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Investigation of formulation approaches to improve the dissolution of SB-210661, a poorly water soluble 5-lipoxygenase inhibitor

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Abstract

Several formulation approaches were used in an attempt to improve the dissolution of SB-210661. In the present study, incorporation of surfactants in formulations significantly enhanced SB-210661 dissolution in water at 37°C. The role of surfactants on dissolution enhancement was also investigated. As an alternative formulation approach, solid dispersions were also prepared using the melt and mechanical activation methods for PEG 8000 containing dispersions and using the solvent method for PVP containing dispersions. The dissolution of SB-210661 from the solid dispersions was significantly greater than that observed for the surfactant containing formulations. The physical characteristics of these solid dispersions were investigated by X-ray powder diffraction and FTIR. The X-ray powder diffractograms suggest that the PEG 8000 dispersions exist in a partially crystalline state and that the PVP dispersion exists in a totally amorphous state. The FTIR results suggest that SB-210661 does not interact with PEG 8000 but interacts with PVP through intermolecular hydrogen bonding. Following storage of solid dispersions at 25°C/60% relative humidity (RH) for 1 year, there was no significant change in the dissolution profile for the PVP dispersion, whereas the PEG dispersions showed a slowing in their dissolution rate. X-ray powder diffraction results indicated that SB-210661 was still amorphous in the PVP dispersion, and the FTIR spectrum still supported the hydrogen bonding of SB-210661 and PVP. The lack of change in the dissolution profile of the PVP dispersion may be related to the hydrogen bonding interaction causing a stabilization of SB-210661 in the higher-energy, faster dissolving amorphous state.

Keywords: Contact angle; Dissolution; Hydrogen bonding; 5-Lipoxygenase inhibitor; Surfactants; Solid dispersion; SB-210661

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1. Introduction

It is common to find a dissolution-rate limiting component to the oral bioavailability of compounds which are poorly water soluble and poorly wetted. A number of different formulation approaches have been investigated as ways of overcoming this problem (Yalkowsky, 1981). One of the simplest approaches in industrial practice is to incorporate a surfactant into the formulation (Shangraw and Demarest, 1993). Surfactants, such as the commonly used sodium dodecyl sulfate (SDS) and polysorbates (Tweens), have been shown to increase the dissolution rate of a number of drugs by micellar solubilization and improved wetting (Schott et al., 1982; Bakatselou et al., 1991). A second, more complex approach involves altering the physical properties of the compound via the formation of solid dispersions where the compound is dispersed within an 'inert' carrier in the solid state (Chiou and Riegelman, 1971; Ford, 1986).

SB-210661 ((S)-*N*-hydroxy-*N*-(2,3-dihydroxy-6-(2,3-difluorophenylmethoxy)-3-benzofuranyl)urea; Fig. 1), a potent inhibitor of 5-lipoxygenase (5-LO), displays poor in vitro dissolution behavior in water because of its poor solubility in water (16 μg/ml at 25°C) and its poor wettability. The primary purpose of this study was to evaluate whether surfactant incorporation and/or solid dispersion formation would significantly improve the dissolution rate of SB-210661 in water. The secondary purposes of this study were the following: (1) to compare the effect of two distinct solid dispersion preparation techniques (i.e. the fusion method and the mechanical activation method) on the dissolution profiles of the resulting dispersions; and (2) to evaluate the long-term stability of the dissolution behavior of the resulting dispersions following storage for 1 year at simulated room temperature conditions (i.e. 25°C and 60% relative humidity (RH)).

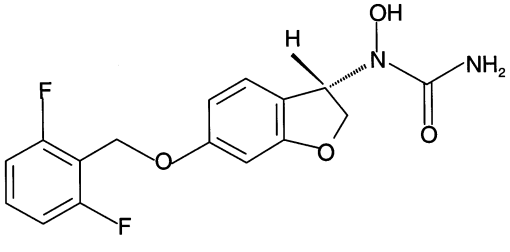

Fig. 1. Structure of SB-210661.

2. Materials and methods

2.1. Materials

SB-210661 (99.4% purity) was synthesized by the Chemical Development Department at SmithKline Beecham Pharmaceuticals (King of Prussia, PA). Sodium dodecyl sulfate (SDS, Mallinckrodt), Tween 40 (Sigma), PEGs (Carbowax), PVP (TCI) and microcrystalline cellulose (Emcocel, Mendell) were used as received. The solvents used were high performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade, and the water used was deionized then filtered through a Milli-Q Water Purification System prior to use.

2.2. Surfactants studies

2.2.1. Preparation of formulations

Three formulations were prepared. The first was a physical mixture of SB-210661 and Emcocel (1:9) which was prepared by blending in a mortar. The remaining two formulations had the same ratio of drug to Emcocel as described for the physical mix but also contained either 0.5% (w/w) Tween 40 or 0.5% (w/w) SDS. These formulations were prepared by blending aqueous solutions of the surfactants with the drug and Emcocel. The resulting wet mass was then dried at 40°C for 2 h. The content of drug in formulations was assayed by HPLC.

2.2.2. Determination of surface tension and contact angle

The Wilhelmy plate method was used to determine the surface tensions and contact angles of 0.5% Tween 40 and 0.5% SDS in the presence of SB-210661 at 20°C. The measurements were performed on a KRÜSS K121 Contact Angle and Adsorption Measuring system using platinum plates and an immersion depth of 5 mm. The

surface tension and contact angle values were calculated using the resultant force–depth isotherms and the following equation:

$$\cos\theta = F_W/L\sigma \quad (1)$$

where θ is the contact angle; F_W is the Wilhelmy force; L is the wetted length; and σ is the surface tension.

The contact angles of water, 0.5% Tween 40, and 0.5% SDS on the SB-210661 were obtained by glass slide method which gives a more realistic value for powders and does not require compaction of the powder prior to testing (Dove et al., 1996). Glass slides were sprayed with an adhesive (3M Spray Mount Adhesive), and left for 1 min. Drug powder was then tapped on the coated glass slide. Excess powder was blown off each slide using nitrogen gas. The contact angle was then measured.

2.2.3. Solubility

The aqueous solubility of SB-210661 was determined, in duplicate, at 25°C. Excess solid SB-210661 (i.e. 50 mg) was added to 10 ml glass centrifuge tubes with Teflon-lined screw caps. Five milliliters of water or aqueous solutions containing surfactants or polymers were added to each tube, and the tubes were placed on a VI-BRO-Mixer (Chemap AG, Switzerland) which was set in a water bath maintained at 25°. The tubes were agitated for 24 h. (Preliminary studies showed that this was ample time to attain equilibrium solubility). Then the solutions were filtered through 0.45 μm PTFE syringe filters. The pH of the subsequent filtrate was taken, and the filtrate was assayed by HPLC.

2.3. Preparation of the solid dispersions

2.3.1. Dispersions of SB-210661 in PVP

These dispersions were prepared by the solvent method. The required amounts of SB-210661 and polyvinylpyrrolidone (PVP K30) were co-dissolved in a minimal amount of a 40:60 mixture of CH_2Cl_2 and ethanol in a round-bottom flask. The solvent was then removed at 55°C using a rotary evaporator. The resultant residue was dried for at least 24 h at room temperature under vacuum.

2.3.2. Dispersions SB-210661 in PEG 8000

These dispersions were prepared by either the fusion or mechanical activation method. For the fusion method, PEG 8000 was heated in a beaker to 105°C then the required amount of SB-210661 was added with stirring to give a homogeneous melt. This melt was poured into a stainless steel beaker which was placed in cold water until solidification occurred. The resulting solid mass was triturated in a mortar with a pestle. For the mechanical activation method, PEG 8000 and the required amount of SB-210661 were milled for 4 h in a vibrating ball mill (SPEX Industries, Metuchen, NJ) using two 1-cm metal balls. Preliminary studies revealed that milling for 30 min or 4 h had little impact on the dissolution rate.

2.3.3. FTIR analysis

FTIR analysis was performed on a Nicolet 800 FT-IR spectrophotometer equipped with a mercury-cadmium-telluride detector which was cooled with liquid nitrogen. FTIR microscopy spectra were also obtained using the above FTIR interfaced with a NICPLAN FTIR microscope. A small amount of sample was placed under the microscopic plates as a thin layer. Data were collected over a spectral region from 4000 to 650 cm^{-1} with a resolution 4 cm^{-1} and 100 scans.

2.3.4. Powder X-ray diffraction

The powder X-ray diffraction analyses were performed at the University of Minnesota on either a Siemens Model D500 or a Scintag Model XDS 2000 diffractometer using Ni-filtered, CuKα radiation, a voltage of 45 kV, and a current of 40 mA. The instrument was operated in the continuous scan mode over a 2θ range of 5 to 35°.

2.4. Dissolution testing

Hand-filled, hard gelatin capsules of the formulations of interest (which contained about 30 mg of drug) were used for the dissolution testing. The testing was conducted with USP Apparatus II using a paddle speed of 100 rpm. The dissolution medium was 900 ml of water which was maintained at 37($\pm$0.2)°C. The dissolution medium was not buffered because the pK_a of SB-210661 is

10.46 (Mcloughlin et al., 1998); hence, the solubility of the compound is pH independent below pH 7. Aliquots were pulled at 6, 15, 25, 40 and 60 min and analyzed by HPLC. The dissolution of each formulation was run in triplicate.

2.5. HPLC analysis

The HPLC analyses were performed on a Shimadzu system equipped with a 4.6×250 mm Cosmosil 5C18-AR column which was maintained in a column oven at 40°C. The mobile phase consisted of a 58:42 (%v/v) mixture of water and acetonitrile; the flow rate was 1.0 ml/min; the detection wavelength was 226 nm; the injection volume was 20 μl; and the run time was $\sim$6 min. Data acquisition and integration was performed with a Nelson System 6000 and Nelson Access*Chrom (version 1.8) software.

3. Results and discussion

3.1. Effect of incorporation of surfactants

To evaluate the effect of incorporating surfactants into the formulation, the dissolution behaviors of three different formulations were compared to that of drug alone. As shown in Fig. 2, the rate and extent of SB-210661 dissolution in water at 37°C increased in the following order: (drug alone) < (drug:Emcocel = 1:9) < (drug:Emcocel:SDS = 1:8.95:0.05) < (drug:Emcocel:Tween 40 = 1:8.95:0.05). The $\sim$2-fold increase in the extent of dissolution seen when Emcocel is mixed with the drug can be accounted for by a dilutive effect which minimizes drug agglomeration. Drug agglomeration can have negative impact on dissolution by reducing the surface area of drug exposed to the dissolution medium. The $\sim$4- to 5-fold increase in the extent of dissolution seen when the surfactants are incorporated into the drug:Emcocel mixes can be attributed, in part, to the dilutive effect and to increases in the aqueous solubility and wettability of SB-210661 in the micro-environment of the dissolution medium (Schott et al., 1982).

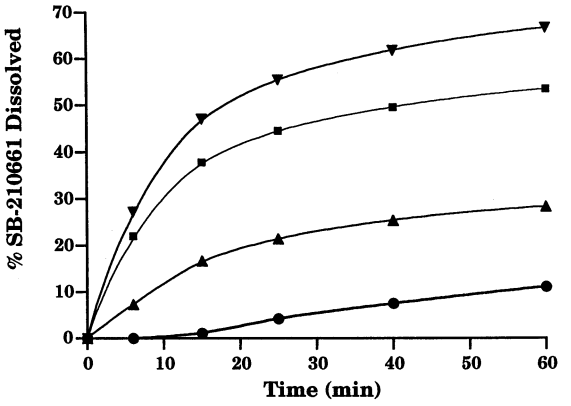

Fig. 2. Effect of excipients on the dissolution of SB 210661. Key: (●) SB-210661 alone; (▲) SB-210661:Emcocel = 1:9 (physical mixture); (■) SB-210661:Emcocel:SDS = 1:8.95:0.05; (▼) SB 210661:Emcocel:Tween 40 = 1:8.95:0.05.

In order to understand the effect of surfactants on the dissolution of SB-210661, solubility, surface tension and contact angle studies were performed. Tables 1 and 2 show that there is no significant difference in the solubility and surface tension data for SB-210661 in the presence of either surfactant. However, the data in Table 2 show that there is significant difference in the contact angle data which indicates that SDS imparts better wettability (Luner et al., 1996). Interestingly, neither the solubility, surface tension nor contact angle data can explain the difference seen in the dissolution rates of the formulations containing SDS and Tween 40. This difference may be related to the differences in the critical micellar concentrations (CMC) which are shown in Table 2. The CMC of Tween 40 is over a 100-times lower than that of SDS. This may provide Tween 40 with greater solubilizing ability in the microenvironment. Additionally, the difference may also be related to the viscous nature of Tween 40 which may result in more intimate contact with the drug than SDS. The ability of Tween to form 'films' on a substance has been well documented (Duchene et al., 1970; Heng and Wan, 1985). For a poorly soluble drug substance, an improvement in dissolution should be achieved for the surfactant which is more closely associated with the drug. This closer association can result in a more efficient wetting and micellar solubilization in the

Table 1
Solubility (mg/mL) of SB-210661 at 25°C in water containing varying concentrations of surfactant and polymer

	0.5	1	2	3	4	5
Surfactant concentration (%w/v)						
SDS	0.15	0.33	0.62	0.84	1.12	1.36
Tween 40	0.14	0.28	0.53	0.79	1.04	1.30
Polymer concentration (%w/v)						
PEG 8000	ND[a]	0.020	ND	ND	0.033	0.038
PVP	0.021	0.025	0.037	0.045	0.054	0.065

[a] ND is not determined.

micro-environment which will translate into improvement of dissolution rate (Schott et al., 1982).

3.2. Formation of solid dispersions

In preliminary studies, 1:1, 1:3 and 1:4 drug/PVP (%w/w) dispersions were prepared. The 1:3 and 1:4 dispersions showed similar dissolution profiles which were superior to the 1:1 dispersion. Hence, a 1:3 dispersion was chosen for additional study since it maximized the dissolution rate while minimizing the polymer content. Preliminary studies of solid dispersions of drug in PEGs of varying molecular weight (at a 1:9 weight ratio) showed similar dissolution profiles. Hence, a 1:9 dispersion of drug in PEG 8000 dispersion was chosen for further study. Fig. 3 compares the dissolution profiles of the drug alone, of the solid dispersions, and of the corresponding physical mixtures in water at 37°C. Although significant increases in the rate and extent of SB-210661 dissolution (i.e. 50–60% dissolved within 60 min) were observed by the addition of surfactants to the formulation (Fig. 2), even more pronounced increases were observed by the formation of solid dispersions (i.e. about 90% of SB-210661 dissolved within 60 min).

For the PEG dispersion prepared by the fusion method, a temperature of 105°C was required to completely dissolve SB-210661 within the molten PEG 8000. In general, a processing temperature of 105°C is undesirable from a large-scale manufacturing standpoint and may cause problems with the chemical stability of thermally-labile drug. Hence, mechanical activation (using a ball mill) was studied as an alternate preparation procedure. The benefit of the ball-milling method is that it does not require or generate excessive heat when 'melting' the polymer. As shown previously (Fig. 3), the dissolution characteristics of the dispersions prepared by the fusion and mechanical activation methods were similar.

To understand the mechanisms by which the solid dispersions enhance the dissolution behavior of SB-210661, the solubility of SB-210661 was evaluated in the presence of both PVP and PEG 8000, and the physical state of SB-210661 in the various preparations was evaluated by X-ray powder diffraction and FTIR. As shown in Table 1, both polymers increased the solubility of SB-210661 in a linear fashion which can contribute to an enhanced dissolution rate (Betageri and Makarla, 1995).

The X-ray diffraction patterns for SB-210661, PVP, the solid dispersion containing PVP, and the corresponding physical mixture are shown in Fig. 4. As can be seen, pure SB-210661 is crystalline as demonstrated by the sharp and intense diffraction peaks, whereas PVP is amorphous. The physical mixture showed diffraction peaks which are consistent with the presence of crystalline SB-210661, whereas the solid dispersion showed no diffraction peaks which is consistent with the absence of crystalline SB-210661. In contrast, the diffractograms for the solid dispersions containing PEG 8000 (which are not shown) revealed that SB-210661 existed in a partially crystalline form and that the extent of crystallinity appeared to be independent of the method of preparation (i.e. melting or ball-milling). Interestingly, even

Table 2
Surface tension (γ) and contact angle data for SB-210661

Medium	Solubility (mg/ml)	CMC[a] (g/ml)	γ (mN/m)	Advancing contact angle
Water	0.016	—	72.7	122.5 ± 1.2
0.5% SDS	0.15	2.36×10^{-3}	37.2	72.6 ± 1.9
0.5% Tween 40	0.14	3.00×10^{-5}	37.3	79.1 ± 2.7

[a] CMC represents the critical micellar concentration for the given surfactant.

though the PEG dispersions were partially crystalline, their dissolution profiles were comparable to the totally amorphous PVP dispersions.

The infrared spectra of SB 210661, PEG 8000, the solid dispersions containing PEG 8000, and the corresponding physical mixtures (which are not shown) display no significant differences. In contrast, the similar spectra for the PVP systems showed significant differences (Fig. 5). The type of behavior observed has also been seen previously with other PVP dispersions (Doherty and York, 1987; Sekizaki et al., 1995; Taylor and Zoggrafi, 1997). As shown in Fig. 5, the absorption of the O–H bond stretching for SB-210661 occurs at 3464 cm^{-1}, whereas the absorption is upshifted to 3496 cm^{-1} when the drug is present in the PVP solid dispersion. Both of these absorption frequencies are down-shifted from 3600 cm^{-1} which is typically observed for the O–H bond stretching. It is well established that both intra- and inter-molecular hydrogen bonding in alcohols result in a downward frequency shift (from 3600 cm^{-1}) in the absorption peak. Additionally, in-

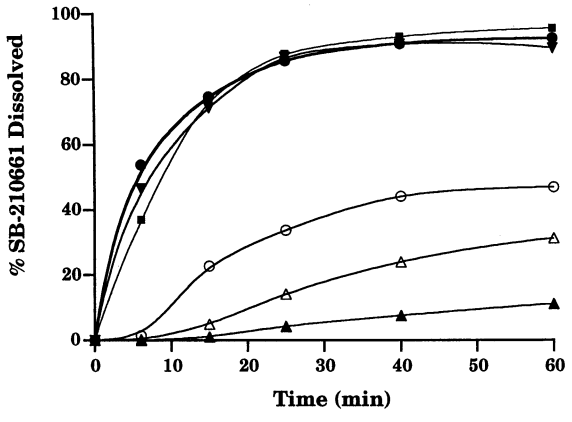

Fig. 3. Dissolution profiles of SB-210661 physical mixture and solid dispersions. Key: (▲) SB-210661 alone; (△) SB-210661:PVP K30 = 1:3 (physical mixture); (○) SB-210661: PEG 8000 = 1:9 (physical mixture); (●) SB-210661:PEG 8000 = 1:9 solid dispersion (Ball-milling); (▼) SB-210661:PEG 8000 = 1:9 solid dispersion (Fusion method); (■) SB-210661:PVP K30 = 1:3 solid dispersion (Solvent method).

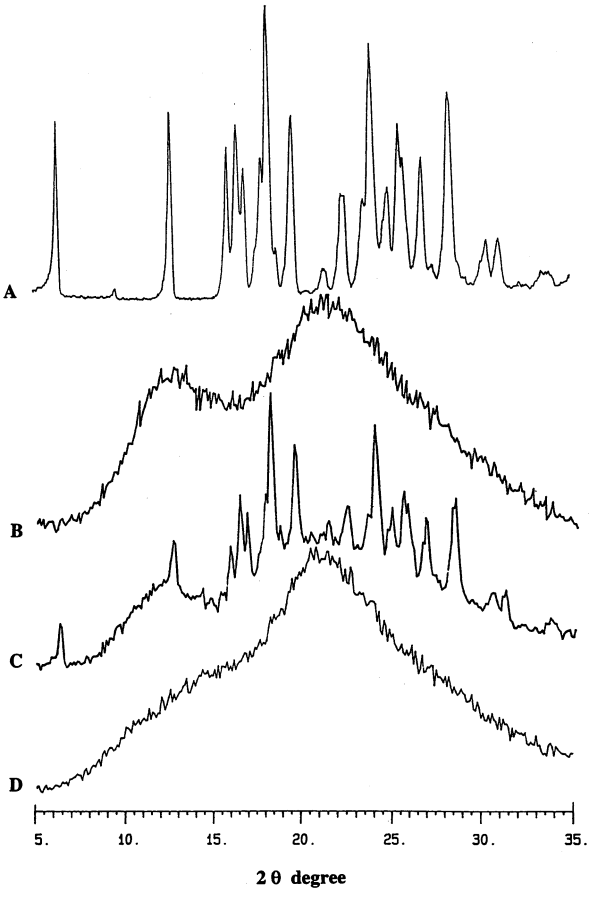

Fig. 4. Powder X-ray diffraction patterns. Key: A, SB-210661 alone; B, PVP alone; C, SB-210661:PVP = 1: 3 (physical mixture); D, SB-210661:PVP = 1:3 (solid dispersion).

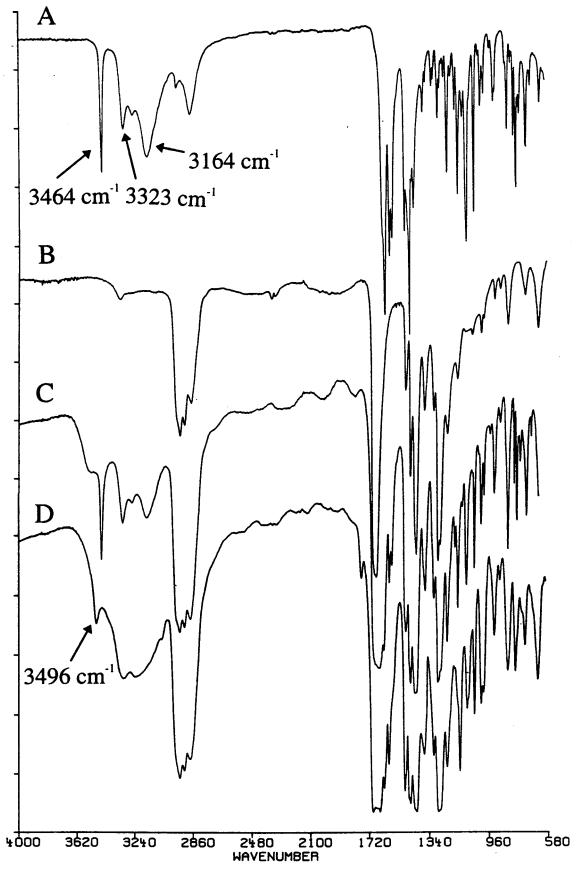

Fig. 5. FTIR spectra. Key: A, SB-210661 alone; B, PVP alone; C, SB-210661:PVP = 1:3 (physical mixture); D, SB-210661: PVP = 1:3 (solid dispersion).

tramolecular hydrogen bonding yields a greater downward frequency shift than intermolecular hydrogen bonding (Bellamy, 1975). The results may suggest that intramolecular hydrogen bonding occurs between the O–H and C=O moieties of SB-210661 in its unadulterated form (this would account for the downward shift to 3464 cm^{-1}), whereas, in the presence of PVP, the O–H group of SB-210661 may now interact with the C=O group of PVP (this would account for the less pronounced downward shift to 3496 cm^{-1}). Additionally, the absorption of the NH_2 bond stretching observed at 3323 and 3164 cm^{-1} for SB-210661 were broaden and shifted downward in frequency in the presence of PVP. This may suggest that the NH_2 moiety of SB-210661 interacts with C=O moiety of PVP via hydrogen bonding (Doherty and York, 1987).

One of the major limitations of the solid dispersion approach is that the dissolution rate of the drug in the dispersion may slow upon aging. In general, a formulation must not demonstrate a significant slowing in dissolution over at least a 2-year interval to be 'commercializable'. If one of the primary mechanisms for the enhanced dissolution, seen with a solid dispersion, is a change in the physical state of the drug to a higher energy, faster dissolving form (e.g. a loss or decrease in crystallinity) then if the drug converts to a more thermodynamically stable, lower energy form, the driving force for the increased dissolution rate is lost.

To assess the long-term stability of the dissolution behavior of the solid dispersions of SB-210661, the dispersions were stored at 25°C and 60% RH in an open container (open containers were used to simulate worst-case conditions). The dissolution profiles for the various solid dispersions following storage for 1 year are shown in Table 3. As can be seen, the PVP solid dispersion showed no significant change in its dissolution behavior over this interval; the X-ray powder diffractogram revealed that SB-210661 still existed in an amorphous state; and the FTIR spectrum demonstrated that the interaction between the SB-210661 and PVP was intact. These results suggest that the postulated hydrogen-bonding interaction between the drug and PVP stabilizes the amorphous form of the drug in the dispersion. Similar findings have been reported for PVP dispersions of indomethacin (Imaizumi et al., 1983). In contrast to what was seen for the PVP dispersions, the PEG dispersions showed a slowing in their dissolution behavior over the 1-year interval. The decrease observed in the dissolution performance of the PEG dispersions might be due to an increase in the crystallinity of SB-2106621 in the matrix. This contention is difficult to support because the X-ray powder diffractograms are not easily differentiable in the PEG 8000 dispersions because of the low drug load.

Table 3
Dissolution data (%dissolved) for SB-210661 dispersions stored at 25°C/60% RH for 1 year

Time (min)	PEG dispersion (fusion)		PEG dispersion (ball-milling)		PVP dispersion	
	Initial	1 year	Initial	1 year	Initial	1 year
6	53.9 (31.3)[a]	33.5 (9.3)	66.6 (4.8)	31.2 (14.1)	37.0 (22.5)	30.4 (15.1)
15	74.7 (8.7)	58.7 (15.5)	71.4 (0.8)	58.1 (17.8)	73.7 (8.6)	74.5 (0.8)
25	85.8 (4.8)	71.3 (14.5)	86.9 (0.5)	78.7 (4.0)	87.9 (3.3)	88.4 (1.0)
40	91.0 (2.2)	78.6 (10.2)	90.8 (3.4)	83.0 (1.6)	93.1 (2.0)	93.8 (0.6)
60	92.6 (0.7)	84.0 (5.4)	89.6 (1.0)	84.7 (1.4)	95.9 (0.4)	95.7 (1.3)

[a] The numbers in parenthesis are the standard deviation.

4. Conclusions

The results clearly show that the incorporation of relatively small amounts (i.e. 0.5% w/w) of commonly-used surfactants (i.e. SDS or Tween 40) into solid formulations of SB-210661 can improve its dissolution rate. Additionally, it was shown that greater increases in the dissolution rate of SB-210661 were achievable via the formation of solid dispersions. The increases observed with the PEG 8000 dispersions were independent of the preparation technique utilized (i.e. fusion or mechanical activation). However, the dissolution rate of SB-210661 in the PEG dispersion slowed significantly following storage for 1 year at 25°C/60% RH. In contrast, the dissolution rate of SB-210661 in the PVP dispersion was unchanged following storage for 1 year at 25°C/60% RH. This may be attributed to a hydrogen-bonding interaction occurring between SB-210661 and PVP, which can maintain SB-210661 in an amorphous state during storage.

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