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Research paper

Effect of powder processing on performance of fenofibrate formulations

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Abstract

In this study, the effect of the order in which powder blending and jet-milling were performed for the production of the bulk powders on the performance of 200-mg dose orally disintegrating tablets (ODTs) of fenofibrate was evaluated. Bulk powders composed of fenofibrate, mannitol, copovidone S630, and docusate sodium in a 10:10:2:1.2 ratio were prepared by the following three processes: *process A*: fenofibrate + excipients → blending; *process B*: fenofibrate → jet-milling → blending with excipients; *process C*: fenofibrate + excipients → blending → jet-milling. The bulk powders were granulated followed by blending and tableting. The materials were tested for Differential Scanning Calorimetry (DSC), drug particle sizing post-reconstitution, dissolution, optical micrography, Scanning Electron Microscopy (SEM), Energy Dispersive X-ray Spectroscopy (EDS) and disintegration of the ODTs. It was found that the crystallinity of fenofibrate was not impacted by the blending and jet-milling processes. Process A produced materials having poorer fenofibrate reconstitution as compared to processes involving jet-milling. It was discovered that milling a blend of fenofibrate/excipient (process C) was advantageous over milling the raw drug alone (process B). Process C yielded bulk powder that showed rapid dissolution and ODTs which exhibited rapid disintegration.

Keywords: ODTs; Fenofibrate; Poorly soluble; Jet-milling

1. Introduction

Latest advances in combinatorial chemistry and high-throughput screening have produced new chemical compounds. Roughly 40% of these have poor aqueous solubility and subsequent limited absorption in the body due to poor dissolution rates [1–4]. Because of low oral bioavailability, some new chemical entities have to be delayed or abandoned in preclinical development due to their lipophilicity [5]. Hence the poor dissolution rates and solubility in body fluids are the limiting factors in many cases because generally drugs having high lipophilicity exhibit high permeability [5].

One strategy employed by formulation scientists to improve the dissolution rate of hydrophobic (poorly water soluble) drugs is to produce particles of the active pharmaceutical ingredient (API) in nanometer or micrometer size range [3–6]. According to the Noyes–Whitney equation, reducing the particle size would increase the overall surface area, which would subsequently increase the dissolution rate of a poorly water soluble drug [3]. Also, it has been found that the diffusion layer around small particles is thinner, which results in faster distribution of the dissolved molecules [5]. A variety of techniques including solvent precipitation, crystallization, spray drying, fluid bed drying, solvent extraction, phase inversion, solvent evaporation, supercritical fluid method and high energy wet and dry milling, have been employed for this purpose [5,7,8]. Different types of milling processes and equipment, such as, hammer mills, ball mills, roller mills, disc grinders, and jet mills, have been used to date [9].

ODTs dissolve or disintegrate rapidly in the patient's mouth without chewing or the need for water within a short time frame (typically within a minute). Because of their ease of administration, such dosage forms are

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potentially useful for a variety of applications [10,11]: (i) pediatrics, (ii) geriatrics, (iii) patients with dysphagia (difficulty in swallowing), (iv) decrease in time of onset of action due to a reduction of lag time between administration of dose and physical presentation of the API associated with disintegration of the dosage form and distribution of the API, and (v) facilitating buccal absorption of the drug into the bloodstream, thus reducing any first pass effect of the liver on the oral bioavailability of the API from a unit dose.

Preparation of ODT formulations using microparticles of poorly water soluble drug combines rapid disintegration of the ODT of the poorly water soluble API and rapid dissolution of the API as a result of microparticulate size of the drug. An additional advantage in using small microparticulate drug particles is that it eliminates or reduces the feeling of grittiness found with conventional ODT formulations of poorly soluble drugs [10].

Fenofibrate was chosen as a model drug for this study, as it is poorly water soluble and has a bioavailability that is known to be affected by particle size and dissolution rate. Increase in dissolution rate and bioavailability for fenofibrate have been achieved by preparing pH-sensitive self-assembling micelles from block copolymers and by formulating it as a solid dispersion with polyethylene glycol 6000 and povidone [12–14]. Increasing the dissolution rate of fenofibrate by particle size reduction using supercritical carbon dioxide and other mechanical processes have been reported in the literature [15–23]. These studies involve use of complicated and technically challenging processes to increase the dissolution rate of fenofibrate. In this study, conventional, simple and commercializable unit pharmaceutical processes like dry powder blending and jet-milling were employed to enhance the performance of fenofibrate formulations. Notably, it has been found that the order in which these processes are used is critical. Also, this study illustrates for the first time the successful preparation of ODT formulation of the poorly water soluble drug, fenofibrate and the processes described herein could potentially be utilized to prepare ODTs of other poorly water soluble drugs.

The primary goal of this study was to compare the in vitro performance of 200-mg dose ODT dosage forms of fenofibrate. These ODT dosage forms were produced from granules of bulk powders, which were prepared by three different processes that involved dry powder blending and jet-milling. The effect of the order in which powder blending and jet-milling were performed for the production of the bulk powders on a number of material properties is described.

2. Materials and methods

2.1. Material production

The various types and quantities of excipients used for blending, jet-milling, granulation and tableting processes were based on previous studies that involved screening and optimization of excipient types (sugars, amino acids, polymers, surfactants and disintegrants) and levels as well as finalization of processing conditions.

The following raw materials were used during various processes: fenofibrate (Onbio Inc., Ont., Canada), mannitol USP (Pearlitol 100SD from Roquette America Inc.), copovidone S630 (Plasdone S630, ISP Technologies Inc.), DOSS (Docusate sodium USP; Cytec Corporation), xylitol USPNF (Xylisorb 700, Roquett America Inc.) and crospovidone USPNF (Polyplasdone XL, ISP Technologies Inc.).

Due to the sticky/waxy consistency of DOSS, it was difficult to use it in the raw form in dry powder blending processes. Hence it was incorporated with mannitol in 10:1.2 ratio in a lyophilized form as follows: the solution of mannitol and DOSS in water was first frozen at −80 °C, and then lyophilized using the Virtis L125 lyophilizer at ambient temperature. The lyophilized excipient cake was screened through 20 mesh (850 μ) standard US stainless steel sieve before blending with other components of the blend.

Fig. 1 provides a summary of the processes used to make bulk powders, granules and tablets.

Bulk powders with a formulation composed of fenofibrate, mannitol, copovidone S630, and DOSS in a 10:10:2:1.2 ratios were prepared by the following three processes:

Process A: fenofibrate + excipients → blending,
Process B: fenofibrate → jet-milling → blending with excipients,
Process C: fenofibrate + excipients → blending → jet-milling.

The blending for the above processes was conducted using a Turbula™ T2F mixer in a stainless steel jar for 30 min at 96 rpm. The jet-milling (for processes B and C) was performed on a Fluid Energy Aljet jet mill (pressure to mill 190 psi, injector gas pressure 8.0 bar, grinding gas pressure 4.0 bar).

Granulation of the bulk powders was performed to improve processability, and to enable preparation of the final ODT formulations. This was conducted by top-spraying deionized water over fluidized bed of the powder in a Vector MFL.01 fluid bed processor. The following process conditions were used: the liquid feed rate ranged from 0.8 to 3.6 g/min, the fluid bed process gas was supplied at a rate ranging from 70 LPM to 200 LPM, the nozzle atomization pressure rate ranged from 10 psi to 15 psi, the inlet temperature ranged from 60 to 90 °C, and the outlet temperature ranged from 20 to 25 °C. The granules were screened through 100 mesh (150 μ) standard US stainless steel sieve before subjecting to further analysis or processing.

For preparation of the final ODT product, the granules were first blended (using a Turbula™ T2F mixer) with xylitol USPNF and crospovidone USPNF for 10 min at

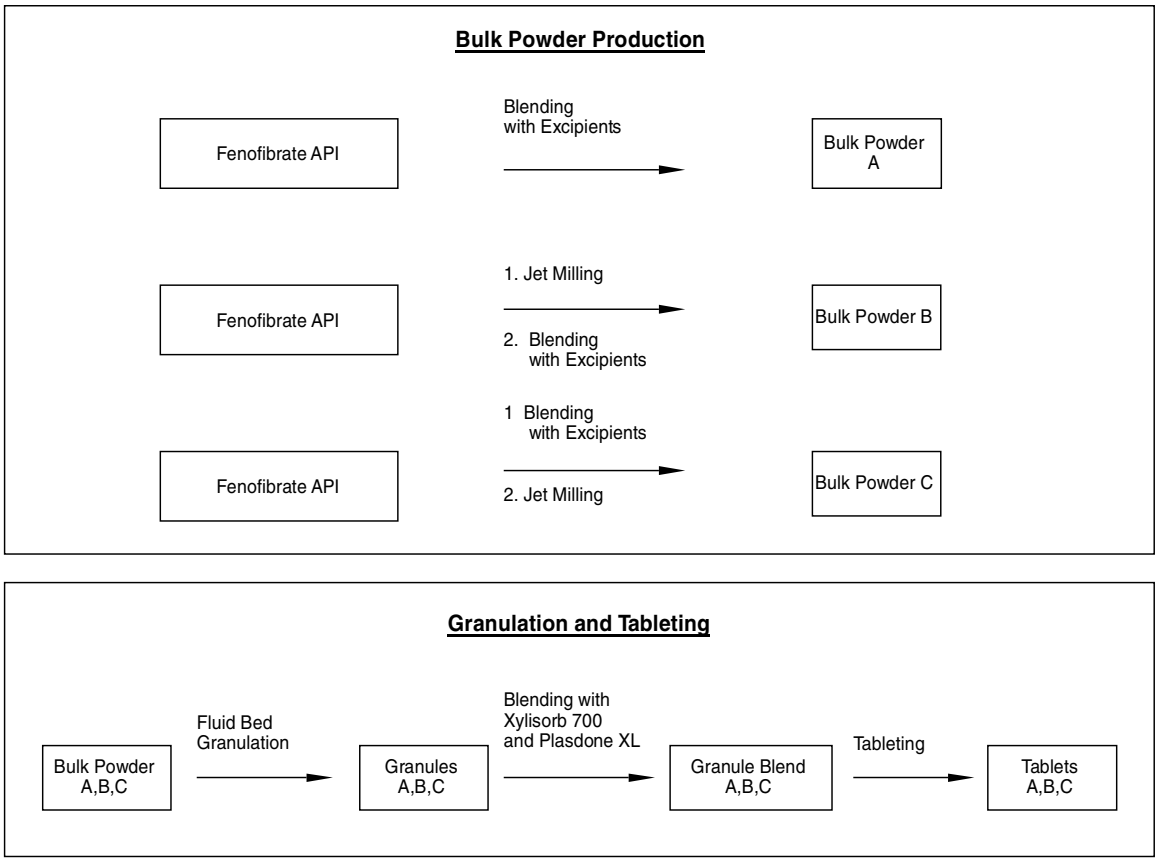

Fig. 1. Summary of processing techniques.

96 rpm. The mass ratio of granules:xylitol:crospovidone in the blend was 1:1:0.3. This powder blend was subjected to tableting (14 mm standard concave tooling and 1000 lbs pressure in an automatic Carver Tablet Press) to produce 200-mg dose fenofibrate orally disintegrating tablets (weighing approximately 1028 mg).

2.2. Analytical methods

DSC analysis of the fenofibrate API and bulk powders from the three processes was conducted using the Perkin-Elmer Differential Scanning Calorimeter (DSC 7). The samples were sealed in an aluminum pan with a pin-hole and the thermal events were recorded by scanning the sample at 10 °C per minute in an inert (nitrogen) environment.

The bulk powders were examined by SEM and EDS for chlorine (only present in fenofibrate) and sodium (only present in DOSS). The SEM and EDS images were generated by Rocky Mountain Laboratories, Inc. (Golden, CO). The powders were first distributed evenly on a conductive carbon adhesive tape, and coated with a thin layer of gold. The EDS elemental mapping was conducted at an accelerating voltage of 20 kV of an area imaged using Backscattered Electron signals where contrast is based on atomic number. The instrumentation was a JEOL 6400 Scanning Electron Microscope with an iXRF Model 500 EDS data acquisition system.

The size of the fenofibrate particles post-reconstitution of bulk powder and granules was evaluated in 0.01 N HCl at 37 °C by a light scattering method (Coulter LS230, Beckman Coulter, Fullerton, CA) with and without sonication (15 s). Particle sizing with sonication was conducted to deaggregate the materials to determine the inherent size of the individual fenofibrate particles. The suspensions resulting from the reconstitution assay had a fenofibrate concentration of approximately 50 mg/ml. The samples was analyzed in duplicate.

Compacts of the bulk powders and granules were prepared to test the effect of the powder compression process on the reconstituted fenofibrate particle size. For preparation of compacts (200-mg dose), the bulk powders or granules were compressed using 14 mm standard concave tooling and 1000 lbs pressure in an automatic Carver Tablet Press. The compacts were then manually pulverized and the resultant powder was tested for reconstitution (particle size as described above).

Optical micrographs of the reconstituted samples were generated using the Olympus model BH-02 microscope equipped with Hitachi model KPD50 color digital camera and Image-Pro Plus software.

The dissolution rate of the bulk powders from the three processes was examined using the SR8Plus Dissolution Test System (Hanson Research). The samples were analyzed in triplicate. The analytical conditions employed were

as follows: dissolution system-USP Apparatus II (paddle); dissolution medium – 0.01 N HCl with 0.025 M SDS; dissolution temperature – 37 °C; dissolution speed – 75 rpm; dissolution volume – 1 L; fenofibrate concentration – 200 μg/ml. The samples were filtered through a 0.2 μm GHP filter to remove undissolved fenofibrate, and then 10 μl were analyzed by HPLC (Waters) with UV detection at 293 nm on a YMC J'Sphere ODS-H80 250 × 4.6 mm I.D. S-4 μm, 8 nm column at 40 °C with acetonitrile:water pH adjusted to 2.5 with phosphoric acid (85:15) as the mobile phase and a flow rate of 2.25 ml/min.

The disintegration times of the ODT formulations were evaluated in 800 ml deionized water at 37 °C using the Electrolab Disintegration Tester from GlobePharma. The samples were analyzed in triplicate.

3. Results and discussion

The DSC of fenofibrate API and the bulk powders from the three intermediate processes shows a thermal event in the 82–85 °C range (Fig. 2). This corresponds to the melting endotherm for fenofibrate. The enthalpy (ΔH) values for melting for bulk powders from the three processes were similar and were observed to be approximately 43% of the corresponding value for fenofibrate API sample. The enthalpy value was expected based on the fenofibrate concentration in the powder blend composition. As evident from the DSC profiles, the blending and jet-milling steps for the three intermediate processes (A, B and C) did not affect the crystallinity of fenofibrate. This could be because the blending and jet-milling operations are performed under sufficiently gentle conditions that these do not impact the physical nature of the fenofibrate API. This is contrary to multiple examples found in the literature, where mechanical micronization and comminution produced varying degrees of amorphous material from crystalline samples [24–29]. However, there have also been a small number of articles in the literature describing no change in crystallinity upon milling of crystalline materials [30] or even an increase in crystallinity of partially or fully amorphous materials after high speed homogenization [31].

The processes used and the order of processing in the production of the bulk powders affect the uniformity of the distribution of the fenofibrate particles among the excipient particles in the dry powder state, as seen in the SEM–EDS images of the bulk powders in Fig. 3. In the case of process A, the bulk powder is jet-milling deprived, and the native, untreated fenofibrate particles (in a broad particle size range) are unevenly distributed in the powder mixture. When jet-milling of fenofibrate is performed prior to blending with excipients (process B), fenofibrate rich areas (seen as clusters of smaller particles) and excipient rich areas (larger particles) are observed. When blending of drug with excipients is performed prior to jet-milling (process C), the fenofibrate is more uniformly distributed among the excipient particles.

Table 1 illustrates the particle size of fenofibrate post-reconstitution (with and without sonication) of the bulk powders, compacts of bulk powders, granules and compacts of granules originating from the three core processes. The optical microscopy images of the reconstituted mixture (pre-sonication) from the bulk powders and granules are shown in Fig. 4, which correlate with the particle size data seen in Table 1.

For process A, the reconstituted particle size (pre- and post-sonication) for the bulk powder, compacts of the bulk powder, granules and compacts of granules were large and broadly distributed, representing the inherent particle size of the fenofibrate API.

For process B, the fenofibrate API (only) is first jet-milled, which reduces the inherent drug particle size. The milled API is then dry blended with excipients producing the bulk powder. For bulk powder, compacts of the bulk powder, granules and compacts of granules, the reconstituted particle size was smaller than that seen for process A, which corresponded to the drug being milled. However,

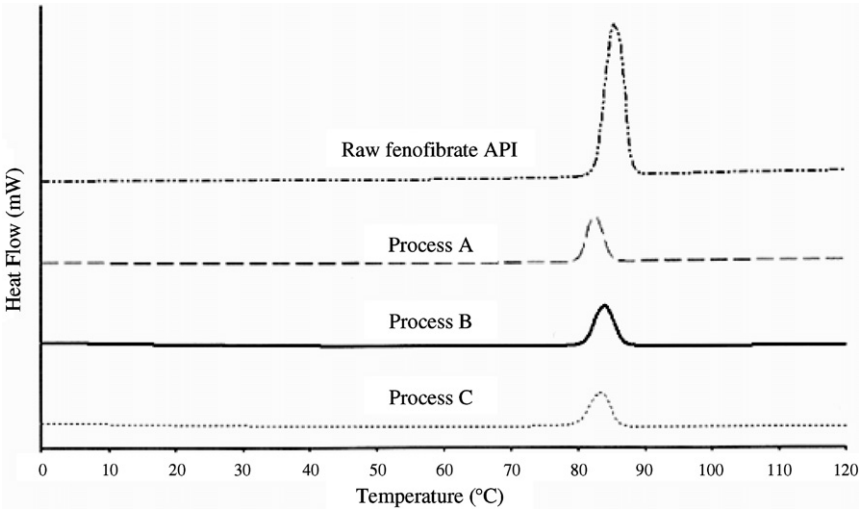

Fig. 2. DSC of the raw API powder and materials produced from the three bulk powder processing techniques.

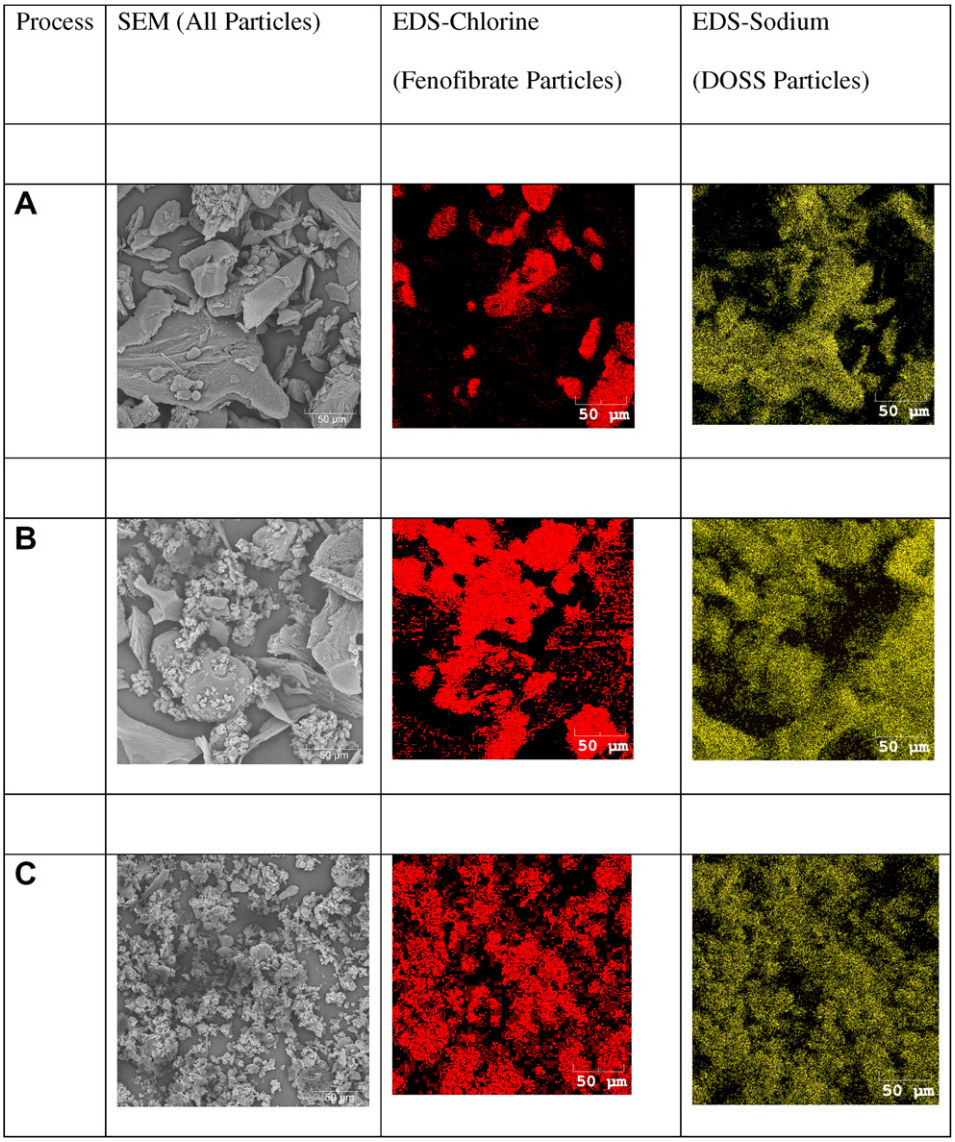

Fig. 3. SEM image and corresponding EDS images of bulk powder from the three processes.

Table 1
Particle size of the bulk powder and compacts post-reconstitution from the three processes

Formulation/process	Bulk powder analysis				Compact (of powder) analysis			
	Pre-sonication		Post-sonication		Pre-sonication		Post-sonication	
	Volume mean (μm)	D90[a] (μm)	Volume mean (μm)	D90[a] (μm)	Volume mean (μm)	D90[a] (μm)	Volume mean (μm)	D90[a] (μm)
Process A (no granulation)	129.70	200.90	108.50	174.20	98.11	169.10	88.86	166.20
	106.40	164.70	107.80	171.60	123.20	216.20	75.84	175.40
Process A (granulation)	141.10	261.30	91.91	166.80	95.94	174.30	39.17	104.10
	135.10	235.20	105.30	166.50	90.12	166.20	24.15	52.57
Process B (no granulation)	15.37	25.78	35.73	108.00	20.43	51.29	57.50	168.60
	28.81	93.90	12.86	26.56	23.38	61.58	12.59	30.16
Process B (granulation)	13.23	34.31	7.76	16.86	13.96	34.90	10.77	25.25
	12.57	30.28	7.35	15.46	20.20	51.04	11.91	29.29
Process C (no granulation)	5.60	12.06	5.82	12.78	9.46	19.35	6.99	13.77
	5.64	12.09	5.58	12.09	10.17	20.90	7.36	15.09
Process C (granulation)	6.45	13.47	5.87	12.41	10.91	25.26	5.92	12.83
	6.42	13.41	6.23	13.65	10.91	26.11	5.84	12.53

[a] Ninety percent of the particles are smaller than this size on a volume basis.

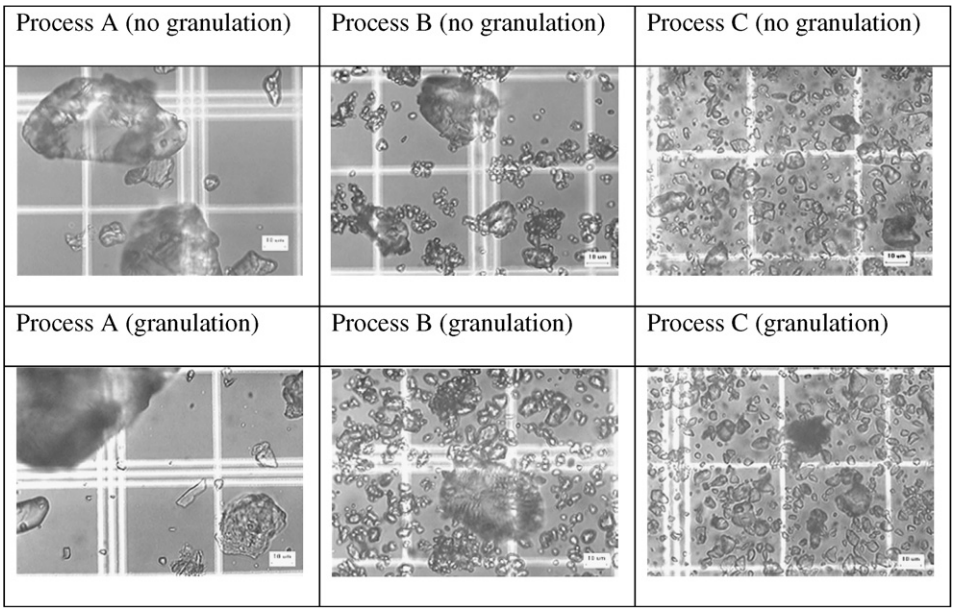

Fig. 4. Optical micrographs of the reconstituted suspensions from the three processes (reconstitution of bulk powder with no sonication).

the milled fenofibrate particles, which were observed to be aggregated in the SEM–EDS images of the bulk powder, remained aggregated post-reconstitution. The aggregates had a broad particle size distribution and heterogeneous shape. Sonication appeared to deaggregate granules into dispersed individual particles with an inherent size of approximately 7 μm, but did not significantly deaggregate bulk powder, compacts of bulk powder or compacts of granules, suggesting that strong aggregates of fenofibrate particles were present. The milling of drug particles may cause production of electrostatic (triboelectric) cohesive/adhesive forces, thereby yielding a thermodynamically unstable system [32–34]. There are no excipient particles to stabilize the fenofibrate surface and hence bulk of the drug particles are extensively aggregated (confirmed by SEM and optical microscopy images). Other events, e.g. van der Waals forces and hydrogen bonding, may also be contributing to this phenomenon [32–35]. Milling a poorly water soluble drug crystal creates a surface that is hydrophobic and poorly wettable [5].

Process C produced materials that gave the best results. The reconstitution of bulk powder and granules resulted in well-dispersed material (as observed in optical microscopy images), with particle sizes in 5–7 μm range. For the reconstituted bulk powder and granules, sonication had no significant effect on the particle size. However, sonication caused deaggregation of the material from compacts, with observed fenofibrate particle size decreasing from 9 to 11 μm (pre-sonication) to the 6–7 μm range post-sonication. Jet-milling the drug/excipient blend resulted in drug particles (<7 μm) uniformly distributed in the powder blend (confirmed by SEM–EDS). The excipient particles keep the fenofibrate particles separated from each other, thus inhibiting drug particle aggregation. This results in optimum reconstitution of the drug particles from the powder mixture, post-wetting/hydration. In addition, milling in presence of surfactant (DOSS) and hydrophilic polymer (copovidone S630) causes hydrophilization of the newly created drug crystal surface [5]. This leads to improved wetting of the surface, and efficient reconstitution of the drug in suspension.

In Fig. 5, the average dissolution results for the bulk powders from the three processes are compared. The time required for approximately 70% drug dissolution for the three processes, A, B and C, were 120, 30 and 6 min, respectively. There was a correlation between the in vitro dissolution and particle size (reconstitution) results (the smaller the observed API particle size in suspension, the more rapid the dissolution). The liberated individual drug particles rapidly dissolve in the aqueous medium. For the bulk powder from process B, due to the aerophilicity of such a milled hydrophobic material and the aggregation

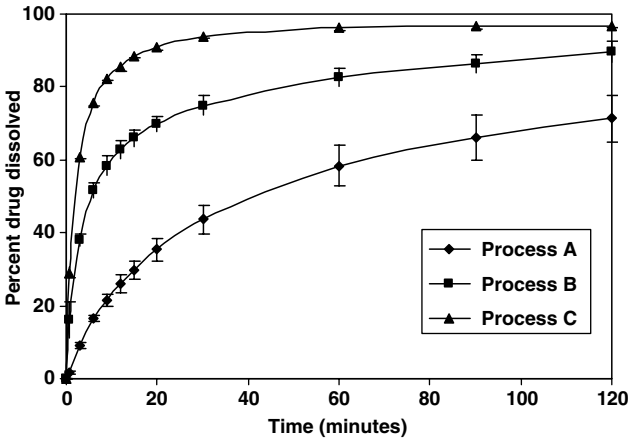

Fig. 5. Dissolution of fenofibrate from powders prepared from the three core processing techniques (using USP Apparatus II (paddle) and 0.01 N HCl/0.025 M SDS dissolution medium).

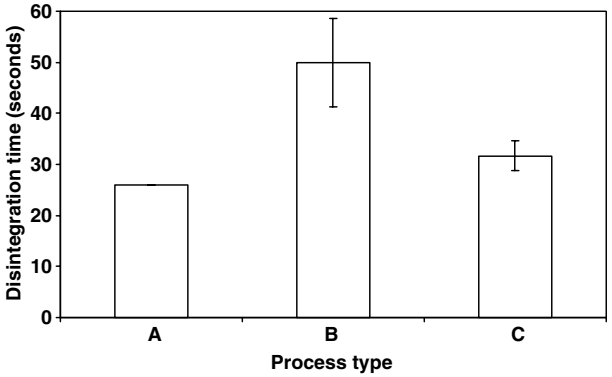

Fig. 6. Disintegration times for the fenofibrate ODTs prepared from the three processes. Error bars shown are standard deviations. The disintegration times for all replicates for process A were identical, and thus the standard deviation is zero.

of the hydrophobic particles milled in the absence of mannitol, the dissolution rate is not increased. This is what would be expected from the Noyes–Whitney equation [5] when the aggregated particle size, not the inherent particle size, is considered. Unless the newly created drug surface is hydrophilized, and the individual drug particles disperse into discrete, non-aggregated, drug particles, the dissolution rate would not increase [5]. The hydrophilicity and wettability is increased for fenofibrate particles from process C, since they are co-processed with excipients.

The disintegration times (DTs) of the ODT formulations prepared from granulated material from the bulk powder prepared from the three processes are exhibited in Fig. 6. The DTs of ODTs prepared from the three processes were <60 s. This DT is typical of marketed ODT products. This showed that the combination of the bulking/wetting agent, xylitol and the superdisintegrant, crospovidone, produced an optimum porous matrix structure, which enabled rapid wicking of water to facilitate speedy disintegration of the tablets.

4. Conclusions

The crystallinity of fenofibrate was not impacted by the blending and jet-milling events from the three processes. Process A (which omitted jet-milling) showed poorer fenofibrate reconstitution than the jet-milled processes. Process C (which milled a blend of drug and excipient) yielded material that exhibited the best performance: the reconstitution of fenofibrate was optimal (volume mean size ~6 μm) coupled with excellent disintegration time values (~30 s) for the ODTs. The dissolution of fenofibrate was relatively faster from the formulation prepared from process C as compared to processes A and B. Process B (which milled fenofibrate first, followed by blending with excipients) exhibited performance that was intermediate of processes A and C.

In conclusion, it was found that the order of jet-milling was important; milling a blend of fenofibrate/excipient was advantageous over milling the raw drug alone (followed by blending with excipients). Fenofibrate bulk powder made by Process C (blending followed by jet-milling) was shown to have rapid dissolution, and was further processed into orally disintegrating tablets which were shown to have rapid disintegration.

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