Improved physical stability for co-amorphous simvastatin and glipizide combinations prepared by co-milling

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Abstract

In this study, mechanical activation (ball- and cryomilling) was successfully applied to obtain co-amorphous mixtures of two BCS class II drugs, simvastatin (SVS) and glipizide (GPZ). This pharmacologically relevant combination of two drugs could produce a promising candidate for formulations intended for combination therapy of metabolic disorders. The co-amorphous SVS-GPZ mixtures (molar ratios 2:1, 1:1 and 1:2) were characterized with respect to their thermal properties, possible molecular interactions, dissolution properties and physical stability, and compared to the behaviour of pure amorphous forms and their physical mixtures. Flory-Huggins interaction parameter predicted the absence of favourable SVS-GPZ interactions and thus immiscibility of the components. Nonetheless, formation of single phase co-amorphous mixtures with mixture ratios of 2:1, 1:1 and 1:2 was detected by differential scanning calorimetry (DSC). The observed single, concentration dependent T_gs were found to be lower than predicted by the Gordon-Taylor equation indicating absence of intermolecular interactions between the two drugs which was verified by Fourier transform infrared spectroscopy (FTIR) spectral data analysis. By formation of co-amorphous single-phase mixtures only the dissolution rate of GPZ could be improved. The co-amorphous mixtures showed improved storage stability compared to the pure amorphous forms and the amorphous physical mixtures. It was concluded that this was attributable to the molecular level mixing of SVS with GPZ upon milling and GPZ is acting as an anti-plasticizer in these mixtures.

Keywords: co-amorphous, dissolution, stability, simvastatin, glipizide; co-milling

1 Introduction

Poorly soluble compounds comprise an increasingly large percentage of new chemical entities (NCEs) being developed today [1, 2]. One approach to overcome the problem of poor aqueous solubility is to convert crystalline drugs into their amorphous counterparts, thus increasing dissolution rate and apparent solubility of the compounds [2,3]. The main drawback of this approach is that amorphous systems are thermodynamically unstable and tend to recrystallize during manufacturing, administration or storage [2, 4, 5].

The physical stability of amorphous drugs can be increased by preparing a molecular dispersion or glass solution of the drug in a glassy polymer matrix [3, 6-12]. However, the number of pharmaceutical products on the market based on solid dispersions is rather low due to long-term stability problems and difficulties with manufacturing and processing into dosage forms [7, 9, 12, 13]. Thus, development of stable amorphous systems and ensuring feasibility of pharmaceutical products containing them requires more efficient means.

In order to avoid the disadvantages of glass solutions, such as the hygroscopicity and high bulk volumes, the concept of co-amorphous systems has been introduced [14, 15]. In these systems, a combination of two small molecules (drugs) is used instead of drug-polymer mixtures. These systems have been found to provide high stability and enhanced dissolution rates for the drugs, primarily due to solid-state interactions between the two drugs present in the system. Binary mixtures of indomethacin and ranitidine hydrochloride (IND/RAN), naproxen and cimetidine (NAP/CIM) and naproxen/indomethacin (NAP/IND) (at molar ratios of 2:1, 1:1 and 1:2) have been found to form amorphous one-phase systems upon ball milling or quench cooling, respectively [14-16]. In all cases, the 1:1 molar mixtures exhibited a significant increase in stability due to specific molecular interactions between the two co-amorphous components in a 1:1 molar fashion. Furthermore, a synchronized drug release was observed [15, 16]. In the case of NAP/IND this was found to be attributed to formation of a hetero-dimer [16].

In this study, the drug pair simvastatin-glipizide (SVS-GPZ) in different molar ratios was investigated. SVS and GPZ are widely used for the treatment of hypercholesterolemia and diabetes, respectively. With both drugs being BCS class II drugs, i.e. poorly soluble but sufficiently permeable, formation of a better dissolving and stable co-amorphous mixture could provide a promising candidate for combination therapy formulations for treatment of increasingly common metabolic disorders. The co-amorphous SVS-GPZ mixtures were prepared by mechanical activation (ball milling or cryomilling)

and characterized with respect to their thermal and structural properties, possible molecular interactions, physical stability and dissolution properties. These were compared to the behaviour of amorphous drugs alone and physical mixtures of them in different molar ratios.

2 Materials and methods

2.1 Materials

Simvastatin (SVS, purity >97%) and glipizide (GPZ, purity >98%) were purchased from Hangzhou Dayangchem Co. Ltd (Hangzhou, China) and Tecoland Co. (Edison, NJ, USA), respectively.

2.1.1 Sample preparation

SVS and GPZ were converted to amorphous forms (SVS CM and GPZ CM) by cryomilling. Co-amorphous mixtures of SVS-GPZ were prepared by ball milling (SVS-GPZ BM, in molar ratios of 2:1 and 1:1) and cryo-milling (SVS-GPZ CM, in molar ratios of 2:1, 1:1 and 1:2). Physical mixtures (PM) were prepared from crystalline SVS and GPZ, and amorphous physical mixtures (APM) were prepared from amorphous SVS CM and GPZ CM by gentle mixing in a mortar.

2.2 Methods

2.2.1 Flory-Huggins interaction parameter calculation

Theoretical assessment of miscibility of SVS and GPZ with each other was conducted by the Flory-Huggins interaction parameter (χ) approach which has been used for predicting the thermodynamic miscibility of polymers and small molecules in binary mixtures [17, 18]. The Flory-Huggins interaction parameter (at 298 K) was calculated by using the Material Studio Blends module (Accelrys Inc., San Diego, CA) [19]. The detailed calculation protocol has been presented elsewhere [18].

2.2.2 Characterization methods

X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) were used to detect the amorphousness/crystallinity, glass transition

temperatures (Tg) and possible molecular interactions of the samples, respectively. To estimate the theoretical T_g-values the Gordon-Taylor equation was used. Principal component analyse (PCA) was performed for the FTIR spectral data (400 – 4,000 cm^{-1}, excl. region 1800 - 2720 cm^{-1}). For this purpose, standard normal variate (SNV) transformation was applied to the spectral data in order to remove spectral differences unrelated to the sample. The algorithm used in the model was Non-linear Iterative Partial Least Squares algorithm (NIPALS).

The powder dissolution profiles were measured using the USP basket method, with a rotation speed of 50 rpm and 500 ml of USP phosphate buffer (pH 6.8) as dissolution medium at 37 °C. SVS and GPZ concentrations were analysed simultaneously with HPLC using a Phenomenex Gemini-NX 5u C18 110A (250x4.60mm) column, mobile phase of 70% acetonitrile (ACN) and 30% of H_2O, flow rate of 1.2 ml/min and column temperature of 40°C. The UV-detection wavelength was 225 nm for GPZ and 238 nm for SVS. The dissolution rates were given by the slope (µg/min) of the linear fit of the dissolution curves. The three first time points (2, 6 and 10 min) and the last point were excluded from the analysis, i.e. the analysis was made using only the linear part of the dissolution curve. The calculated dissolution rate values were compared by performing single-factor ANOVA analysis. Differences were considered significant with p-values < 0.05 (95% confidence level).

2.2.3   Stability studies

The APMs were stored at 25°C/0% RH and 25°C/60% RH, while all other samples were stored at 4°C/0% RH in addition. The samples were analysed regularly with XRPD and FTIR until onset of crystallisation was observed.

3   Results and discussion

To achieve one-phase co-amorphous mixtures, the two components have to be thermodynamically miscible during processing. In this study, the thermodynamic miscibility of SVS and GPZ was investigated theoretically by the Flory-Huggins interaction parameter (χ) approach [18, 20]. Generally, interaction parameters close to or less than zero indicate miscibility and athermal or slightly exothermic mixing [18, 20]. In the case of SVS-GPZ mixtures, the calculated Flory-Huggins interaction parameter (χ = 5.5 ± 2.0) suggested that favourable interactions were not likely between SVS and GPZ and that these two molecules might not be miscible with each other in an equilibrium state.

Transformation of the pure crystalline drugs to the amorphous form was only observed upon cryomilling for 60 min (Fig. 1a). However, ball milling for 110 mins was able to convert 2:1 and 1:1 SVS-GPZ mixtures to a co-amorphous form but the 1:2 mixture retained some crystallinity (excess GPZ, Fig. 1b). In contrast, with cryomilling for 60 mins, all mixtures could be converted to amorphous forms (diffractograms not shown) which was expected since cryomilling is known to be more efficient in preparation of amorphous drugs than ball milling, due to the lower processing temperature [14].
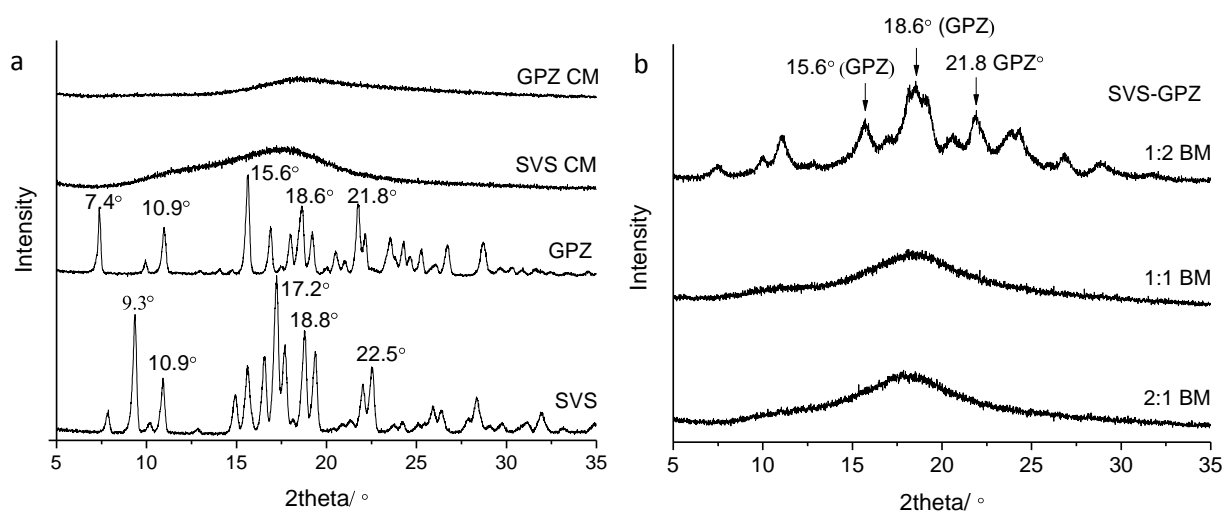

Figure 1. X-ray diffractograms of a) crystalline starting materials and SVS CM and GPZ CM and b) SVS-GPZ 2:1, 1:1 and 1:2 BM mixtures.

All co-amorphous mixtures were found to have one composition-dependent T_g value between the individual T_g values of the pure drugs (Table 1). In general, the higher the amount of GPZ in the mixture, the higher was the observed T_g which is in accordance with previous findings for co-amorphous mixtures [14-16]. Thus, ball- and cryomilling forced the components to mix at the molecular level and to form an amorphous single phase system (a non-equilibrium state) [20, 21]. In the case of the 2:1 and 1:1 mixture ratios, the T_gs obtained from samples produced with different milling methods were found to be identical. The observed T_g values of the mixtures were found to be slightly lower (albeit not statistically significantly) than the corresponding theoretical T_gs, obtained from the Gordon-Taylor equation (Table 1) possibly indicating an overall loss in the number and strength of hydrogen bonding upon mixing [22, 23]. This supported the Flory-Huggins predictions, which suggested that interactions might not occur between SVS and GPZ.

Table 1: Observed and theoretical glass transition temperatures (T_g) of the materials studied.

Material	Observed T_g [°C]	Theroretical T_g [°C][1]
SVS	32.6±0.2[2]	
GPZ	nd[3]	
SVS CM	31.5±2.4	
GPZ CM	69.9±0.3	
SVS-GPZ 2:1 BM	41.1±6.2	42.3
SVS-GPZ 1:1 BM	46.3±6.6	48.4
SVS-GPZ 2:1 CM	41.5±5.1	42.3
SVS-GPZ 1:1 CM	46.7±5.2	48.4
SVS-GPZ 1:2 CM	53.6±5.3	54.9

[1]Form Gordon-Taylor equation
[2]by quench cooling in DSC
[3]GPZ degrades after melting, thus no T_g could be measured

The FTIR spectra of the co-amorphous mixtures were compared to the spectra of the corresponding physical mixtures of the individual amorphous drugs (APMs). It was found that the spectra of all co-amorphous mixtures were similar to the spectra of the corresponding APMs (Fig. 2, showing the 1:1 mixtures as an example).
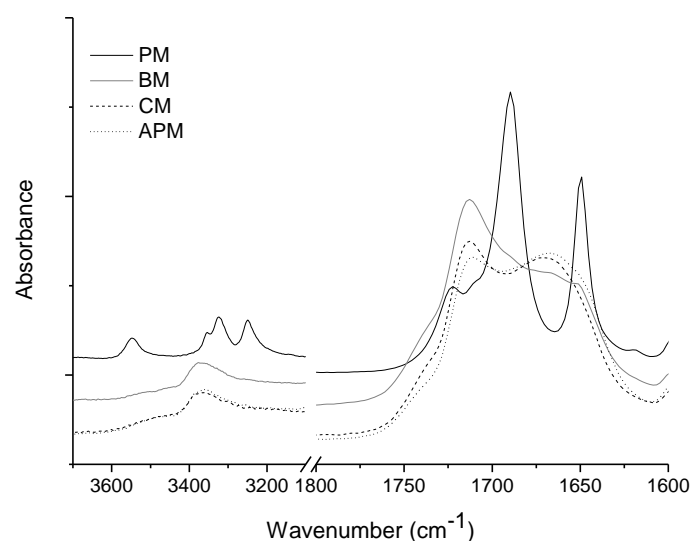

Figure 2. FTIR spectra of SVS-GPZ 1:1 PM, co-amorphous BM and CM mixtures, co-amorphous and APM (regions from 3700 cm⁻¹ to 3100 cm⁻¹ and 1800 cm⁻¹ to 1600 cm⁻¹).

A PCA analysis of the spectral data revealed that two principal components (PCs) could explain 95% of the variation of the data. The score plot (Fig. 3a) shows that the first PC (PC-1) describes variation arising from the different chemical compositions of the samples. There is a positive correlation to the amount of GPZ and negative correlation to the amount of SVS. By comparing the scores of the amorphous samples (SVS CM, GPZ CM, APMs and BM and CM mixtures) it can be seen that the

second PC (PC-2) differentiates between crystalline and amorphous systems. SVS CM and GPZ CM form their own clusters, as do all the 2:1, 1:1 and 1:2 samples (APM, BM, CM), indicating similarity within these groups. This can be confirmed by viewing the loadings plot (Fig.3b) which shows that the loading of PC-1 is identical to the subtraction spectrum of GPZ CM and SVS CM, thus PC-1 explains the difference in composition. Furthermore, the loading of PC-2 is identical to the subtraction spectrum of SVS-GPZ 1:1 PM and SVS-GPZ 1:1 CM which means that PC-2 explains the difference between crystalline and amorphous state. This confirmed that no interactions between SVS and GPZ exist in co-amorphous mixtures since the PCA model classifies APMs similar to the co-amorphous mixtures. Instead, as predicted by the positive interaction parameter value, the components of the mixture will interact rather with similar molecules than with each other [18, 20] and the single-phase systems formed were not thermodynamically stable which would eventually lead to phase separation and crystallization.
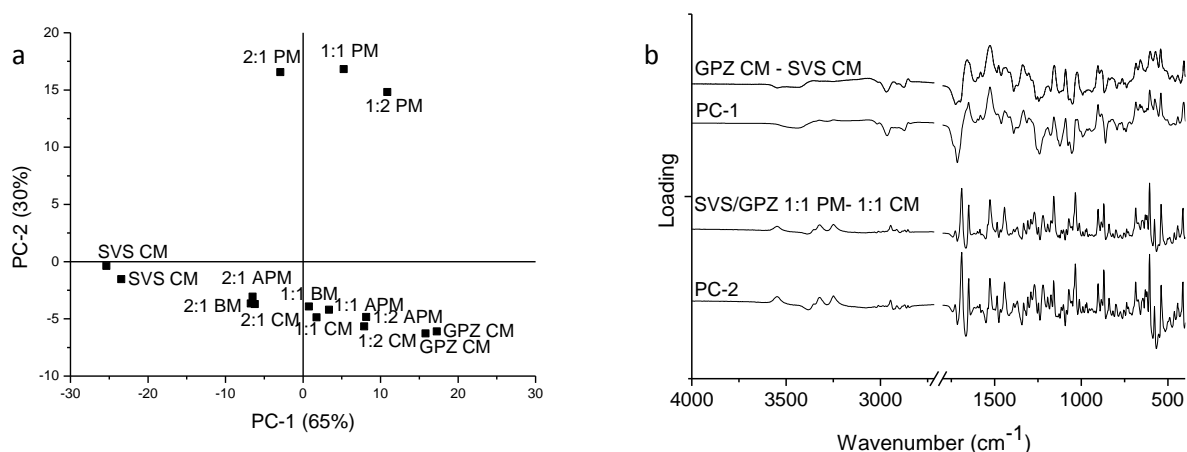

Figure 3. PCA analysis of the FTIR spectra a) score plot of 2:1, 1:1 and 1:2 SVS-GPZ PMs, APMs, co-amorphous mixtures (CM and BM) and amorphous drugs and b) loadings plot showing PC-1 compared to the difference between the spectra of GPZ CM and SVS CM and PC-2 compared to the difference between the spectra of 1:1 SVS-GPZ CM and SVS-GPZ PM.

The powder dissolution profiles of the materials studied were measured and the calculated dissolution rates (µg/ml) and amounts dissolved (mg) in two hours are shown in Table 2. The dissolution studies revealed that formation of the amorphous form and/or co-amorphous mixture of SVS and GPZ did not improve the dissolution of SVS. However, the dissolution of GPZ was significantly enhanced from co-amorphous mixtures and even from APMs (Table 2).

Table 2: Powder dissolution rates of the materials studied and the amounts dissolved after two hours (n=3, ± sd).

Material	Dissolution rate µg/min ± sd	Amount of drug released after two hours mg
SVS	6.7 ± 1.4	0.81 ± 0.39
GPZ	7.6 ± 2.9	1.1 ± 0.6
SVS CM	0.60 ± 0.57*	0.74 ± 0.32
GPZ CM	21 ± 10	3.3 ± 1.3*
SVS-GPZ 2:1 BM	SVS: 2.9 ± 1.7* GPZ: 16 ± 5*	SVS: 0.97 ± 0.34 GPZ: 1.9 ± 0.6
SVS-GPZ 2:1 CM	SVS: 4.3 ± 1.1 GPZ: 31 ± 10*	SVS: 1.2 ± 0.3 GPZ: 3.5 ± 0.7*
SVS-GPZ 2:1 APM	SVS: 4.6 ± 2.0 GPZ: 18 ± 5*	SVS: 0.52 ± 0.02 GPZ: 2.4 ± 0.5*
SVS-GPZ 1:1 BM	SVS: 4.6 ± 1.9 GPZ: 28 ± 11*	SVS: 0.72 ± 0.17 GPZ: 3.2 ± 1.3
SVS-GPZ 1:1 CM	SVS: 5.1 ± 1.6 GPZ: 24 ± 15	SVS: 0.56 ± 0.18 GPZ: 2.8 ± 1.8
SVS-GPZ 1:1 APM	SVS: 0.66 ± 0.22* GPZ: 31 ± 4*	SVS: 0.30 ± 0.02 GPZ: 4.6± 0.8*
SVS-GPZ 1:2 CM	SVS: 4.1 ± 2.9 GPZ: 46 ± 32	SVS: 1.1 ± 0.4* GPZ: 5.6 ± 3.8
SVS-GPZ 1:2 APM	SVS: 2.8 ± 4.0 GPZ: 27 ± 12*	SVS: 0.52 ± 0.04 GPZ: 3.8 ± 1.8

*significantly different from the value of corresponding crystalline drug

For the evaluation of physical stability, the amorphous samples were stored at 4°C/0% RH, 25°C/0% RH and 25°C/60% RH and the onset of recrystallization was analysed with XRPD and FTIR at regular time intervals (diffractograms and spectra not shown). The onset of recrystallization was reflected by the appearance of peak shifts of certain functional groups in the spectra of the stored samples towards the corresponding peaks in crystalline GPZ and SVS. The XRPD diffractograms were analyzed in regard to recrystallization peaks arising from the amorphous halo structure. Interestingly, differences between the physical stability of co-amorphous mixtures and APMs were observed (Table 3).

Table 3: Summary of the stability data (in days) obtained from XRPD and FTIR measurements after storage at 4°C/0% RH, 25°C/0% RH and 25°C/60% RH.

	Crystallisation detected (measurement day XRPD/FTIR)		
Material	**4°C/0% RH**	**25°C/0% RH**	**25°C/60% RH**
SVS CM	67/65	11/9	5/2
GPZ CM	74/79	60/46	25/16
SVS-GPZ 2:1 BM	128/133	44/14	8/2
SVS-GPZ 2:1 CM	74/79	53/58	46/46
SVS-GPZ 2:1 APM	-	32/23	3/9
SVS-GPZ 1:1 BM	128/139	52/35	16/8
SVS-GPZ 1:1 CM	88/85	74/79	74/65
SVS-GPZ 1:1 APM	-	49/51	3/9
SVS-GPZ 1:2 CM	95/92	74/72	74/58
SVS-GPZ 1:2 APM		49/46	10/9

The 2:1 and 1:1 mixtures, prepared by ball milling were found to be less stable than the corresponding CM samples when stored at 25°C. When stored at 4°C, BM mixtures were stable over 4 months, while the stability of the CM mixtures changed little. Differences in the stability of amorphous materials prepared by different techniques have been observed previously [24, 25]. However, in the case of SVS-GPZ, the T_gs of the mixtures prepared by BM and CM were identical and no differences between the FTIR spectra could be established. Interestingly, APMs were found to be stable over approx. the same time period than the co-amorphous mixtures when stored at 25°C/0% RH (Table 3), but when humidity was increased (60%), the APMs remained amorphous only few days while the 1:1 and 1:2 co-amorphous mixtures were stable for over two months. At each storage condition the stability was found to increase as the function of increasing amount of GPZ and thus, increasing T_g in the co-amorphous mixture. Consequently, 1:2 mixtures were the most stable (over two months at all storage conditions). When recrystallized, features of both SVS and GPZ, identical to those of the original crystalline drugs, were found in the diffractograms (not shown). These findings are in contrast to what has been observed previously for co-amorphous systems [14-16]. In all those systems, 1:1 molecular interactions, such as the formation of a hetero-dimer between naproxen and indomethacin [16], were found to lead to superior stability of 1:1 mixtures compared to 2:1 and 1:2 mixtures even though the 1:1 co-amorphous mixtures had a glass transition temperature in between the T_gs of the 2:1 and 1:2 mixtures. In addition, usually the excess component did recrystallize first during storage from 2:1 and 1:2 mixtures [14-16].

The better stability of co-amorphous mixtures over APMs might be explained by differences in mixing. In a well-mixed binary system (such as the co-amorphous mixtures of this study), where the

components are intimately mixed at the molecular level, only one amorphous phase would be present. However, the positive Flory-Huggins interaction parameter value for SVS-GPZ predicted that phase separation and recrystallization to the pure components (due to the lack of interactions) will eventually occur since the molecularly mixed state is not an equilibrium state. The interaction parameter does not give any information on how fast this equilibrium state will be reached since the speed of the process depends on time and storage conditions (temperature and humidity) as shown in the stability study. In contrast, a system with more than one amorphous phase present (the APMs) have different amorphous regions with different SVS-to-GPZ ratios and recrystallization occurs fast, e.g. under storage at 25°C/60% RH in SVS rich areas [26]. In contrast, in the co-amorphous systems, stabilization can be considered to occur similarly as in drug-polymer systems; i.e., one amorphous component of the mixture acts as a stabilizer for the other [20], which in this case would be the anti-plasticizer GPZ, with a higher T_g than SVS.

4   Conclusions

In this study, mechanical activation (ball- and cryomilling) was successfully applied to obtain co-amorphous mixtures of two BCS class II drugs, simvastatin (SVS) and glipizide (GPZ). Formation of single phase co-amorphous mixtures with mixture ratios of 2:1, 1:1 and 1:2 was detected by DSC. The observed single, concentration dependent T_gs were found to be lower than predicted by the Gordon-Taylor equation indicating absence of intermolecular interactions between the two drugs which was also predicted by a positive Flory-Huggins interaction parameter value and verified by FTIR spectral data analysis. By formation of co-amorphous single-phase mixtures, only the dissolution rate of GPZ could be improved compared to the crystalline drug. Stability studies revealed increased storage stability and showed that the most stable mixtures (1:1 and 1:2 CM mixtures) were stable for over two months at all storage conditions. The improved compared to the amorphous physical mixtures stability can be attributed to the formation of a SVS-GPZ molecular mixture where GPZ acts as a stabilizing component (anti-plasticizer), which is beneficial for stability even in the absence of molecular interactions.

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