Hindawi
Journal of Nanomaterials
Volume 2023, Article ID 1672030, 11 pages
https://doi.org/10.1155/2023/1672030

Research Article

Solidifying Fenofibrate Nanocrystal Suspension: A Scalable Approach via Granulation Method

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Received 14 October 2023; Revised 27 November 2023; Accepted 5 December 2023; Published 26 December 2023

Academic Editor: Arun Thirumurugan

The pharmaceutical industry has highlighted particle-size reduction via preparing aqueous suspensions containing nano- or submicron drug particles. Owing to the risk of agglomeration and complications during the manufacturing of solid dosage forms, the problems associated with the solidification of nanosuspensions need to be addressed. Herein, the nanocrystallized suspension of fenofibrate (Feno) was prepared using the wet-milling technique, and then two solidification methods, mixing (liquid mixing) and granulation (dry powder blending and wet massing) methods, were investigated. The solidification process involved the adsorption of Feno as a very thin layer on the high-surface-area Florite® to prevent drug accumulation. The critical quality attributes, particle size and dissolution rate, were performed. Infrared spectroscopy, X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy were also used to monitor the existence and physical state of drug molecules in the carrier. The final solidified powders and tablets containing Feno nanocrystals improved the dissolution profile (>90% in 15 min), in which the physical properties of Feno were maintained during solidification and tableting. In general, the granulation method is more advantageous than the mixing method in terms of maintaining amorphous proportion and dissolution rate. These results implied a potential approach for manufacturing solid dosage forms from nanoscale products.

1. Introduction

The Biopharmaceutical Classification System (BCS) categorizes most active pharmaceutical ingredients (APIs) as belonging to class 2 or 4 (low aqueous solubility), which indicates that they are challenging to formulate as oral dosage forms, such as tablets and capsules. To increase the bioavailability and clinical efficacy of these APIs, the drug development process requires several physical manipulations to improve their dissolution and solubility [1–3]. Among the different techniques, the top-down approach is the most effective in terms of the number of commercialized APIs (if not the only technique that has provided oral drugs to the market) [4]. While dry milling is more popular in different industries, the wet-milling technique has been increasingly utilized pharmaceutically owing to several advantages such as milling capacity, energy efficiency, and its ability to produce nanosized particles [5–7]. Fenofibrate (Feno) is a typical model API for wet milling investigations. As Feno belongs to BCS group 2 (low solubility and high permeability), reducing its particle size increases its surface area and improves its solubility, dissolution rate, and bioavailability [1, 2, 8, 9]. In fact, the marketed product that contains Feno nanoparticles (Lypanthyl NT 145®, also called Tricor®) has a modest dose (145 mg), which is bioequivalent to a 200 mg dose of other tablets or capsules (prepared as Feno microparticles) [1, 2, 8, 9]. The successful application of Feno nanoparticles in the market makes them an ideal model drug for dosage forms and pharmaceutical development [4]. This study applied

a wet-milling technique in which a planetary ball mill apparatus was used [4, 10–12] to prepare Feno nanosuspensions in both amorphous and crystalline forms. Although amorphous forms are more soluble, they are less stable than crystalline forms, which contrarily have lower solubility [13, 14].

The preparation of tablets or other solid dosage forms from nanoparticles poses some challenges. Importantly, nanosuspensions can be unstable and prone to degradation or aggregation over time, leading to changes in drug release and efficacy [9, 15]. Therefore, the solidification of these nanosuspensions should be studied to maintain the particle size (at the nanoscale), physical state (amorphous, crystalline, or mixed state), and more importantly, the dissolution profile [4, 16, 17]. Previously, the solidification of nanosuspensions was mostly performed via freeze drying and spray drying [8, 12, 18, 19], and the obtained powders were found to exhibit hygroscopic and less compressible properties [4, 12]. Nonetheless, adsorbing nanoparticles onto high-surface-area carriers, where the obtained products are in a solid form, has been reported to facilitate the preparation of oral solid dosage forms with favorable properties [1, 5, 20]. Using this method, drugs prepared in the form of solutions (drug molecules), solid lipid nanosuspension, and liquid self-nanoemulsifying drug delivery systems are dispersed uniformly into specific adsorbents to maintain particle sizes in the nanoscale range (<500 nm) [19, 21–23]. Currently, there are no reports on the adsorption of Feno-nanocrystal suspensions following wet milling. This study used a wet-milling technique and a novel solidification technique to reduce formulation difficulties and maintain batch-to-batch consistency and quality control.

In this study, the solidification of Feno nanocrystal suspensions was proposed via the wet granulation process with a functional role of a porous silicate carrier, Florite® (FLR). FLR is practical for the solidification process because of its specifically high surface area (157.9 m^2/g) and total pore volume of 0.65 cm^3/g [24–26]. Due to its porous structure (interparticle and intraparticle pores), both water and oil absorption into intraparticles were reported [24, 25]. Aiming for large-scale production, a mixture of hydrophobic FLR with more-hydrophilic microcrystalline cellulose (MCC) and lactose (popular excipients in tablet production) was prepared as the adsorbent for Feno nanosuspension [27]). Technically, Feno nanoparticle adsorption can be achieved by: (i) mixing adsorbents with a suspension in liquid form or (ii) multiple granulations of the Feno suspension onto the adsorbents in the solid and dry stages. Herein, the adsorbed powders were prepared by both methods. The products were characterized by determining their dissolution profile, surface morphology, thermal properties, X-ray diffraction (XRD) characteristics, and infrared spectra to elucidate the physical state of the drug.

2. Materials and Methods

2.1. Materials. Fenofibrate (Feno; 99.9%, USP43) was purchased from Oceanchinachem (Hubei, China). Florite-R®, FLR, was purchased from Tomita Pharmaceutical Co., Ltd. (Tokushima, Japan), and docusate sodium (DOSS) was purchased from Solvay SA (Belmont, WV, USA). Hydroxylpropyl methyl cellulose (HPMC E6) was provided by Corlocon (Indianapolis, PA, USA). Tribasic sodium phosphate, sodium lauryl sulfate (NaLS), potassium thiophosphate, and acetonitrile were purchased from Sigma–Aldrich (Merck, Darmstadt, Germany). Lactose monohydrate and sucrose were obtained from Evonik (Darmstadt, Germany). Microcrystalline cellulose (MCC 101; Mingtai Chemical, Bah-Der, Taiwan), croscarmellose sodium (Bionique Pharma, Surat, India), crospovidone CL (Polyplasdon CL, Ashland, Covington, KY, USA), and talc and magnesium stearate (Aurora Industry, Liaoning, China) were used without modification.

Table 1: Formulation design for wet-milling process.

Ingredients	NP1	NP2	NP3	NP4	NP5
Feno (g)	15	15	15	15	15
HPMC E6 (g)	0.25	0.25	0.25	0.5	1.0
NaLS (g)	0.04	–	–	–	–
DOSS (g)	–	0.04	0.08	0.08	0.08
Water (mL)	50	50	50	50	50

2.2. Methods

2.2.1. Preparation of Nanosuspensions via Wet-Milling Process. The drug and excipients were weighed according to Table 1. An aqueous stabilizer solution was prepared with HPMC E6 and surfactants at different concentrations (NP1–NP5). Figure 1(c) illustrated a 500 mL milling chamber with a cylinder shape, in which Feno raw materials and 500 g of 5 mm zirconium milling beads were submerged in the stabilizer solution. The wet milling was conducted via a planetary ball mill (Tencan XQM-2A, Hunan, China) with four separating milling chambers per time, and the rotation rate of 500 rpm for 5 hr (15 min rest per hr) [28, 29]. After that, the beads were separated using a 500 μm sieve. The obtained filtrate was considered a suspension of Feno particles.

2.2.2. Solidification of Feno Nanosuspension. The Feno NPs were solidified via two methods: (i) solid–liquid mixing and (ii) granulation. The adsorbent mixtures contained FLR, MCC 101, and lactose at specific ratios (Table 2), the process-flow diagrams were presented in Figures 1(a) and 1(b).

(1) Mixing Method (*Solid–Liquid Mixing*). An adsorbent mixture (Table 2) was slowly added to the Feno nanosuspension, and the suspension was gently stirred at 100 rpm for 30 min (overhead stirrer HT-50 AX, Daihan Sci., Shanghai, China). To facilitate the drying process, the obtained mixture (from liquid to semisolid state) was then mixed with lactose (the second mixing) before putting in drying chamber. Based on previous study, the ratio of Feno : adsorbent was kept at 3 : 8 (w/w) [1], therefore, for 145 mg Feno (per tablet), the adsorbent mixture was kept at 386 mg per tablet (equivalent to Feno : adsorbent of 3 : 8, w/w). The wet mass was dried at 40°C until the moisture content was less than 5% (Daihan vacuum dryer, Shanghai, China). The formed powders were sieved through a 500 μm sieve.

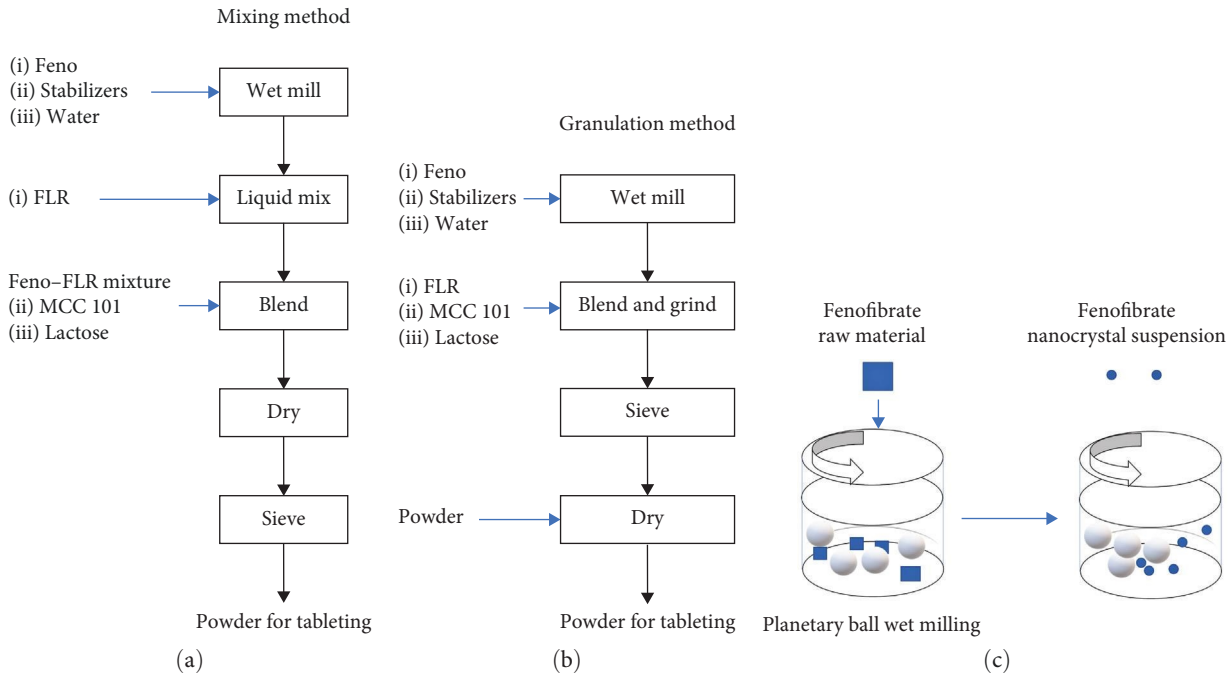

Figure 1: Solidification methods: (a) mixing method, (b) granulation method to prepare Feno powder, and (c) illustration of the ball-milling chamber.

Table 2: Formulation design for solidification process (batch size of 20 g).

Formulation	Feno : FLR (w : w)	Nanosuspension eq.* Feno (mg)	Ingredients for adsorbent (mg)			Adding lactose
			FLR	Lactose	MCC	
		Mixing method				
F41	4 : 1	145	36.25			350
F43	4 : 3	145	108.75			277
F45	4 : 5	145	181.25			205
F41-CT1	4 : 1	145	36.25		145	205
F41-CT2	4 : 1	145	36.25	72.5		277
F41-CT3	4 : 1	145	36.25	72.5	145	132
		Granulation method				
P33	3 : 3	145	145			
P38	3 : 8	145	386.67			
P315	3 : 15	145	725			
P38-CT3	3 : 3	145	145	80.5**	161**	
P38-CT4	3 : 0	145	0	133**	266**	

*Feno was in form of nanosuspension. **The ratio of lactose: MCC was selected according to F41-CT3.

(2) Granulation Method (Multiple Granulation Method Was Used for Layering the Feno Nanosuspension onto Adsorbents). The mixing adsorbents were prepared according to Table 2. The nanosuspension was slowly added to the carrier (FLR, MCC 101 (if any), lactose (if any)) by kneading and mixing continuously in a ceramic mortar until the corresponding drug content was sufficient (Table 2). In the initial granulation phase, the adsorbent mixture (Table 2) was mixed with enough Feno nanosuspension to obtain a wet mass, which were then dried and sieved (500 μm) to get the first granules. This process was repeated for the remaining Feno nanosuspension. Depending on the formulation composition, the process was repeated from two to four times. The final granules were obtained using a 500 μm sieve and then dried in an oven (Daihan vacuum dryer, Shanghai, China) until the moisture content of the granules was less than 5%.

2.2.3. Tablet Preparation. Solidified powders (equivalent to 145 mg Feno) were mixed with external disintegrants (35 mg croscarmellose and 30 mg crospovidone), MCC 101 (adequate to 650 mg per tablet), and glidants (3.25 mg magnesium stearate and 13 mg talc) to make a batch size of 50 tablets. This mixture was compressed into oblong tablets

(length 18 mm, width 8 mm, weight 650 mg, hardness of 10 $\pm$ 2 kP) using a rotary tablet press (8-punch compression, Shakti, India).

2.2.4. Characterization of Feno Nanosuspension.
(1) Particle Size Measurement. Samples (wet-milling suspension or solidified powders) were diluted with distilled water to a count rate of 200–400 kcps. Afterward, the diluted samples were measured using a Zetasizer Ultra Malvern instrument (Malvern Panalytical, Malvern, UK) at 25 $\pm$ 2°C (173° angle, $n = 3$).

(2) Determination of Drug Content. The Feno assay of the final products was performed using a UV–vis method at a wavelength of 289 nm [30]. An accurate volume of nanosuspension (equivalent to 10 mg Feno) was transferred to a 100 mL volumetric flask, 10 mL MeOH was added before placing it in an ultrasonic bath for 10 min. An adequate amount of NaLS solution (0.025M) was added to the volume, followed by sonication for 10 min. The obtained solution was centrifuged (5,000 rpm), the supernatant was diluted 10 times with NaLS 0.025M to have the final sample solution (about 10 μg/mL). The NaLS (0.025M) solution (with 1% MeOH) was used as the blank sample. The standard sample was prepared by dissolving 25.0 mg of Feno into 25 mL of MeOH; then the standard solution was diluted with NaLS 0.025M solution to have the final working solution (about 10 μg/mL). This quantification method was validated with the following criteria: accuracy (RSD < 2%), precision (RSD < 2%), and linearity (R^2: 0.9994).

(3) Flowability Properties of Feno Powder after Solidification. The powder density and Carr's index were determined according to United States Pharmacopeia (USP) 48 (powder flow: 1174). The bulk volume, V_b, and tapped volume, V_t, of the powder were recorded and the Carr's index was calculated [31]:

$$\text{Carr's index}\,(\%) = \frac{V_b - V_t}{V_b} \times 100\,(\%). \quad (1)$$

2.2.5. Dissolution Studies. A powder quantity equivalent to 145 mg of Feno or a Feno tablet was placed in a US Pharmacopoeia paddle apparatus containing 900 mL of NaLS 0.025M solution (37 $\pm$ 0.5°C, 50 rpm) (Pharmatest, Hainburg, Germany). At the predetermined time points, test solutions were collected via 0.45 μm filters for dissolution testing, followed by 10,000 rpm centrifugation; the supernatant was filtered through a 0.2 μm syringe filter before evaluation (diluted with dissolution medium, if required). The test was based on USP, Fenofibrate tablet monograph, test 1 (NaLS 0.025M) [30], in which, NaLS concentration was selected as "sink conditions," referred to the condition in which the concentration of the drug in the dissolution medium remains significantly lower than its solubility. The factor f_2 was calculated to measure the similarity between two dissolution profiles [32]:

$$f_2 = 50 \times \lg\left\{\left[1 + (1/n).\sum_{i=1}^{n}|R_i - T_i|^2\right]^{-0.5} \times 100\right\}, \quad (2)$$

where f_2 value (over 50%) indicates an equivalence of the two curves [32].

2.2.6. Drug Content after Centrifugation. Because mild centrifugation (1,000 rpm, 5 min) can accelerate particle sedimentation, this experiment was conducted to compare the stabilizing properties of the wet-milled nanosuspension and reconstituted suspensions (from product powders). This evaluation is particularly useful when samples contain insoluble inactive or active ingredients at the microscale level. After centrifugation, the percentage of the drug in the supernatant (%DS, 1 cm from the suspension surface) was compared with that of the original suspension:

$$\text{Percentage of the DS} = \frac{\text{Amount of Feno in the } 1 - \text{cm supernatant}}{\text{Total amount of Feno}}. \quad (3)$$

2.2.7. Infrared (IR) Spectra. The Fourier transform infrared (FTIR) spectroscopy samples included raw material samples, (Feno, FLR, lactose, MCC 101, HPMC E6), the physical mixture, and the obtained solidified powders. Each sample was mixed with KBr in a mass ratio of 1 : 10, then pressed into pellets before scanning (400 to 4,000 cm^{-1}, FTIR-4000 JASCO, Tokyo, Japan) [1, 24].

2.2.8. Determination of the Physical State of the Drug Being Adsorbed on the Carriers. The products prepared by the two methods were analyzed using XRD and differential scanning calorimetry (DSC).

(1) X-Ray Diffraction. Samples were placed in measuring cuvettes and flattened on a surface; XRD measurement was conducted with specific conditions: scanning angle (2θ), temperature 25°C (Bruker AXS D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany) [1, 24].

(2) Differential Scanning Calorimetry. Samples (3–10 mg) were placed in a DSC pan. The instrument was run at the following conditions: a temperature range from 20 to 250°C, heating rate of 10°C/min, N_2 gas flow of 50 mL/min (Mettler Toledo DSC, Columbus, OH 43240, USA) [1, 24].

2.2.9. Statistical Analysis. All data were processed and graphed using the GraphPad Prism software. The results are presented as $x \pm$ SD, where x is the mean, and SD is the standard deviation ($n = 3$).

3. Results and Discussion

3.1. Nanocrystal Preparation Using the Milling Technique. Different formulations (Table 1) of Feno nanosuspensions were prepared to determine the effects of different surfactants (NP1 and NP2), surfactant concentrations (NP2 and NP3), and polymer concentrations (NP3–NP5). First of all, the products of wet-milling process were all at nanosized scale, all formulations from NP1 to NP5 exhibited a low Z

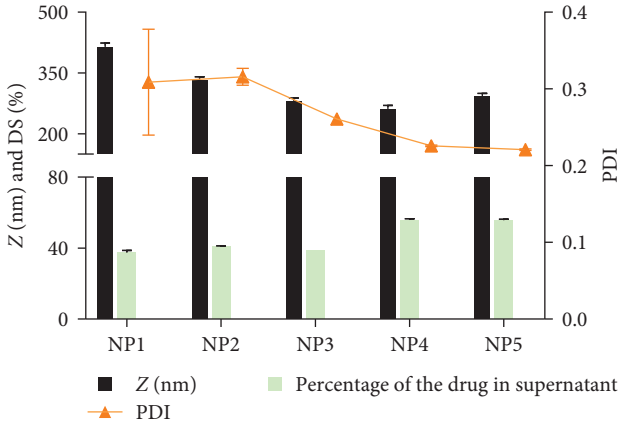

Figure 2: Formulation factor effects on Feno nanoparticles prepared by the wet-milling technique: Z (particle size), PDI (polydispersity index), and %DS (%drug in supernatant).

(less than 500 nm) with a low PDI (less than 0.4). Feno raw material was in the micron range with D50 of 7.92 μm (D90 : 18.1 μm). As the stabilizers (HPMC, NaLS, or DOSS) are water-soluble substances, the obtained results particle size measurement was solely based on Feno nanoparticles.

When comparing NaLS and DOSS at the same concentration (0.08% w/v, NP1 and NP2, respectively), the product properties were significantly improved in NP2. In detail, % DS was significantly improved (37.82% and 41.18%, respectively), and particle size (Z) was significantly reduced (418 and 337 nm, respectively).

As shown in Figure 2, when DOSS was increased from 0.08% to 0.16%, NP3 (0.16% DOSS) exhibited a lower particle size (286.4 $\pm$ 1.86 nm) and lower PDI value (0.261) than those of NP2. Therefore, DOSS 0.16% was selected for further studies.

Regarding the effect of HPMC (NP3, NP4, and NP5), although increasing HPMC did not affect Z, NP4 and NP5 had higher %DS values. In this case, increasing the viscosity (by adding HPMC) delayed the aggregation of Feno nanoparticles, making the suspension more resistant to centrifugation. Therefore, NP5 was selected as the final suspension.

Due to the hydrophobicity of Feno, ionic surfactants are preferred over nonionic surfactants because they improve drug wetting and lower surface tension [4, 13]. The high HLB value of NaLS (40) and its higher foaming ability had a negative impact on the milling processes [33] and also interfered with the function of the stabilizing polymer (HPMC E6) [33]. HPMC can improve the wetting properties of drug particles through its hydrophilicity, thereby facilitating drug breakdown. Once the milling process was completed, HPMC was expected to form a multimolecular film around the drug nanoparticles, acting as a recrystallization inhibitor to ensure a homogeneous distribution of drug particles in the suspension [33]. In general, wet milling is considered a rational approach for Feno, in which the formed particle size (NP5, less than 400 nm) is predicted to improve Feno solubility and dissolution [1, 34, 35]. Regarding the wet-milling apparatus, the planetary ball mill used in this study is one of the most common and practical approaches for industrial scale-up [36].

3.2. Nanosuspension Solidification

3.2.1. Solidification Using the Mixing Method. As shown in Figure 1, FLR was added to the liquid nanosuspensions with constant stirring (100 rpm, overhead stirrer). The experimental design is presented in Table 2. The dissolution profiles of these solidified powders are presented in Figures 3(a) and 3(b), and the other powder properties are shown in Table 3.

First, Feno : FLR (w : w) ratios of 4 : 1, 4 : 3, and 4 : 5 (F41–F45, respectively) were screened. Higher FLR contents resulted in the liquid state transforming into a semisolid or solid state (which was so dense that mixing did not progress effectively). In this method, F45 was the formulation with the highest FLR content in which stirring was maintained. Table 3 shows that the reconstituted suspensions of the 4 : 1, 4 : 3, and 4 : 5 formulations had Z (nm) values in the range of 300–400 nm, with homogeneous dispersity (PDI < 0.3). When the amount of FLR gradually increased (from F41 to F45), the %DS after centrifugation decreased. This result is consistent with that of the dissolution study (Figure 3(a)); increasing the FLR : Feno ratio (from F41 to F45) reduced the dissolution rate (Figure 3(a)). However, it should be noted that the Feno-FLR mixtures showed significantly enhanced dissolution rates compared to the Feno raw material.

In this study, the mixing method was based on the mechanism by which FLR was supposed to "catch and hold" Feno nanoparticles owing to the hydrophobic interaction of FLR and Feno in the liquid. Higher proportions of FLR adsorbed higher amounts of Feno and other components to form bigger aggregates [15]. However, FLR is considered to be an inert excipient (calcium silicate is insoluble in water). The hydrophobic interface of FLR reduced the dissolution rate of Feno (comparing F45 to F41). Therefore, we hypothesized that adding more hydrophilic ingredients such as lactose or MCC to the mixture during the adsorption process would result in the formation of new water capillaries, which would improve dissolution (Figure 3(b)). Among the three formulations (F41-CT1, F41-CT2, and F41-CT3), F41-CT3 showed a faster dissolution profile than F41 (>90% in the first 10 min). In fact, F41-CT3 displayed the highest dissolution rate, smallest particle size, and highest %DS among the mixing method formulations. In general, FLR plays a functional role in maintaining the properties of Feno nanoparticles; however, technical processes and additional ingredients are required to optimize this function.

3.2.2. Solidification Using the Granulation Method. The goal of the multiple granulation method was to allow Feno nanoparticles to adsorb slowly onto the surface of the carrier (specifically, FLR). The slow rate of addition of the Feno suspension allowed for better control of the adsorption process to prevent the aggregation or precipitation of nanoparticles. This is the main difference between the operational procedures of the mixing and granulation methods. Different Feno : FLR ratios were prepared at 3 : 3 (P33), 3 : 8 (P38), and

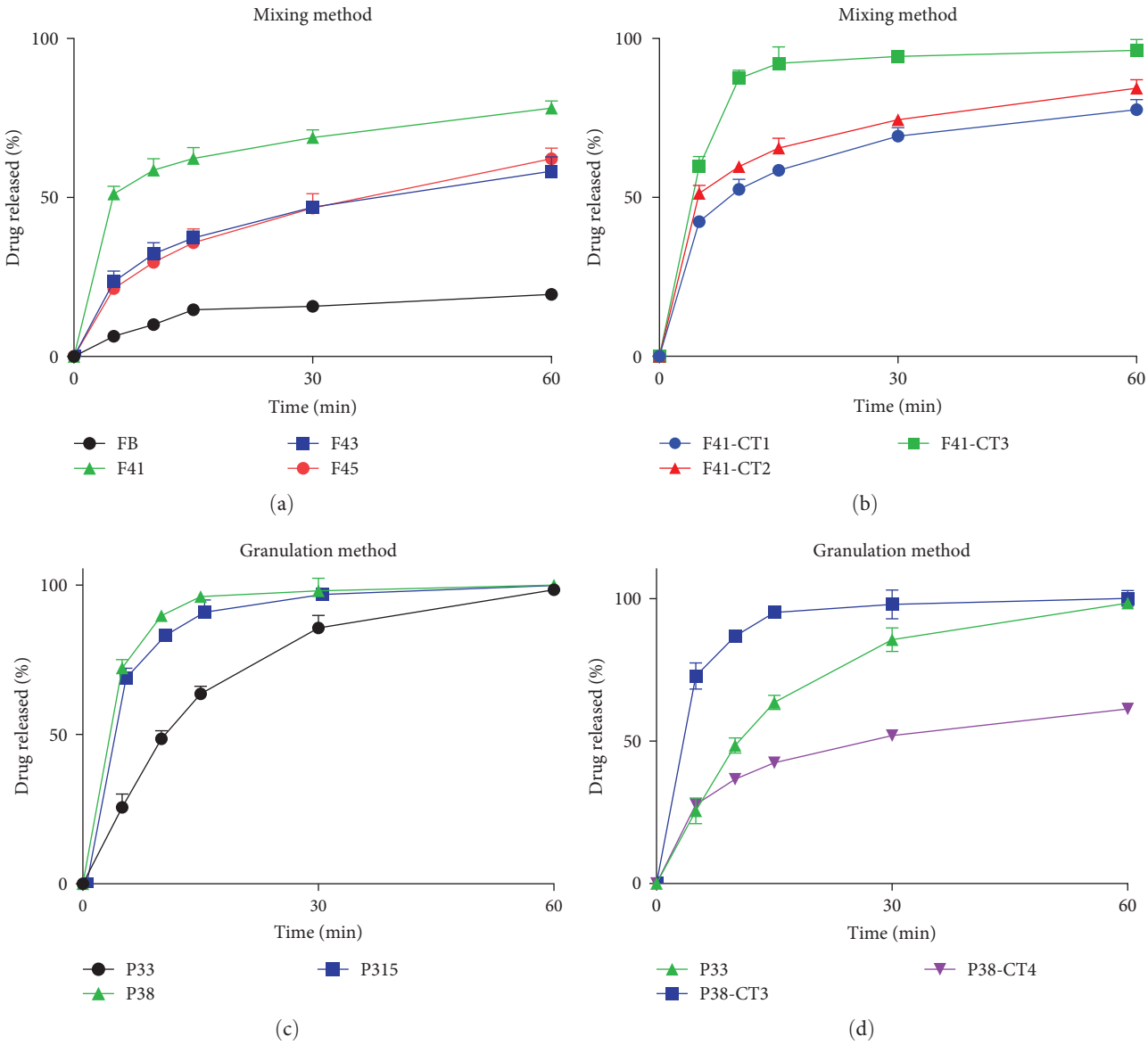

Figure 3: Formulation factor effects on dissolution profiles of solidified powders. Mixing method (a, b) and granulation method (c, d).

3 : 15 (P315); the results are presented in Figures 3(c) and 3(d) and Table 3. The suspension formed by reconstituting the solidified powder confimed particles at nanoscale with low PDI values, a single peak was reported in the size report (Supplement Data S1).

As shown in Figure 3(c), granulation-method powders significantly improved the dissolution rate of Feno compared to raw materials (after 60 min, over 90% drug release) and the mixing method products. Increasing FLR (from P33 to P38) improved the Feno dissolution rate. However, P315 (increasing FLR at high concentrations) did not improve dissolution compared with P38 (Figure 3(c)). Although P33 had the slowest rate of dissolution (compared to P38 or P315), P33 also released and dissolved over 90% Feno at 60 min. The slow dissolution rate of P33 at the early time points can be explained by its small surface area (lowest FLR content) and the requirement for four granulations, in which the aggregated Feno particles prevented each other from exposure to the medium.

About the physical properties shown in Table 3 (for both methods), increasing FLR proportion reduced the density of the granules (from F41 to F45 or P33 to P315). FLR is a high surface area material with a low density (0.1 g/mL, FLR-R) and a high Carr's index (44.7). Thus, formulations with higher FLR content (F45, P38, or P315) had lower flowability (higher Carr's indexes, Table 3), which is not recommended for tablet production [37, 38]. Based on results of the number of granulations and dissolution, the ratio of Feno : carrier = 3 : 8 (double granulation) and the ratio of Feno : FLR = 3 : 3 (90% Feno dissolved at 60 min) were selected. Therefore, in further studies, the ratio of Feno : FLR was maintained at 3 : 3, and the remaining amount of FLR in the P38 formulation was replaced with a lactose : MCC mixture (1 : 2, w/w). As shown in Figure 3(d), P38-CT3 exhibited a dissolution

Table 3: Formulation factor effects on product properties.

Form.	Feno : carrier (w : w)	Blending ability	Physical state	Z (nm)	PDI	(%) DS	Density (g/mL)	Carr's index
Mixing method								
F41	4 : 1	++	Liquid	334.7 ± 5.76	0.205 ± 0.023	8.70 ± 0.95	0.462 ± 0.079	22.50 ± 2.12
F43	4 : 3	+	Semisolid	364.7 ± 4.49	0.276 ± 0.041	5.85 ± 3.09	0.389 ± 0.032	25.33 ± 3.21
F45	4 : 5	−	Solid	302.5 ± 4.66	0.161 ± 0.002	3.97 ± 052	0.318 ± 0.063	29.00 ± 3.46
F41-CT1	4 : 1	+	Liquid	415.7 ± 4.14	0.280 ± 0.045	6.55 ± 1.41	0.477 ± 0.061	21.67 ± 2.01
F41-CT2	4 : 1	+	Liquid	381.7 ± 4.2	0.270 ± 0.025	37.43 ± 5.70	0.582 ± 0.035	19.00 ± 1.41
F41-CT3	4 : 1	−	Semisolid	268.7 ± 6.512	0.281 ± 0.029	55.86 ± 15.27	0.582 ± 0.025	21.33 ± 1.41
Granulation method								
P33	3 : 3	+	Solid	454.1 ± 23.29	0.178 ± 0.06	4.01 ± 0.66	0.473 ± 0.025	24.50 ± 3.54
P38	3 : 8	+	Solid	460.0 ± 22.89	0.172 ± 0.07	7.30 ± 2.96	0.314 ± 0.023	33.00 ± 5.19
P315	3 : 15	+	Solid	559.4 ± 46.56	0.174 ± 0.12	10.23 ± 0.23	0.250 ± 0.029	37.00 ± 1.41
P38-CT3	3 : 8	+	Solid	454.1 ± 4.188	0.254 ± 0.006	9.92 ± 2.01	0.701 ± 0.059	22.19 ± 0.92
P38-CT4	3 : 8	−	Solid	–	–	4.53 ± 1.98	0.718 ± 0.032	23.16 ± 0.04

Z, particle size; PDI, polydispersity index; %DS, percentage of the drug in the supernatant.

pattern similar to that of P38 and a faster dissolution rate than P33. The P38-CT3 powder had a significantly lower Carr's index than the P38 powder, probably owing to the addition of higher density materials (lactose and MCC). To confirm the role of FLR, P38-CT4 was prepared without FLR (FLR was replaced with lactose/MCC at the same ratio as P38-CT3). The P38-CT4 mixture was so wet that it required multiple granulations; however, this formulation also showed slow drug release; this finding implied that the Feno nanocrystals were precipitated to form larger Feno particles. This result also suggested the important role of FLR in the adsorbent mixture. Overall, P38-CT3 was selected as the final formulation for granulation and further characterization.

3.3. Tablet Preparation. The powders obtained using these solidification methods were collected, mixed with other ingredients (see the tablet preparation method), and compressed into tablets. Based on previous results, FLR plays an important role beside MCC and lactose as a filler for tableting. Therefore, P38-CT3 and F41-CT3 were selected to compare the effect of two different ways of adding FLR. Figure 4(a) shows the dissolution profiles of tablets prepared from F41-CT3 and P38-CT3 powders. In this experiment, the studied tablets were compared to commercial Lypanthyl NT (145 mg).

However, as shown in Figure 4(a), the release pattern of the mixing method-based formulation did not meet the dissolution equivalence of the reference ($f_2 < 50\%$), whereas the granulation method-based formulation showed an $f_2 > 50\%$ (equivalent to commercial product). Compared to the dissolution of P38-CT3 powder ($97.9 \pm 5.03\%$ in 30 min), P38-CT3 tablets exhibited a lower dissolution ($89.9\% \pm 3.28\%$ in 30 min). A similar trend was also reported for F41-CT3 tablets ($82.06\% \pm 3.4\%$ in 30 min). The reduced dissolution may be a result of compression, which introduces the need for disintegration time. The difference in dissolution between the P38-CT3 and F41-CT3 tablets also suggests an advantage of the granulation method.

3.4. Physical Characterization of Tablets and Solidified Powders. FTIR results (Figure 4(b)) showed that the powder samples after adsorption still retained peaks at 2,983 (1), 1,730 (2), 1,599 (3), 1,600 (4), 925 (5), and 765 cm^{-1} (6). FTIR was used to identify the various ingredients present in the final formulations. The spectra indicated that the final products, F41-CT3 or P38-CT3 tablets, contained all the ingredients with no chemical reactions had occurred.

In the XRD patterns (Figure 4(c)), Feno exhibited various high-intensity peaks attributed to its crystalline structure. The solidified powders (prepared using the two methods) maintained a number of diffraction peaks with reduced intensity compared to that of raw Feno. The XRD indicated a significant number of Feno crystals in the solidified powder samples, which is also a specific characteristic of milling technology [39, 40]. In comparing the two investigated methods, the peak intensity of the granulation powder sample (P38-CT3) was weaker than that of the mixing method (F41-CT3), although the proportion of FLR in the mixing method was lower than that in the granulation method. A similar trend was observed for the corresponding tablets. As solidified powders contained the same amount of Feno, and tablet samples from the two methods were prepared with the same weight (650 mg per tablet), shape, compression force, and drug content (145 mg Feno per tablet), XRD results indicated a difference in the proportion of Feno crystalline [1, 6]. The proportion of Feno crystalline (in P38-CT3) was lower than F41-CT3.

According to DSC analysis (Figure 4(d)), the endothermic peak of raw Feno is around 81–82°C, which is typical of the melting point of Feno [1, 8]. For the solidified powders and powdered tablets, a lower energy peak was observed in the P38-CT3 than in the F41-CT3 samples. Similar to the XRD data, the DSC results suggested that the products obtained using the granulation method (P38-CT3) had a lower crystallized form of Feno than those obtained using the mixing method (F41-CT3). Additionally, both the DSC and XRD data showed that the physical state of Feno was

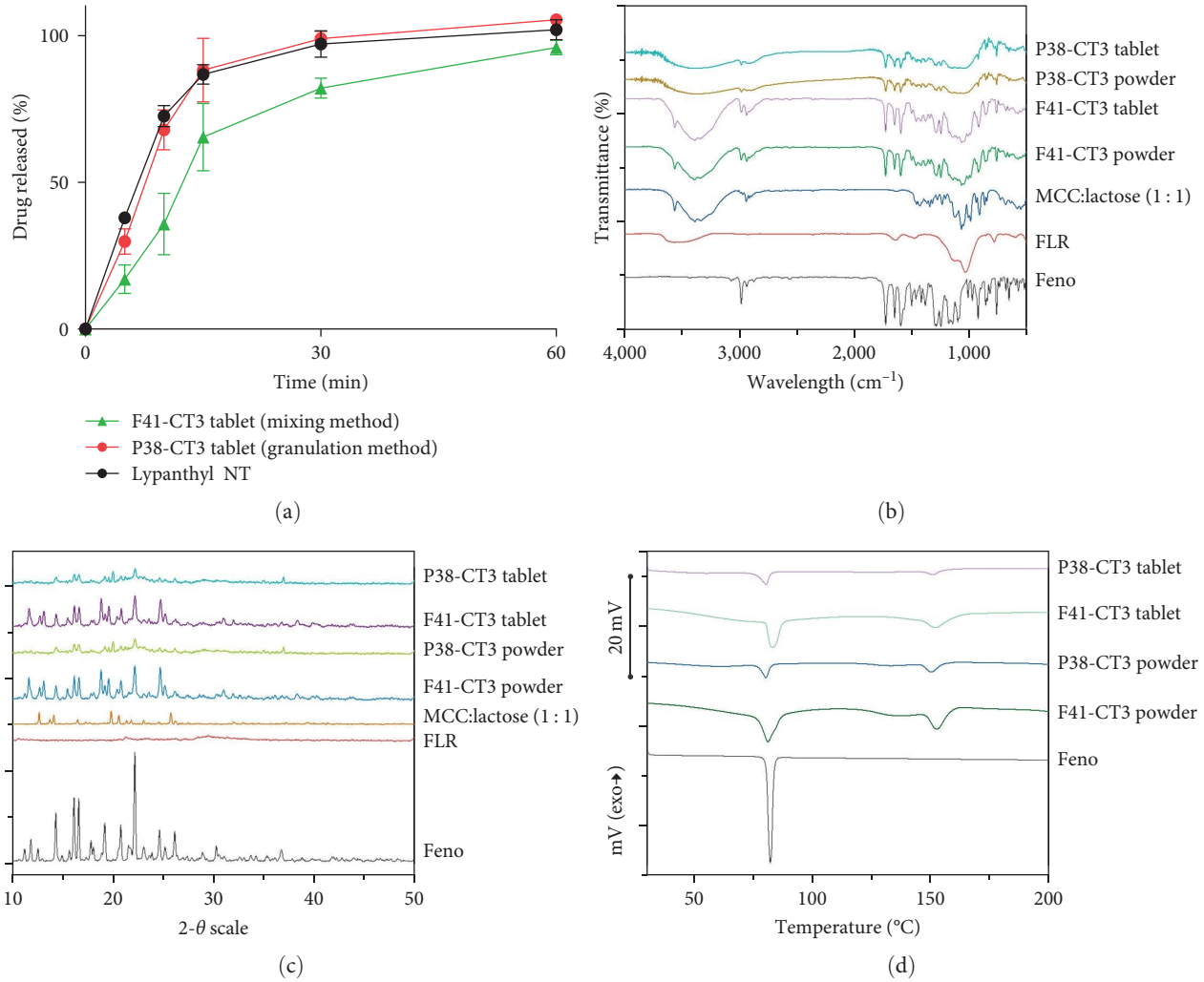

Figure 4: Characterization of tablets and powders: (a) dissolution profiles of tablets, (b) FT-IR spectra, (c) XRD pattern, and (d) DSC curves. "F41-CT3" prepared by mixing method and "P38-CT3" prepared by granulation method.

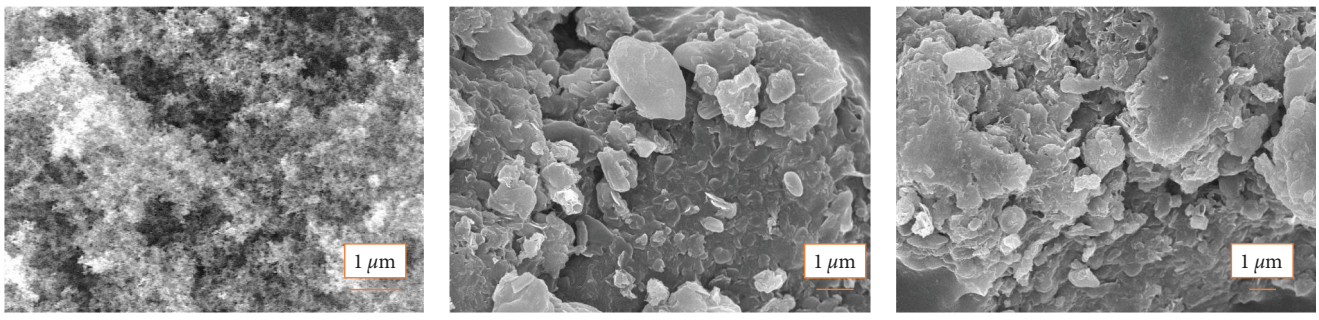

Figure 5: SEM images: (a) granulation method-based placebo powder, (b) granulation method-based powder (P38-CT3), and (c) granulation method-based powdered tablet (P38-CT3).

maintained during tableting. These findings are promising for future industrial applications, in which, the functional role of carrier mixture in maintaining the physical state of wet-milling products. In general, the granulation method was more advantageous than the mixing method in terms of reducing the Feno crystalline proportion, which is consistent with the dissolution results.

3.5. Surface Morphology Characterization. In the SEM image (Figure 5(a)), the placebo mixture (carrier matrix) appeared

as porous petals. Figure 5(b) depicts that the pores and surfaces of the carriers in the granulation method powder sample were filled with lighter particles, implying the presence of Feno nanocrystals. These SEM images confirmed the abovementioned results that Feno was adsorbed on the FLR surface at the nanoscale level (~500 nm), confirming the DLS results.

Using a planetary milling apparatus, the movement of the chamber and the forces exerted by the milling balls should have produced spherical Feno nanocrystals. However, because the granulation method is supported by a mortar and pestle and the interaction with the porous surface of the FLR, these spherical shapes were stressed and more eclipse-shaped (Figure 5(b)). As shown in Figure 5(c), after preparation, the tablets were ground into a fine powder for SEM imaging. Interestingly, the morphology of the nanoparticles was similar to that shown in Figure 5(b). These results confirm the protective effects of FLR during the compression step.

FLR is a type of porous silicate carrier, with a final product particle size of 30 μm [26, 41]. Figure 5(a) shows that the pores of the carrier (darker area) have diameters at approximately 500 nm to 1 μm, which is similar to previous reports [24, 41]. In this case, the pore size of the carriers coincided with the particle size of the Feno nanoparticles (Table 3; 454 nm, as measured by DLS). The similarity in terms of the pore size of the carrier and Feno nanoparticles can help distribute Feno uniformly on the surface of the FLR.

4. Discussion

In this study, wet milling was used to prepare Feno nanocrystals. The final nanosuspension (NP5) was a liquid suspension containing both crystalline and amorphous forms of the drug [39, 40]. For the first time, two alternative methods—mixing (liquid mixing) and granulation (dry powder blending and wet massing)—were used to solidify the final product. The solidification process involved the adsorption of Feno onto carrier mixtures, and the high-surface-area material (FLR) facilitated the adsorption of Feno as a very thin layer to prevent drug accumulation during drying. The adsorption of Feno onto the adsorbent mixture was confirmed by Feno assay, XRD, and DSC results; these results provided insights into the physical states of Feno within the adsorbent.

While the mixing method enabled FLR and Feno to form large hydrophobic aggregates and sediments that separated from the liquid phase, the granulation method resulted in the formation of Feno as layer-by-layer on the FLR surface. In the nanosuspension, the presence of DOSS, HPMC (as discussed in Section 3.1), and the porous material were responsible for maintaining the physical state of the drug during solidification (Capsmorph system). The slow rate of addition of the Feno suspension in the granulation method prevented the crystallization of Feno nanoparticles, allowing nanoparticles (Feno nanoparticles covered by DOSS and HPMC) to be entrapped in the porous structures of the carrier [1, 14, 42]. Both the XRD and DSC results showed that the granulation method maintained a lower proportion of Feno crystalline. The dissolution rates of Feno from the granulation method powders and tablets were significantly higher than those from the mixing method. In detail, the granulation method was more advantageous than the mixing method in terms of maintaining the low proportion of Feno crystalline (XRD and DSC data), preventing Feno aggregation (%DS after centrifugation), and, importantly, increasing the dissolution rate. Beside preparing drugs into nanorange to improve dissolution (via increasing surface area), the physical states of drugs (amorphous or crystalline) also impact different properties. Amorphous substances exhibit a lack of long-range order, resulting in molecules being arranged in many conformational states, as opposed to the highly organized structure found in crystalline substances [6]. Therefore, even in nanoscale range, amorphous forms have higher solubility compared to crystalline forms [13, 14]. Via, XRD, an amorphous state should be recorded with a halo pattern, a lower intensity and curve bands should replace the sharp peaks of crystalline state of the same substance [6]. In our study, via wet-milling method, the patterns of XRD implied that P38-CT3 had a significantly higher amount of amorphous Feno (and lower crystalline proportion) than F41-CT3. Therefore, from quality point of view, nanomaterials should be measured not only by particle size distribution but also crystallization state via XRD or DSC.

In addition, these findings infer the role of FLR as a protective agent during the tableting process minimizing the negative effects of tablet compression on nanoparticles along with other inactive ingredients. Calcium silicate has a high surface area and porous structure, which help in absorbing some of the mechanical forces, further reducing the impact of compression on the Feno nanoparticles [25, 26, 41].

5. Conclusions

In this study, Feno raw material was ground into nanocrystals using wet milling. Subsequently, a solidification technique with scaling-up potential was investigated. Using the granulation method, Feno nanocrystal suspensions were successfully granulated with the absorbent mixture, in which, FLR plays an important role. The formed solidified powders and tablets (P38-CT3) then released the drug at a high rate (more than 90% after 30 min) that was similar to those of commercial tablets. The physicochemical properties of Feno were maintained during tableting, demonstrating the potential of this solidification technique.

Abbreviations

APIs: Active pharmaceutical ingredients
Feno: Fenofibrate
FLR: Florite®
HPMC: Hydroxypropyl methyl cellulose
XRD: X-ray diffraction
DSC: Differential scanning calorimetry.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Chien Ngoc Nguyen contributed to project administration, conceptualization, methodology, supervision, writing, reviewing, and editing. Bao Ngoc Tran contributed to methodology, investigation, data curation, and writing. Hiep Tuan Tran contributed to methodology and writing. Giang Thi Le contributed to investigation and data curation. Khanh Ngoc Le and Anh Hoang Dao contributed to methodology and investigation. Bao Ngoc Tran and Hiep Tuan Tran contributed equally to this work.

Supplementary Materials

Supplement Data S1: these supplement data are to support Table 3. The formulation of P38-CT3 is presented in Table 2. The solidified CT38-CT3 was reconstituted with water to create a nanosuspension; in which size report showed nanoscale particles with low PDI values (a single peak). (*Supplementary Materials*)

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