Current Drug Delivery, 2021, *18*, 460-470

RESEARCH ARTICLE

It is Possible to Achieve Tablets With Good Tabletability From Solid Dispersions – The Case of the High Dose Drug Gemfibrozil

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Abstract: ***Background*:** Solid Dispersions (SDs) have been extensively used to increase the dissolution of poorly water-soluble drugs. However, there are few studies exploring SDs properties that must be considered during tablet development, like tabletability. Poorly water-soluble drugs with poor compression properties and high therapeutic doses, like gemfibrozil, are an additional challenge in the production of SDs-based tablets.

***Objective*:** This study evaluates the applicability of SDs to improve both tabletability and dissolution rate of gemfibrozil. A SD-based tablet formulation was also proposed.

***Methods*:** SDs were prepared by ball milling, using hydroxypropyl methylcellulose (HPMC) as a carrier, according to a 2^3 factorial design. The formulation variables were gemfibrozil:HPMC ratio, milling speed, and milling time. The response in the factorial analysis was the tensile strength of the compacted SDs. Dissolution rate and solid-state characterization of SDs were also performed.

***Results*:** SDs showed simultaneous drug dissolution enhancement and improved tabletability when compared to corresponding physical mixtures and gemfibrozil. The main variable influencing drug dissolution and tabletability was the gemfibrozil:HPMC ratio. Tablets containing gemfibrozil-HPMC-SD (1:0.250 w/w) and croscarmellose sodium showed fast and complete drug release, while those containing the same SD and sodium starch glycolate exhibited poor drug release due to their prolonged disintegration time.

***Conclusion*:** SDs proved to be effective for simultaneously improving tabletability and dissolution profile of gemfibrozil. Tablets containing gemfibrozil-HPMC-SD and croscarmellose sodium as disintegrating agent showed improved drug release and good mechanical strength, demonstrating the potential of HPMC-based SDs to simultaneously overcome the poor dissolution and tabletability properties of this drug.

ARTICLE HISTORY

Received: July 20, 2020
Revised: August 12, 2020
Accepted: September 25, 2020

DOI:
10.2174/1567201817666201023121948

Keywords: Gemfibrozil, solid dispersion, tabletability, tablet, drug dissolution, solubility.

1. INTRODUCTION

Solid Dispersions (SDs) are dispersions consisting of one or more drugs in inert carriers (usually polymers) at a solid-state. They have been considered one of the most promising strategies to improve the dissolution profile and oral bioavailability of poorly water-soluble drugs [1, 2]. Among the various methods available for obtaining SDs, ball-milling the drug together with a polymeric carrier is a solvent-free, environmentally friendly and low-cost method that is easy to scale up [3, 4].

Despite the advantageous properties of SDs, the number of SD-based products commercially available is still disappointingly low. This is due to difficulties in the large-scale manufacture of effective, stable and robust dosage forms from SDs [5-7]. Also, there is still limited knowledge on how processing techniques might influence parameters such as the tableting behavior of SDs and their formulations. However, this is a fundamental aspect since it acquires knowledge indispensable for further formulation development [8].

The preferred dosage form used in the formulation of SDs is a tablet [9]. However, tableting of SDs can be hindered by poor compression properties, providing a major obstacle to their large-scale production [5-7]. Poor powder tabletability impairs the mechanical strength of the manufac-

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1875-5704/21 $65.00+.00

tured tablets, and mechanically weak tablets cannot withstand stresses to which they are subjected during packaging, shipping and handling [10].

Often, the amount of SD powder in a tablet is relatively high. The manufacturability of SDs, therefore, will influence the compaction properties of the final formulation and the success of tablet manufacturing [11]. Besides that, drugs with high therapeutic doses are an additional challenge in the production of tablets containing SDs. This is because the use of high carrier/drug ratios is generally required to obtain SDs with satisfactory drug dissolution rate and physical stability [9, 11], hindering the production of tablets of viable size for oral administration of high dose drugs.

Thus, drugs that simultaneously exhibit low aqueous solubility, poor compression properties and high therapeutic doses are quite challenging for the development of SDs. Gemfibrozil, as a poorly water-soluble and poorly compressible drug [12], available in the world pharmaceutical market in the form of capsules or tablets with 300, 600 or 900 mg/unit doses, was selected as a model drug for obtaining SDs in this study. A smart and practical solution to mitigate the limitations highlighted above could be to employ a polymeric carrier which, in low amounts relative to the drug content, may be capable of simultaneously improving the drug dissolution and compression properties.

Table 1. Gemfibrozil-HPMC ball-milled SDs (F1-F11), the corresponding physical mixtures ($PM_{0.250}$, $PM_{0.156}$ and$PM_{0.062}$) and milled gemfibrozil ($MG_{30, 180}$, $MG_{30, 360}$, $MG_{60, 180}$ and $MG_{60, 360}$).

Sample	Gemfibrozil:HPMC (w/w)	Milling Time (min)	Milling Speed (rpm)
F1	1:0.062	30	180
F2	1:0.250	30	180
F3	1:0.062	60	180
F4	1:0.250	60	180
F5	1:0.062	30	360
F6	1:0.250	30	360
F7	1:0.062	60	360
F8	1:0.250	60	360
F9	1:0.156	45	270
F10	1:0.156	45	270
F11	1:0.156	45	270
$PM_{0.250}$	1:0.250	-	-
$PM_{0.156}$	1:0.156	-	-
$PM_{0.062}$	1:0.062	-	-
$MG_{30, 180}$	-	30	180
$MG_{30, 360}$	-	30	360
$MG_{60, 180}$	-	60	180
$MG_{60, 360}$	-	60	360

F9 to F11 are replicates obtained by combining the intermediate levels of the factors in the factorial design.

A wide variety of polymeric carriers are used to achieve specific goals in the development of SDs. HPMC is a nonionic, water-soluble cellulose ether with great importance as an SD carrier due to its potential to prevent drug recrystallization and produce supersaturated solutions [13, 14]. Publications report that HPMC based-SDs can enhance the dissolution profile of many poorly soluble drugs, but there are no studies in the literature on the tabletability of HPMC based-SDs containing poorly compressible drugs.

The present paper evaluates the applicability of SDs to simultaneously improve tabletability and dissolution rate of gemfibrozil. The effects of gemfibrozil:HPMC ratio, milling speed and milling time on both Tensile Strength (TS) and drug dissolution rate of SDs were studied. Additional characterization of SDs was carried out regarding their aqueous solubility and solid-state properties. Also, SD-based gemfibrozil tablets were obtained and characterized in terms of hardness, TS, disintegration time and drug release rate.

2. MATERIALS AND METHODS

2.1. Materials

Gemfibrozil (Nutrifarm, Brazil), HPMC (Methocel™ E5 Premium LV, Dow Chemical Company, USA), croscarmellose sodium (Solutab®, Blanver, Brazil), and sodium starch glycolate (Explosol®, Blanver, Brazil) were used to obtain the SDs and tablet formulations. All other chemicals used were of analytical grade.

2.2. Preparation of SDs, Physical Mixtures and Milled Gemfibrozil

All gemfibrozil-HPMC SDs (30 g of each) were prepared in a ball mill (Retsch PM 200, Germany) with two 125 mL jars, containing three 20 mm-steel balls each. The SD formulations (F1 to F11) were based on a 2^3 factorial design, corresponding to the analysis of the influences of three factors (drug:carrier ratio, milling time, and milling speed) with three central points (Table **1**). The response in the factorial analysis was the TS of the compacted material obtained, from F1 to F11.

Physical Mixtures (PM), 30 g each, were prepared by mixing gemfibrozil and HPMC in a porcelain mortar, with the aid of a spatula, in the same drug:carrier ratios as the corresponding SDs. PMs obtained in the gemfibrozil:HPMC proportions of 1:0.250, 1:0.56 and 1:0.062 (w/w) were designated as $PM_{0.250}$, $PM_{0.156}$ and $PM_{0.062}$, respectively (Table **1**).

In addition, gemfibrozil (30 g) was milled under the same conditions as the SDs, without the addition of HPMC. The resulting milled gemfibrozil (MG) was designated as $MG_{30,180}$, $MG_{30,360}$, $MG_{60,180}$ and $MG_{60,360}$, depending on the milling time (30 or 60 min) and the milling speed (180 or 360 rpm), as described in Table **1**.

2.3. Tabletability Study

Compacts (0.250 g each) were prepared by compressing the samples (SDs, physical mixtures and gemfibrozil) at 1.0

ton for 5 s in a hydraulic press (Protécni, Brazil) equipped with 10 mm-diameter punch and die. The diameter, thickness (caliper 5234, Black Bull, Brazil) and hardness (Ethik 298 DGP II hardness tester, Brazil) of the compacts were determined (n=3). The tabletability of the compacts was evaluated by calculating the TS (MPa) using Equation 1, where "h" is the force (N) required to break the compact (hardness), "d" is the diameter (mm) and "t" is the thickness (mm) of the compact [10].

$$TS = 2h / \pi dt \quad (1)$$

2.4. Solubility Study

Flasks (n=3) containing 25 mL of phosphate buffer (pH 5.8 or 6.8, both prepared according to USP, 2013) and excessive amounts of samples (gemfibrozil, SD or physical mixture) were agitated in an orbital shaker (Braun Biotech Certomat HK, Germany), at 100 rpm, 37°C, for 48 hours. Aliquots were collected in 24 and 48 h, centrifuged at 3000 rpm, for 15 min (Nova Técnica FC0G-0035 centrifuge, Brazil), and quantified by spectrophotometry at 276 nm (Shimadzu 1601PC spectrophotometer, Japan) [11-19].

2.5. Dissolution Study

The dissolution tests (n=3) were performed in a dissolution tester (Nova Ética 299/6, Brazil), using the paddle apparatus (100 rpm), 900 mL of phosphate buffer pH 5.8 at 37°C, without medium replacement (the volume change was adjusted in the calculation). Gelatin capsules containing samples (gemfibrozil, SD or physical mixture) equivalent to 50 mg of gemfibrozil were tested using spiral sinkers. Aliquots (5 mL) were withdrawn at predefined time intervals, centrifuged at 3000 rpm for 15 min (Nova Técnica FC0G-0035 centrifuge, Brazil) and quantified by spectrophotometry at 276 nm (Shimadzu 1601PC spectrophotometer, Japan). The Sink Index (SI) was calculated using Equation 2, where "C_S" is the solubility of crystalline drug, "V" is the volume of dissolution medium, and "Dose" is the total amount of drug in the test sample (equation 2) [20].

$$SI = Cs/(Dose/V) \quad (2)$$

The dissolution efficiency (DE) was calculated as the area under the dissolution curve (AUC) up to a certain time (60 min), expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [16].

2.6. Solid-state Characterization of SDs

2.6.1. Scanning Electron Microscopy (SEM)

Samples mounted onto metal stubs were vacuum-coated with gold (DentonVaccum Desk V, Japan) and analyzed using a scanning electron microscope (Jeol JSM 6701F, Japan).

2.6.2. Differential Scanning Calorimetry (DSC)

DSC curves were obtained using hermetically sealed aluminum crucibles, 3 mg of sample, nitrogen atmosphere (50 mL min^{-1}), temperature range of 25-300°C, and heating rate of 10°C min^{-1} (TA Instruments DSC Q20 calorimeter, USA).

2.6.3. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were acquired on a Spectrum One B spectrophotometer (Perkin-Elmer, USA), using an attenuated total reflectance accessory, with the collection of 12 scans in 400-4000 cm^{-1} region at a resolution of 4 cm^{-1}.

2.6.4. X-Ray Powder Diffraction (XRPD)

XRPD analyses were performed using a θ–θ X-ray diffractometer (D2 Phaser, Bruker, USA), operating with Kα copper radiation (λ = 1.5418 Å), with a current of 10 mA and voltage of 30 kV. Detection was performed on a scintillation counter one-dimensional LYNXEYE detector. Measurements were taken at room temperature, at 2θ scanning from 5° to 40° and with a 0.091° step size.

2.7. SD-Based Gemfibrozil Tablets

SD-based gemfibrozil 300 mg tablets (T1 and T2) were obtained by direct compression (Protécni hydraulic press, Brazil, equipped with 10 mm-diameter punch and die) of F8 (87% w/w) pre-mixed with a disintegrating agent (13% w/w; croscarmellose sodium for T1, and sodium starch glycolate for T2) using a mortar and a pestle. The concentration of the disintegrating agent was based on preliminary tests (low amounts of disintegrating agents produced tablets that did not disintegrate). The diameter, thickness (caliper 5234, Black Bull, Brazil), hardness (Ethik 298 DGP II hardness tester, Brazil), TS (according to Equation 1), disintegration time (USP disintegration apparatus, Nova Ética, Brazil), and drug dissolution rate (as described in section 2.5, using phosphate buffer pH 6.8 as the dissolution medium) of the tablets were determined (n=3).

2.8. Statistical Analysis

The experimental design in section 2.2 was elaborated and analyzed using Design Expert® 9.0.6.2 software (Stat-Easy, USA), generating a response surface graph. Effect selection was implemented to obtain a significant model with a non-significant lack of fit. The data generated from the response were fitted into various polynomial models, and the best-fitting model was chosen based on the coefficient of determination (R2) and lack-of-fit statistics.

Results of TS, Q_{20min}, Q_{60min} (the dissolution percentages at 20 and 60 min), DE and drug solubility were compared by the two-tailed t-test or by one-way ANOVA with Tukey's post hoc analysis at a *p*-value of 0.05 (GraphPad Prism 6.01, USA).

3. RESULTS AND DISCUSSION

3.1. Tabletability Study

The compression properties of powders are very important for the production of tablets of adequate quality. Tabletability is the ability of powder material to be transformed into a tablet of a certain mechanical resistance (hardness and TS) under the effect of compaction pressure, that is, it is a property that can be used to evaluate the compaction capacity of a powder, and can be represented by a graph of TS *versus* compaction pressure [10, 17].

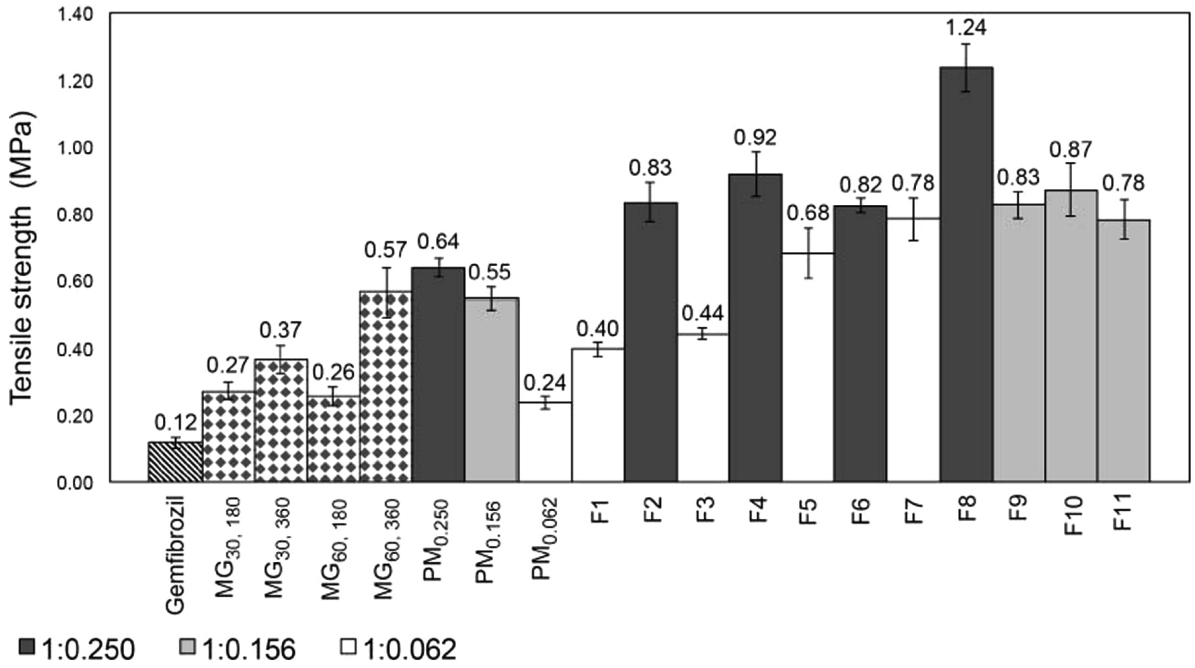

Fig. (1). TS results of gemfibrozil, milled gemfibrozil ($MG_{30,180}$, $MG_{30,360}$, $MG_{60,180}$ and $MG_{60,360}$), SDs (F1-F11) and physical mixtures ($PM_{0.250}$, $PM_{0.156}$ and $PM_{0.062}$).

Gemfibrozil compression was handled with difficulty, as the compacts tended to break during the process. Gemfibrozil compacts obtained intact had a TS of 0.12 MPa (Fig. **1**), much lower than the target value (>1 MPa) typically desired for compressed tablets [18], showing poor tabletability. Gemfibrozil milled under different times and speeds presented higher TSs than gemfibrozil (p<0.05) (Fig. **1**), probably due to the smaller primary particles of the powder (section 3.3) and consequently increased surface area available for inter-particle bonding [19, 20]. The TS values of milled gemfibrozil presented the following order: $MG_{30,180}$ = $MG_{30,360}$ = $MG_{60,180}$ < $MG_{60,360}$ (p≤0.0002). This shows that simultaneously increasing the milling time and speed enhanced the tabletability of milled gemfibrozil relative to the other milling conditions tested.

The TS results for the physical mixtures were $PM_{0.250}$ > $PM_{0.156}$ > $PM_{0.062}$ > gemfibrozil (p<0.01), indicating that the simple association with HPMC increased gemfibrozil tabletability, which is directly proportional to the polymer content.

The TSs of F1 to F11 were higher than those of the physical mixtures containing the respective gemfibrozil:HPMC ratios ($PM_{0.250}$*, $PM_{0.156}$** or $PM_{0.062}$***) (*p<0.01; **p<0.001; ***p<0.05). This demonstrates that the TS enhancement was not caused only by the presence of HPMC, but obtaining the formulations as SDs also contributed to the higher mechanical strength of the compacted material.

In the factorial analysis, the adequacy of the model fitted to the response was based on a p-value of less than 0.05, which indicates that the model is significant. Model selection for TS was based on the coefficient of determination (R^2>0.9), F value (18.13) and adequate precision (15.70). The main terms (gemfibrozil:HPMC ratio, milling time and milling speed) in the TS model were significant at p<0.05. The F-value confirmed that the lack of fit is not significant (p>0.05).

The second-order polynomial equation (equation 3) fitted better the experimental data for the significant model. The magnitude of the gemfibrozil:HPMC ratio (A) effect on TS was more than twice the effect of milling time (B) and 1.6 times the effect of milling speed (C) (p<0.001). Equation 3 shows that the effects of factors A, B and C are positive, *i.e.*, the higher the level of individual factors (1:0.250, 60 min, and 360 rpm), the higher the response, which would explain the higher TS of F8 compared to that of the other SDs (p<0.0001). The interactions showed statistically non-significant effects in the analysis, indicating that the response depends more on the individual variation of the factors than the interactions between them. However, the interactions may increase the response when the AB, BC or ABC factors are combined, both at their upper or lower levels (equation 3).

$$TS=0.78 + 0.19A + 0.081B + 0.12C + 0.043AB - 0.039AC + 0.048BC + 0.034\ ABC \quad (3)$$

Figure **2** represents the 3-dimensional response surface plot for TS, depicting a linear trend of TS in ascending order, with an augmentation of carrier:drug ratio and milling speed. The results of the factorial analysis and the F8' TS of 1.24 MPa (compared to 0.12 MPa of gemfibrozil) demonstrate that HPMC can be satisfactorily used in ball-milled SDs to increase the tabletability of poorly compressible drugs, such as gemfibrozil.

3.2. Dissolution Study

Formulations F2, F7 and F8 were selected for the dissolution study in comparison with gemfibrozil, $MG_{30,180}$, $MG_{60,360}$, $PM_{0.250}$, and $PM_{0.062}$. First, F8 was selected because it was the SD with the highest TS in the tabletability study. Then, the same milling conditions as F8 were maintained, and F7 was selected to study the effect of a lower amount of HPMC on the drug dissolution rate. Finally, the drug:carrier ratio was fixed (as compared to F8), and F2 was selected to study the effect of milder milling conditions on dissolution properties of the SDs.

Considering the information in section 2.5 (V= 0.9 L and Dose = 50 mg) and the results for gemfibrozil solubility (C_S) in Table **2**, SI values of 14.65 and 0.49 were calculated for phosphate buffer pH 6.8 and 5.8, respectively. Although employing sink conditions (SI > 3) is common practice for quality assurance of oral solid dosage forms, the application of non-sink dissolution tests can be recommended in order to evaluate the true performance of formulations and to address the tendency for drug precipitation [15]. Therefore, a phosphate buffer pH 5.8 was selected for the dissolution study of SDs in non-sink conditions.

Milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$) had lower $Q_{20\text{-}min}$, Q_{60min} and DE than those of gemfibrozil (Figs. **3** and **4**) due to the agglomeration of the primary particles of the powder caused by milling (section 3.3). Thus, although milling may raise the dissolution rate of a drug by reducing the particle size and by increasing the surface area in contact with the dissolution medium, this has not been observed for $MG_{30,180}$ and $MG_{60,360}$.

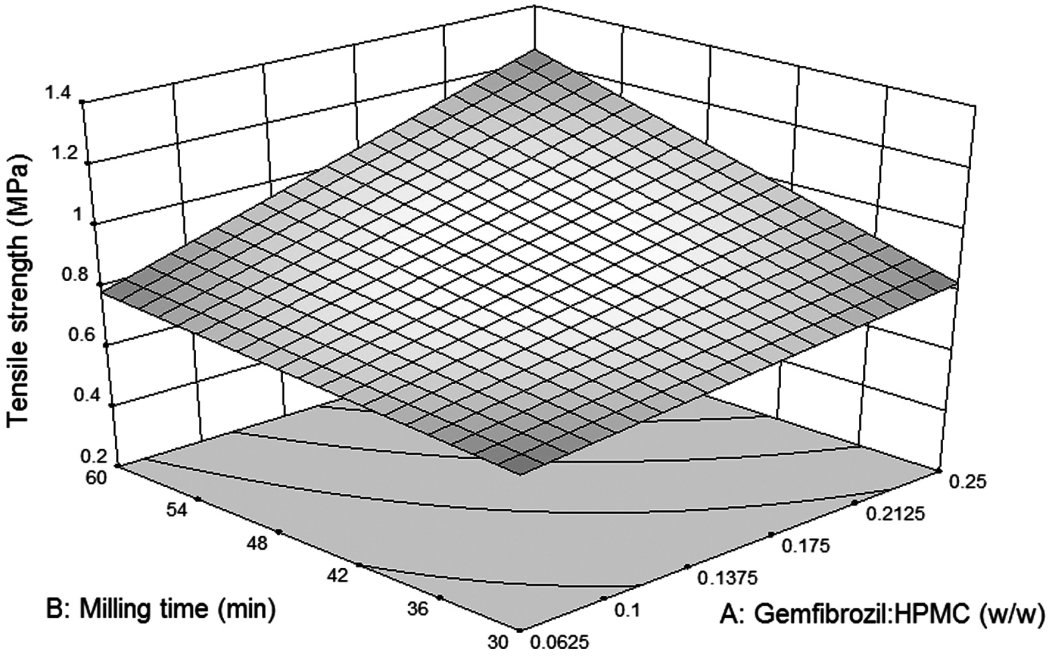

Fig. (2). Response surface graph with the influences of gemfibrozil:HPMC ratio and milling speed on the TS of SDs, when milling time is 60 min.

Table 2. Solubility of gemfibrozil, milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$), SDs (F2 and F8) and physical mixture ($PM_{0.250}$) in phosphate buffer (pH 6.8 or 5.8).

Sample	Solvent (Phosphate Buffer)	Solubility (mg/L)*	
		24 h	48 h
Gemfibrozil	pH 6.8	546.19 ± 64.36	659.33 ± 79.38**
Gemfibrozil	pH 5.8	17.19 ± 0.01	21.97 ± 0.01**
$MG_{30,180}$	pH 5.8	19.50 ± 0.01	30.31 ± 0.01
$MG_{60,360}$	pH 5.8	19.66 ± 0.01	35.65 ± 0.02
$PM_{0.250}$	pH 5.8	33.51 ± 0.02	35.02 ± 0.01
F2	pH 5.8	44.81 ± 0.01	101.4 ± 0.01
F8	pH 5.8	54.07 ± 0.01	113.84 ± 0.01

*Results expressed as average ± standard deviation. ** Solubility of Crystalline drug (C_S) used to calculate the Sink Index (SI).

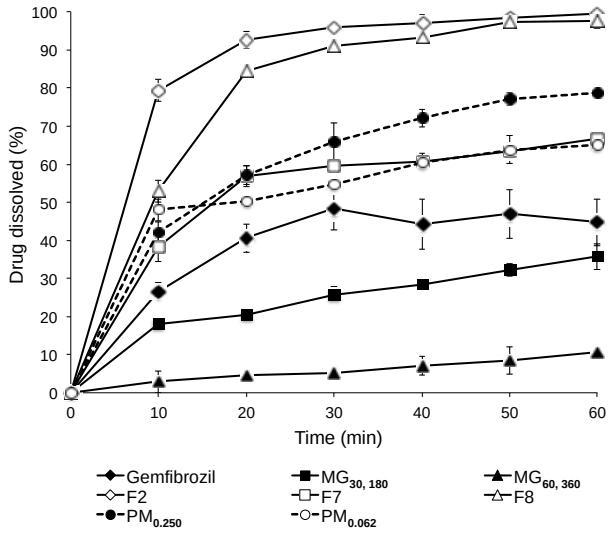

Fig. (3). Dissolution profiles of gemfibrozil, milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$), SDs (F2, F7 and F8) and physical mixtures ($PM_{0,250}$ and $PM_{0,062}$) in phosphate buffer pH 5.8.

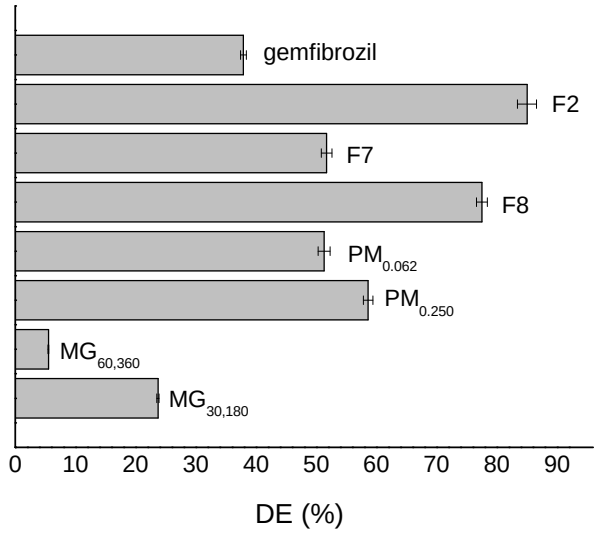

Fig. (4). Dissolution efficiency values of gemfibrozil, milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$), SDs (F2, F7 and F8) and physical mixtures ($PM_{0.250}$ and $PM_{0.062}$).

$PM_{0.250}$ and $PM_{0.062}$ presented higher values of DE, Q_{20min} and Q_{60min} compared to gemfibrozil, and these values were higher for $PM_{0.250}$ than $PM_{0.062}$ (p<0.0001). This shows that the simple association of gemfibrozil with HPMC caused an increased drug dissolution rate, this effect being directly proportional to the polymer concentration (Figs. **3** and **4**).

F7 and F8 were produced using identical milling conditions (360 rpm, 60 min) and different gemfibrozil:HPMC ratios (1:0.062 and 1:0.250 w/w, respectively). The dissolution profiles (Fig. **3**), DE values (Fig. **4**) and the Q_{20min} and Q_{60min}values show that F8 performed much better than F7 (p<0.0001), and that F7 had a drug dissolution rate very close to that of the corresponding physical mixture ($PM_{0.062}$). However, the Q_{20min} of F7 was slightly higher compared to that of $PM_{0.062}$ (p<0.0001); this is insignificant in practical terms. The dissolution results of F7 indicate that obtaining a ball-milling SD with 1:0.062 gemfibrozil:HPMC ratio is not effective in improving the drug dissolution rate, probably due to the very low amount of HPMC in the formulation [19, 20].

On the other hand, F2 and F8 had higher drug dissolution profiles (higher DE, Q_{20min} and Q_{60min} values, p<0.0001) than $PM_{0.250}$, showing the rapid (Q_{20min}>80%) and complete (Q_{60min}> 95%) release of gemfibrozil (Figs. **3** and **4**). Q_{20min} (p<0.0001) and DE (p<0.05) were higher for F2 than for F8, showing that milling conditions may influence the drug release rate. The results show that ball-milled SDs with gemfibrozil:HPMC ratio of 1:0.250 (w/w) are very effective in increasing the gemfibrozil dissolution rate, even in non-sink conditions, in both milling conditions tested.

F2 and F8 were then selected for the solubility study (Table **2**) in comparison with gemfibrozil, $MG_{30,180}$, $MG_{60,360}$ and $PM_{0.250}$. The solubility results of gemfibrozil in Table **2** are consistent with data from the literature that reports the pH-dependent solubility profile of this drug, which increases significantly as the pH rises from ~ 6 to 7 [21-24].

The solubility values (24 and 48 h) of $MG_{30,180}$ and $MG_{60,360}$ were higher compared to gemfibrozil (p<0.0001), which may seem inconsistent with the better dissolution performance of gemfibrozil (Fig. **3**). This occurred because the solubility test was much longer than the dissolution test. In the dissolution test, the particle agglomerates of $MG_{30,180}$ and $MG_{60,\ 360}$ resulted in lower surface area, which, combined with poor drug solubility, produced dissolution rates lower than gemfibrozil during the 60 min of the test. In the solubility experiment, it is possible that $MG_{30,180}$ and $MG_{60,360}$ had lower solubilization rates at the beginning but subsequently reached a greater extent of solubilization than gemfibrozil. This may be related to the milling effect on granulometry of these samples (section 3.3). The longer testing time allowed the disintegration of milled gemfibrozil agglomerates, releasing the small primary particles obtained by milling, leading to larger powder surface area in contact with the solvent, and higher solubility levels in 24 and 48 h.

The solubility results of $PM_{0.250}$ were higher than that of gemfibrozil (p<0.0001), which would explain the better dissolution profile of this physical mixture compared to the neat drug. This was due to the association between the drug and the HPMC, even by simple mixing, which tends to improve the wettability and, consequently, the solubility and dissolution rate of the drug.

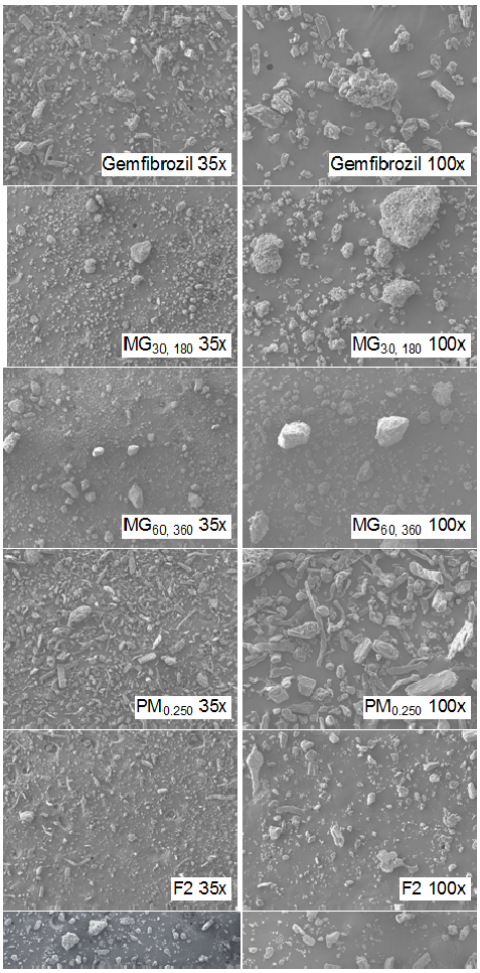

Fig. (5). Micrographs of gemfibrozil, milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$), SDs (F2 and F8) and physical mixture ($PM_{0.250}$).

F2 and F8 had higher solubility results ($p<0.0001$) than gemfibrozil, $MG_{30,180}$, $MG_{60,360}$ and $PM_{0.250}$ (Table **2**). The solubility results of F2 and F8, in 48 h, were 4.6 and 5.2-fold higher, respectively, compared to gemfibrozil, and 2.9 and 3.2-fold higher, respectively, compared to $PM_{0.250}$. This explains the excellent performance of F2 and F8 in the dissolution study and is probably related to the good wettability and small primary particles (section 3.3) of these SDS, as well as the capacity of HPMC in producing supersaturated solutions [21]. For these reasons, the F2 and F8 SDs formulations were selected for further solid-state characterization.

3.3. SDs Solid-State Characterization

3.3.1. SEM

Gemfibrozil showed particles with a crystalline appearance at 35x and 100x magnifications (Fig. **5**). Micrographs of $MG_{30,180}$ and $MG_{60,360}$ exhibited large agglomerates, which appeared denser when formed under more drastic milling conditions (time and speed). This suggests that milling initially reduced the particle size of gemfibrozil, but that these smaller particles were agglomerated in the course of the milling process. Similarly, micrographs of F2 and F8 suggest the reduction of the primary particles (in comparison to $PM_{0.250}$) and the agglomeration of these smaller particles, forming larger agglomerates for the SD milled under more drastic conditions (F8). This occurred because mechanical energy is applied in the milling operation so as to physically divide coarse particles into finer particles, resulting in increased surface area and higher surface free energy, which can promote particle agglomeration [22].

3.3.2. DSC

The DSC curve of gemfibrozil (Fig. **6**) showed a single melting endothermic event (T_{peak} = 61.40 °C; ΔH = 120.00 J/g), evidencing the crystalline nature of the drug. The DSC curves of $MG_{30,180}$ (T_{peak} = 61.04 °C; ΔH = 122.00 J/g) and $MG_{60,360}$ (T_{peak} = 60.55 °C; ΔH = 136.10 J/g) presented the melting peak in the same temperature range as gemfibrozil, without significant melting enthalpy (ΔH) variation, indicating that milling did not alter the crystalline nature of the drug.

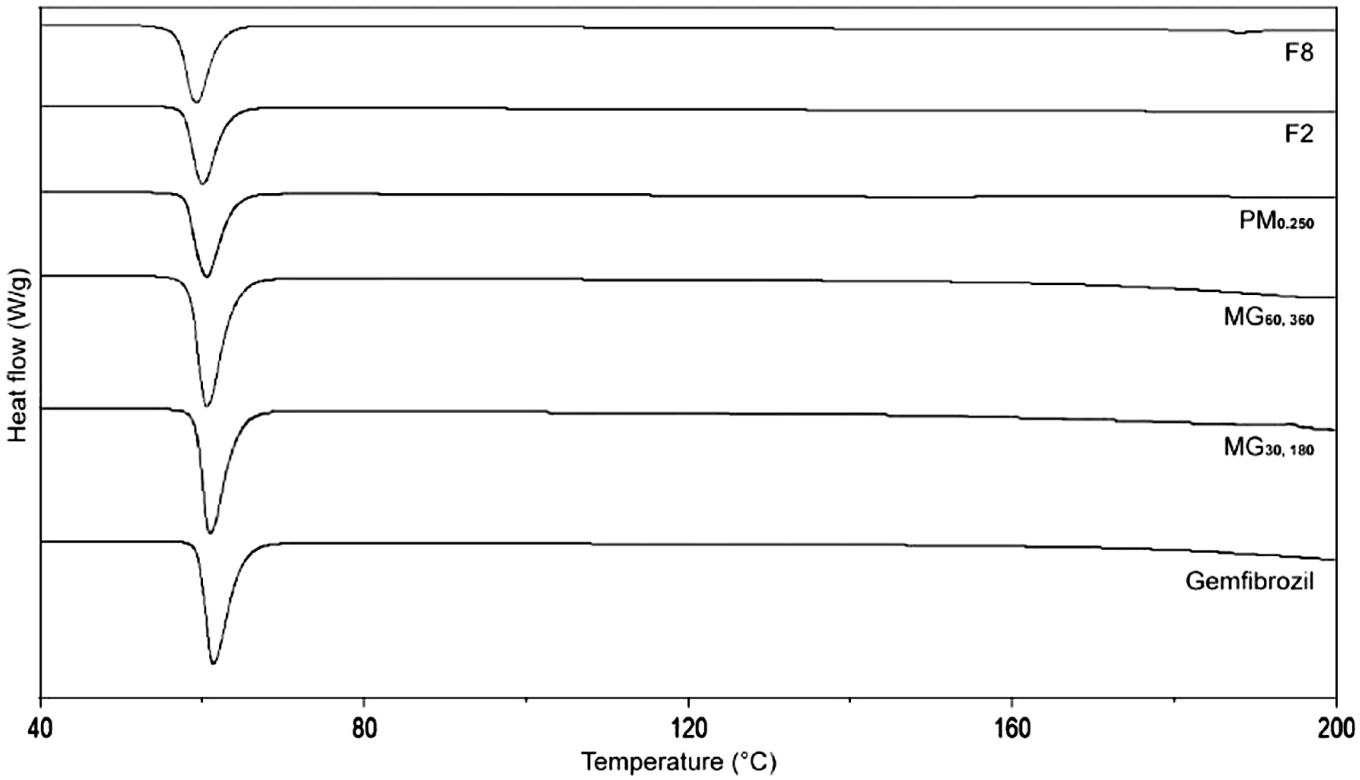

Fig. (6). DSC curves of gemfibrozil, milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$), SDs (F2 and F8) and physical mixture ($PM_{0.250}$).

The melting peak of gemfibrozil was observed in the DSC curve of $PM_{0.250}$ (T_{peak} = 60.52 °C; ΔH = 91.28 J/g), with a reduction of ΔH due to sample dilution by the presence of HPMC. The drug-melting peak was also evidenced in the DSC curves of F2 (T_{peak} = 60.06 °C; ΔH = 78.12 J/g) and F8 (T_{peak} = 59.35 °C; ΔH = 82.30 J/g), in the same temperature range as for gemfibrozil and $PM_{0.250}$, demonstrating that the drug remained essentially crystalline in these SDs. The discrete decrease in ΔH of F2 and F8 as compared to $PM_{0.250}$ indicated the absence of significant reduction in the degree of drug crystallinity of the SDs.

3.3.3. XRPD

The diffractogram for gemfibrozil (Fig. **6**) exhibited the characteristic reflections in accordance with the literature [23], confirming the crystalline nature of the drug. The characteristic diffraction pattern of crystalline gemfibrozil was observed for $MG_{30,180}$ and $MG_{60,360}$. However, the intensity of reflections was reduced at 2θ = 11.57° and 13.88°, and increased at 2θ = 24.07°. These variations in reflection intensities may have occurred due to a preferential orientation effect, whereby the crystals under analysis have a tendency to orient themselves in the sample, exposing certain planes preferentially to the X-ray, which results in greater intensity of the reflections corresponding to these planes and a reduction in intensity of other reflections. This effect may be related to differences in particle morphology or size [24], and justifies the results obtained for $MG_{30,180}$ and $MG_{60,360}$ in comparison to gemfibrozil. Thus, XRPD analyses confirmed that gemfibrozil remained essentially crystalline when milled alone.

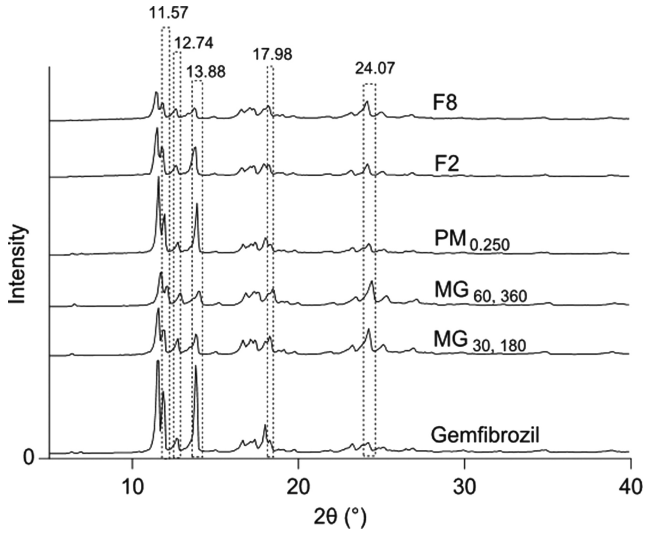

Fig. (7). Diffractograms of gemfibrozil, milled gemfibrozil ($MG_{30,180}$ and $MG_{60,360}$), SDs (F2 and F8) and physical mixture ($PM_{0.250}$).

The $PM_{0.250}$ XRPD pattern (Fig. **7**) was similar to that of gemfibrozil, but with reflections of reduced intensity due to dilution by HMPC. F2 and F8, with identical gemfibrozil:HPMC ratio to $PM_{0.250}$, showed a reduction in intensity of the reflections compared to this physical mixture ($PM_{0.250}$), probably due to a preferential orientation effect. Moreover, as discussed for the DSC results (3.3.2), F2 and F8 may have suffered a small decrease in drug crystallinity, which may also have contributed to the reduction of gemfibrozil reflection intensities in the XRPD patterns of these SDs.

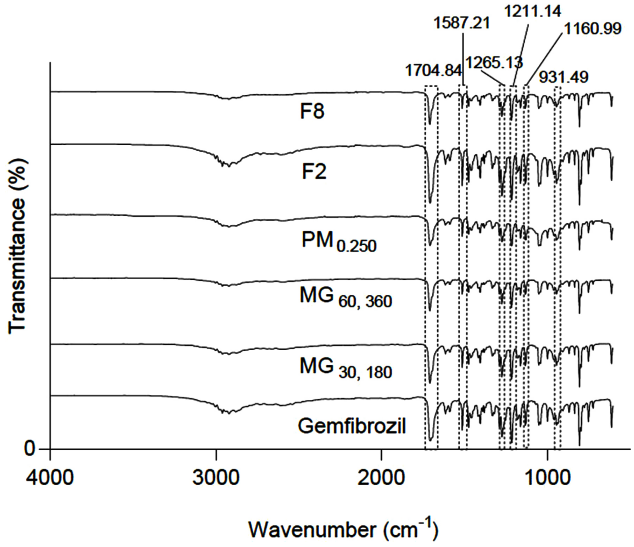

Fig. (8). FTIR spectra of gemfibrozil, milled gemfibrozil ($MG_{30,180}$, $MG_{60,360}$), SDs (F2; F8) and physical mixture ($PM_{0.250}$).

3.3.4. FTIR

Characteristic peaks were observed for gemfibrozil at 2919.8, 1704.8, 1587.2, 1265.1 and 931.5 cm^{-1}corresponding, respectively, to an O-H stretching vibration, C=O stretching vibration, C-C ring stretching, O-H deformation and C-H deformation (Fig. **8**). These peaks are in accordance with the literature [23]. The FTIR spectra of $MG_{30,180}$ and $MG_{60,360}$ remained unchanged compared to gemfibrozil, indicating that milling did not cause drug degradation. All gemfibrozil characteristic bands were observed for $PM_{0.250}$, F2 and F8. Thus, no drug-carrier interactions were evidenced for the SDs, which was attributed to the absence of very strong H-bond donor or acceptor groups in the HPMC molecule, and the consequent inability of this polymer to form strong drug interactions [21].

3.4. SD-Based Gemfibrozil Tablets

F8 was selected for the production of SD-based gemfibrozil 300 mg tablets (T1 and T2) because it showed excellent dissolution properties and better tabletability performance than F2. The results for the characterization of these tablets are shown in Table **3**, and the dissolution profiles in Fig. (**9**). T1 and T2 were compressed at 0.5 ton and 0.75 ton for 5 s, respectively, to obtain similar TS values (p>0.05) in order to eliminate the effect of mechanical strength of the tablets on drug release rate. Phosphate buffer pH 6.8 was used as non-sink dissolution medium for the tablets (V= 0.9 L, Dose = 300 mg, CS = 659.33 ± 79.38 mg/L, SI=2.44) since the medium with pH 5.8 would generate SI = 0.08, which was considered too low. T1 showed rapid and complete release (Q_{20min} =101.5 ± 0.7%; DE = 91.7 ± 1.1%) of gemfibrozil while T2 exhibited poor drug release (Q_{60min}= 59.8 ± 0.3%; DE = 35.5 ± 1.4%). This was because T1 had a faster disintegration time (~ 12 min) then C2 (> 30 min), proving that croscarmellose sodium was a better disintegrating agent than sodium starch glycolate for these tablets and, thus, influenced gemfibrozil release rate. So, the formulation containing gemfibrozil HPMC-based SD (F8) and croscarmellose sodium showed to be promising for obtaining tablets with suitable physical characteristics and drug release [25].

Table 3. Characterization of SD-based gemfibrozil 300 mg tablets.

Test Performed	T1	T2
Weight (g)	0.4302 ± 0.0017	0.4366 ± 0.0038
Hardness (N)	74.3 ± 5.4	77.8 ± 16.6
Diameter (mm)	10.03 ± 0.02	10.02 ± 0.02
Thickness (mm)	5.44 ± 0.04	5.18 ± 0.02
TS (MPa)	0.9 ± 0.1	1.0 ± 0.2
Disintegration (min)	12.7 ± 5.2	> 30

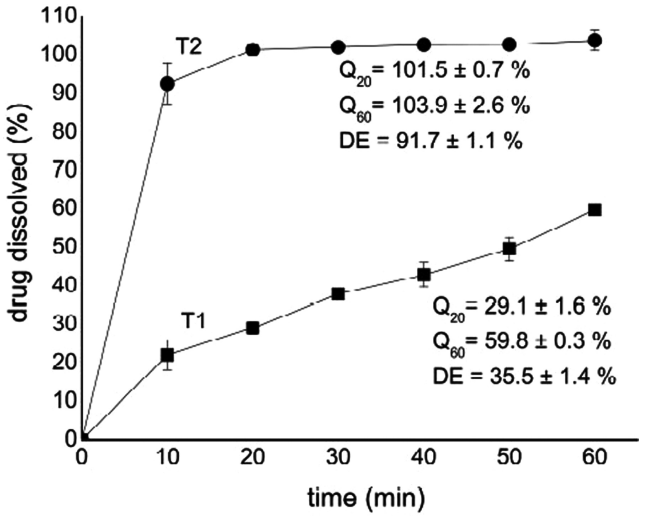

Fig. (9). Dissolution profiles of SD-based gemfibrozil tablets. Q_{20} and Q_{60} are the percentage dissolved in 20 and 60 minutes, respectively. DE is the dissolution efficiency.

CONCLUSION

SDs proved to be effective for simultaneously improving the tabletability and dissolution profile of the poorly water-soluble, poorly compactable and high therapeutic dose-gemfibrozil. The gemfibrozil:HPMC ratio was the main variable

influencing the drug dissolution rate and the tabletability of the developed SDs, while milling time and speed had less influence. No crystalline modifications or drug-carrier interactions were involved in gemfibrozil dissolution enhancement of SDs, which was caused by improved aqueous solubility, probably related to good wettability and fine primary particles, as well as the capability of the HPMC to produce supersaturated solutions.

The SD with gemfibrozil: HPMC ratio of 1:0.250 (w/w) milled under 360 rpm/60 min showed the best performance in relation to the dissolution and tabletability results together. Gemfibrozil tablets containing this SD, and croscarmellose sodium as a disintegrating agent, showed excellent results for drug release and mechanical strength, demonstrating the potential of HPMC-based SDs to simultaneously overcome the poor dissolution and tabletability properties of this high dose drug.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the manuscript.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors acknowledge Colorcon for providing HPMC, and Dr. Adailton J. Bortoluzzi and Tatiane C. Machado (UFSC, Brazil) for the assistance in XRPD analyses.

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