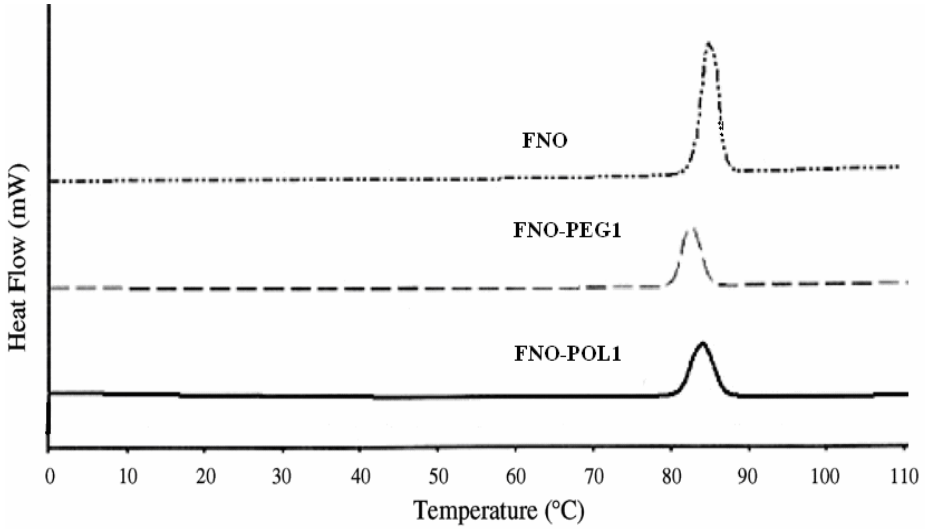

Figure: 3 DSC of the raw Fenofibrate (API) powder and melt granules prepared from PEG and Poloxamer

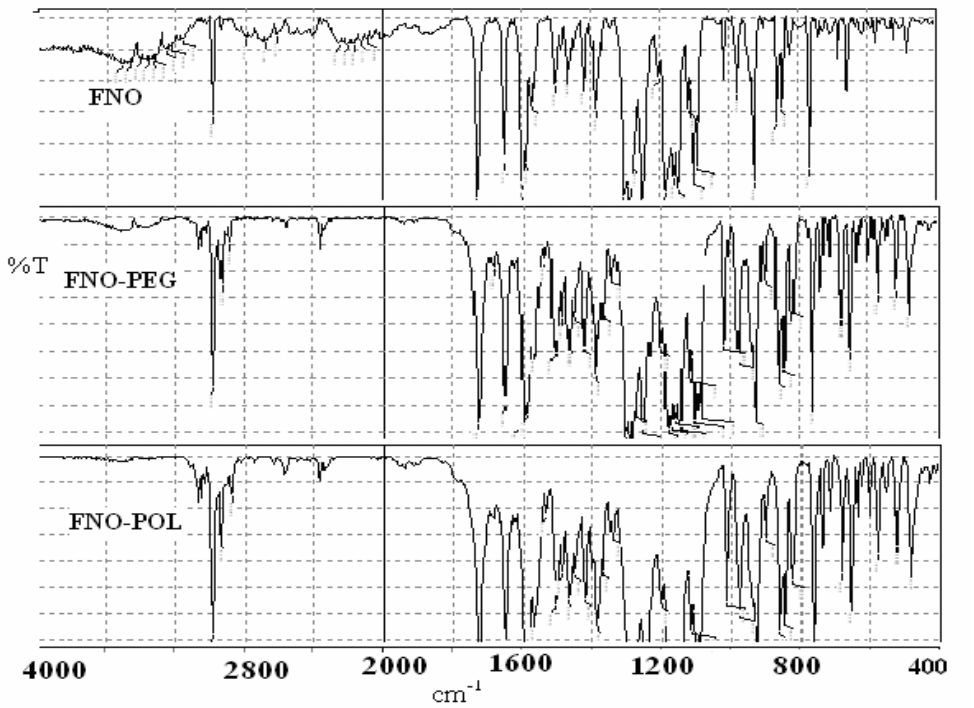

Figure: 4 FTIR of the raw Fenofibrate (API) powder and melt granules prepared from PEG and Poloxamer.

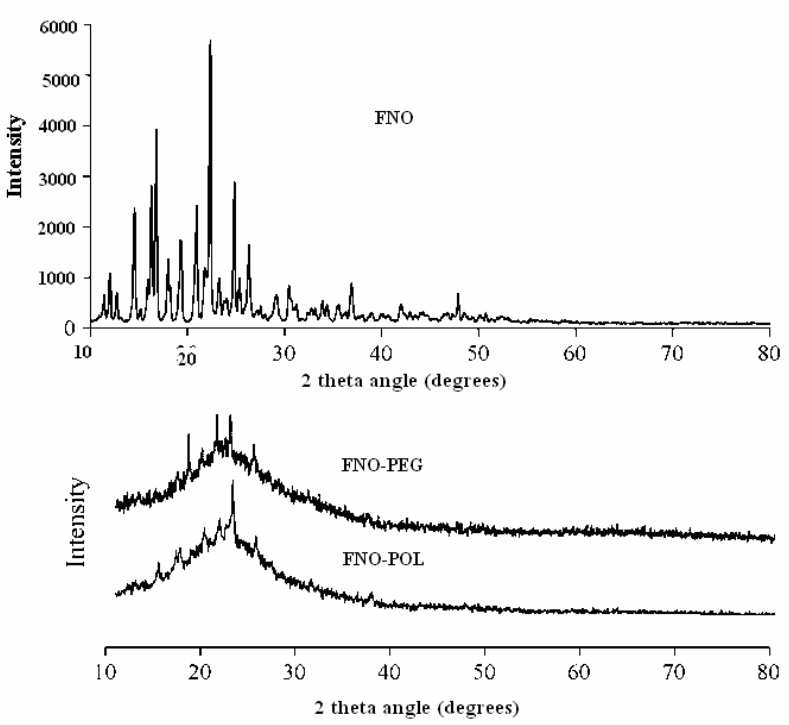

Figure: 5 XRD of the raw Fenofibrate (API) powder and melt granules prepared from PEG and Poloxamer.

RESULTS AND DISCUSSION:

Production yield and Drug content analysis:

The production yield of the prepared granules by melt granulation method shows above 95.0% which was calculated by measuring the weight of the prepared granules by considering the material taken for the granules as 100.0%. Drug content analysis was done on all physical mixtures as well as granulation formulations in triplicate. The FNO contents in the prepared granules shows in range of 90-95% mentioned in table 2.

Saturation solubility:

Table 1 summarizes the experimentally determined solubility of fenofibrate in deionized water. With an aqueous solubility of 87µg/ml, FNO is clearly poorly soluble as compared to literature value of 92 µg/ml[15] .The prepared melted granules with hydrophilic polymers and surfactants were show significantly higher solubility compared to their physical mixture and drug alone. It is to be expected that fenofibrate would be solubilised well in melt granulated form due to adsorption of hydrophilic polymers and surfactants. The solubility of fenofibrate is therefore expected to limit its absorption from the gastrointestinal tract.

Dissolution study:

The in vitro dissolution profiles of the granules prepared by melt granulation were compared with that of pure drug and a physical mixture. The in vitro dissolution rate of all prepared granulates (Fig. 1) was increased compared to the corresponding physical mixtures (Fig.2) and the drug. The dissolution rate of pure FNO was very low, with the amount of drug dissolved in 20 min being less than 20%. Dissolution of prepared melt granules of FNO was substantially higher (50 to 60% release in 20 min) than that of FNO (20% release in 20 min). Drug dissolution of above 90% was obtained in 60min for both melt granules with PEG-6000 and poloxamer-127. The high dissolution rate of prepared granules can be attributed to an increase in the surface area of FNO after adsorption onto the surfactants and polymers. In the case of granules containing PEG as the meltable binder, a large enhancement was observed in the dissolution rate relative to both the physical mixture and the drug alone. In comparison, the ploxomer granules showed a significant increase in the dissolution rate as compared to the drug and physical mixtures. The increase in dissolution rate could be attributed to the higher hydrophilic character of the system due to the presence of water-soluble carriers and that part of the drug dissolves in the binder. These results show that melt granulation can be a useful technique to improve the dissolution rate of FNO.

Technological characterization of the granules:

According to the literature data, powders with a Compressibility Index (CI) between 5 and 15% and a Hausner ratio below 1.25 are suitable for producing tablets. The prepared melt granules formulations had a CI ranging between 12 and 14 while their Hausner ratio was below 1.15.As for the rheological properties, the prepared melt granules revealed a good flowability because of their granular size which reduces the surface area and increases the flow rate.

Powder bed hydrophilicity study:

Table: 2 indicate powder bed hydrophilicity study of FNO and their melted granules. The melt granules showed significantly shortest rising time (** $P<0.01$) of water to its surface as compared to raw FNO crystals represent better wattability of prepared granules as compared to raw FNO. The order of wettability was FNO-PEG2> FNO-POL2>FNO. The reason for the superior wettability with PEG is due to adsorption of polymers on the raw crystals of FNO during preparation.

Stability study:

The pure FNO drug and optimized granules FNO-PEG2, FNO-POL2 were charged on accelerated stability and monitored for appearance, content and in-vitro dissolution study at 1,2 and 3 month. The obtained data were mentioned in table: 3. The stability study reveals no significant variation in appearance, content and in-vitro dissolution study of pure FNO drug and optimized granules FNO-PEG2, FNO-POL2 up to three months.

DSC study:

Figure 3 represents the thermographs of FNO and FNO melted granules. The corresponding melting point depressions, enthalpy of fusion and degree of crystallinity are shown in figure. A depression in melting point of fenofibrate was found in melted granules, which indicates an interaction of fenofibrate with meltable polymer and surfactants. The DSC thermograph of FNO melt granules formulation shows only endothermic peak; the absence of exothermic recrystallization peak may be attributed to interaction between drug and polymers.

Infrared spectroscopy:

State of drug molecule with the different hydrophilic polymers and surfactants was determined using FT-IR. Figure 4 shows IR spectra of FNO and prepared melt granules.IR-spectra of FNO and melted granules are exactly same, and there is no shift of peaks after adsorption of drug onto polymer and surfactants surface; indicating that there is no change in chemical structure of drug after preparing it into melt granules. Specific FNO peaks are observed at 2990, 1740, 1660, and 1600cm−1 and observed same in prepared melt granulation formulation.

XRD study:

Fenofibrate crystals show various diffraction peaks (figure 5) due to its crystalline structure. However, the prepared melt granule shows a loss of drug crystallinity due to drug loading onto polymers and surfactants surface. In optimized melt granules , a few less intense and wide diffraction peaks of fenofibrate are observed, which may be attributed to the adsorption process in

which some of amorphous drug may have crystallized due to higher temperature.

CONCLUSION:

In conclusion, melt granulation technique has been proved to be a important process to increase the solubility, dissolution and other physicochemical characteristics of FNO using PEG and Poloxamer as a melt binder without using any solvents. Adsorption of FNO on hydrophilic polymers and surfactants significantly increases the drug solubility, wettability and dissolution rate. In addition, the adsorption of FNO does not leave any residual solvent in the final formulation because of elimination of use of solvent for preparation of granules. Crystallinity of the melt granules are reduced due to drug–excipients interaction in formulation obtained using melt granulation technique without any chemical interaction and slightly reducing the melting point.

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