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Improvement of the dissolution kinetics of SR 33557 by means of solid dispersions containing PEG 6000

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Abstract

Solid dispersions of SR 33557 in preparations containing from 30 to 80% w/w polyethylene glycol 6000 (PEG 6000) were prepared by the fusion method. The solubility of the drug substance either alone or in solid dispersions was determined in pH 1.2 and 4.5 media (extraction fluid NFXII, without enzyme). A large increase in the solubility was noted from the 80% w/w PEG preparation. A wettability study performed by measuring the contact angle on tablets of either drug substance or PEG 6000, or solid dispersions, revealed a minimal contact angle for the 80% w/w PEG 6000 solid dispersion (eutectic composition of SR 33557/PEG 6000 phase diagram). Dissolution kinetic analysis performed at pH 1.2 on all solid dispersions, on the physical mixtures containing 70 and 80% w/w PEG 6000, and on SR 33557 alone, showed a maximum release rate (100%) for the solid dispersions containing 70 and 80% w/w PEG 6000. The dissolution rate of the physical mixtures was faster than that of the drug substance alone but remained, however, lower than that of the solid dispersions, at the same composition. It was also observed that the dissolution rate, at pH 1.2 and 4.5, of the 70% w/w PEG 6000 solid dispersion was practically pH independent, which was not the case for the drug substance alone. The latter solid dispersion showed a slowing down of the dissolution kinetics after 3 months storage at 50° C whereas no change in the dissolution rate was observed following storage for 12 months at 25° C.

Keywords: SR33557; Polyethylene glycol; Solid dispersion; Dissolution rate; Wettability; Contact angle

1. Introduction

The therapeutic efficacy of a drug product intended to be administered by the oral route depends first of all on its absorption by the gastro-intestinal tract. However, for a drug substance to be absorbed, it needs to be solubilized. Solubilization is the stage that precedes absorption. Numerous works have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. Among the most widely used methods are micronisation which allows the reduction of particle size (Atkinson et al., 1962), the use of surfactants (Khalafallah et al., 1975) and the formation of solid dispersions (Sekiguchi and Obi, 1961; Chiou and Riegelman, 1971; Law et al., 1992).

This work aimed at demonstrating the influence of solid dispersions made from polyethylene

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glycol 6000 on the dissolution of SR 33557 in gastric medium. SR33557 belongs to a new family of calcium antagonists, the 'sulfone indolizines', used for the treatment of cardiovascular diseases (Nokin et al., 1989; Lacour et al., 1990). Taking into account its poor solubility in aqueous medium, it would be interesting to improve its dissolution kinetics. In a previous work (Lheritier et al., 1994), the drug substance and the carrier, as well as their interactions, were studied from a thermodynamic point of view. A binary diagram was established to determine the position of the invariants.

2. Materials and methods

2.1. Materials

SR33557 (CAS114432-13-2), batch 90-03, was used for the work described in this paper. Its chemical structure is $C_{31}H_{38}N_2O_5S$ and its molecular weight 550.726. SR 33557 is a new Sanofi Recherche (France) molecule. It is a white to off-white crystalline powder, poorly soluble in water.

Polyethylene glycol (PEG) with a mean molecular weight of 6000 was used as a carrier. It is a white powder, very soluble in water. PEG distributed is by ICI, France.

2.2. Methods

2.2.1. Preparation of the physical mixtures

SR 33557 and PEG 6000 were thoroughly blended by trituration in a mortar for 5 min then sifted on a 250 μm opening sieve. Four blends were so prepared with percentages of PEG 6000 corresponding to 30, 50, 70 and 80%.

2.2.2. Preparation of the solid dispersions

The solid dispersions were prepared from the above-mentioned physical mixtures by the fusion method (Sekiguchi and Obi, 1961) in an oil bath heated at 95° C. The resulting homogeneous liquid was poured onto a stainless-steel plate and cooled to room temperature (25° C) in a light protected area in a desiccator for 24 h. The comelts obtained were ground in a mortar, then sifted through a 250 μm sieve, and blended in a Turbula mixer for 5 min at 80 rpm. The SR 33557 concentration of each solid dispersion was measured on a UV spectrophotometer at 231 nm after dissolution of the drug substance in hydroalcoholic medium. In a previous work, it had been demonstrated, by differential scanning calorimetry and thermogravimetry, that this drug was stable above its melting temperature (89.1° C) up to 275° C. In addition, a thin-layer chromatography study revealed no degradation of the active substance during preparation by fusion of the solid dispersions (Chauvet et al., unpublished data).

2.3. Solubility study

A solubility study was performed on SR 33557 alone and on the solid dispersions, in media corresponding to the extraction fluid NFXII without enzyme: pH 1.2 (NaCl, 2 g; HCl, 7 ml; purified water, qs. 1000 ml) and pH 4.5 (previous medium pH 1.2 adjusted to pH 4.5 with KH_2PO_4, 6.8 g; 0.2 N NaOH, 190 ml; purified water, qs. 1000 ml). For each assay, 100 mg of drug substance were charged into 10 ml amber glass bottles each containing 5 ml of each medium. All samples were placed on a wheel rotating at 40 rpm, in a water bath thermostatically controlled at 37 ± 0.5° C. They were agitated for 24 h then allowed to stand for 2 h at the same temperature. A sample was withdrawn from the supernatant with a syringe, filtered through a 0.45 mm Acrodisc membrane, and assayed by UV spectrometry, at 231 nm (Gilford, Response II spectrometer).

Results are the mean value of two determinations.

2.4. Wettability

Wettability was determined by measuring the contact angle according to a direct optical method using an apparatus from Sodexim, France. The study was carried out on various samples: SR 33557 alone, PEG 6000, and solid dispersions. 250 mg powder were compressed in a hydraulic press (Enerpac, France) fitted with 11.2 mm di-

ameter flat punches. A 1.5 ton pressure was applied for 15 s. Before each use, the punches were cleaned with acetone. Liquids used corresponded to the two dissolution media (pH 1.2 and 4.5) and were kept at a temperature of 37 ± 0.5° C. A 10 μl liquid droplet was dropped on the surface of the tablet. 10 measurements were made on each sample. Mean measurement and standard deviation were calculated. Variance analysis was carried out, completed by a Newman-Keuls test (Dagnelie, 1984) to check whether or not the values obtained were significantly different ($\alpha = 0.05$).

2.5. Dissolution study

The dissolution test was carried out, using a USP XXI, paddle apparatus model Sotax AT6. The AT6 Sotax was linked to a multitubing peristaltic pump (Gilson, Munipuls type 2) ensuring a 7 ml min^{-1} flow interfaced with a Gilford automatic spectrometer, type Response II. The dissolution media were the same as those used for the solubility study. 1000 ml of each dissolution medium were used, the stirring speed was 100 rpm, and the temperature of the media was maintained at 37 ± 0.5° C. Samples were withdrawn at regular intervals from the shaft of each paddle fitted with a filter. Samplings corresponded to the equivalent of 75 mg SR 33557 (< 30% of the solubility of the drug substance in such media to be in compliance with sink conditions). Measurements were made every 5 min. Dissolution kinetic analyses were carried out at pH 1.2 on the drug substance alone, on the physical mixtures containing 70 and 80% w/w PEG 6000, and on the solid dispersions. They were also performed at pH 4.5 on the drug substance alone and on the solid dispersion containing 70% w/w PEG 6000, the latter being intended to be used for the subsequent formulation of a dosage form.

Results presented here are the mean values of three determinations.

2.6. Storage study

To determine the influence of the storage conditions on the dissolution rate, solid dispersions containing 70% w/w of PEG 6000 were poured into amber glass bottles and stored in an oven under the following conditions: (i) 12 months at 25° C ambient humidity; (ii) 6 months at 35° C ambient humidity; (iii) 3 months at 50° C ambient humidity.

Dissolution kinetic analyses at pH 1.2 were performed at the above time points.

2.7. X-ray diffraction

X-ray diffraction diagrams were constructed using a CGR gonometer fitted with a monochromator and copper as the anticathode ($k\alpha = 1.5405$ Å). Recording was made at the rate of $15° \theta\ h^{-1}$. A Gypse sample was used as standard reference diagram for adjustment. Reproducibility of measurements was 2% on the total diffractogram. X-ray spectra on the drug substance alone, on PEG 6000, on freshly prepared solid dispersion containing 70% w/w PEG 6000, and on the same solid dispersion kept for 3 months at 50° C were recorded.

3. Results and discussion

3.1. Solubility study

Table 1 shows the solubility of SR 33557, alone and from solid dispersions. The solubility at 37° C of SR 33557 alone, according to the method described earlier, was 0.26 mg ml^{-1} in pH 1.2 medium and 0.31 mg ml^{-1} in pH 4.5 medium. The results revealed a better solubility of SR 33557 from solid dispersions at pH 1.2. Solubility was particularly better with PEG-rich composi-

Table 1
Solubility (mg ml^{-1}) of SR 33557 alone and with solid dispersions to pH 1.2 and 4.5

Sample	pH 1.2	pH 4.5
SR 33557 alone	0.26	0.31
Solid dispersion with 30% w/w PEG 6000	0.37	0.26
Solid dispersion with 50% w/w PEG 6000	0.58	0.32
Solid dispersion with 70% w/w PEG 6000	1.38	0.40
Solid dispersion with 80% w/w PEG 6000	3.29	0.90

Table 2
Contact angles measured at 37° C on tablets of SR 33557 alone, of PEG 6000 and of solid dispersions

Sample	θ (°)			
	pH 1.2		pH 4.5	
	Mean	SD	Mean	SD
SR 33557 alone	50.6	1.3	51.4	1.2
Solid dispersion with 30% w/w PEG 6000	42.9	1.3	39.3	1.0
Solid dispersion with 50% w/w PEG 6000	29.6	1.3	28.9	1.0
Solid dispersion with 70% w/w PEG 6000	23.1	1.1	22.1	0.7
Solid dispersion with 80% w/w PEG 6000	19.6	1.2	20.5	0.9
PEG 6000	18.2	1.2	19.8	0.8

tions, in particular, increasing 2-, 5- and 12-fold with the 50, 70 and 80% w/w PEG 6000 solid dispersions, respectively. At pH 4.5, it increased only with the 80% w/w PEG 6000 solid dispersion (3-fold). Solid dispersions appeared to be more effective at pH 1.2 than at pH 4.5. The solubility increase observed for the solid dispersion containing 80% w/w PEG 6000, irrespective of the pH, may be attributed to the presence of an optimum hydrophilic environment as well as to a finer distribution of SR 33557 in PEG 6000 as the solid dispersion corresponds to the eutectic composition (Chauvet et al., unpublished data).

3.2. Wettability study

Table 2 lists the values of the contact angles. The value of the contact angle of the liquid (at pH 1.2 and 4.5) on the surface of the tablet decreased when the PEG 6000 concentration in the solid dispersions increased, by up to 80%.

The results of the variance analysis demonstrate the influence of the composition of the samples on the contact angle. However, the experiment did not reveal any effect due to pH. The Newman-Keuls test showed a significant difference between the six samples ($\alpha = 0.05$). The improvement of the wettability can be explained by the fact that PEG 6000, in the solid dispersion, forms a film around the drug substance particles, thus modifying the hydrophobicity of the tablet surface.

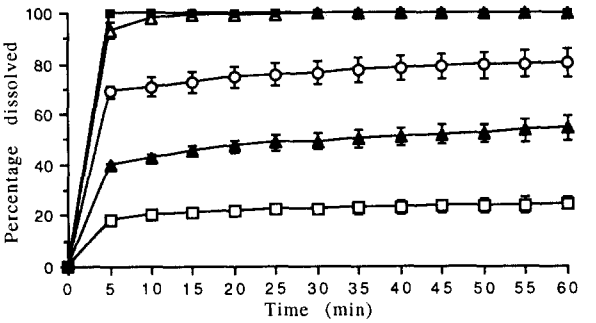

Fig. 1. Dissolution kinetics of SR 33557 alone and of solid dispersions (SD) containing 30, 50, 70 and 80% w/w PEG 6000 at pH 1.2. (□) SR 33557 alone, (▲) SD 30% PEG 6000, (○) SD 50% PEG 6000, (△) SD 70% PEG 6000, (■) SD 80% PEG 6000.

3.3. Dissolution study

Fig. 1 displays the dissolution kinetics of SR 33557 alone and of the solid dispersions at pH 1.2. Better dissolution kinetics were observed for the solid dispersions and the extent of dissolution increased with increasing PEG 6000 concentration. Only the solid dispersions containing 70 and 80% w/w PEG 6000 enabled the total release of the drug substance. The dissolution kinetics at pH 1.2 with solid dispersions containing 70 and 80% w/w PEG 6000, with physical mixtures of the same compositions and with SR 33557 alone are presented in Fig. 2. The results revealed that the dissolution profile of the physical mixtures

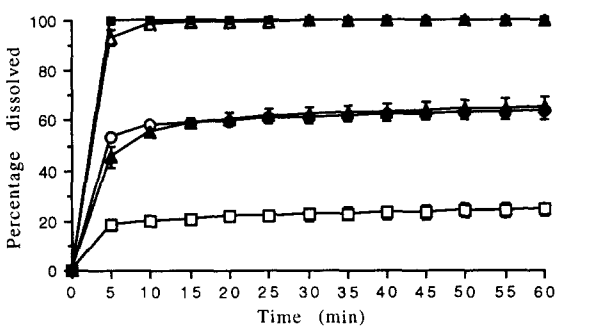

Fig. 2. Dissolution kinetics of SR 33557 alone, physical mixtures (PM), and solid dispersions (SD) containing 70 and 80% w/w PEG 6000 at pH 1.2. (□) SR 33557 alone, (○) PM 70% PEG 6000, (▲) PM 80% PEG 6000, (△) SD 70% PEG 6000, (■) SD 80% PEG 6000.

was much higher than that of SR 33557 alone but lower than that of the solid dispersions at the same concentrations. The dissolution rates at 10 min were almost 100% for the solid dispersions containing 70 and 80% w/w PEG 6000, but only 55% for the physical mixtures, and 20% for SR 33557 alone. The increase in the dissolution kinetics is due to the following factors:

(i) Increased solubility of the drug substance in solid dispersions;

(ii) No further aggregation of SR 33557 particles mixed in PEG 6000, as observed in our experiments, hence more solid-liquid surface of exchange. It should be noted that the dispersion of the powder was less efficient in the physical mixtures, which might be due to differences in the solid-state structure;

(iii) Modification of the surface properties of the particles in the solid dispersions, and hence a reduction of the value of the contact angle, which in turn improves the wettability of the powder.

Fig. 3 shows the dissolution kinetics of SR 33557 alone and of the solid dispersion containing 70% w/w PEG6000, as determined in pH 1.2 and 4.5 media. The results revealed that the dissolution kinetics of SR 33557 alone was pH dependent. The dissolution rate at 30 min was about 23% at pH 1.2 and 65% at pH 4.5. The 70% w/w PEG 6000 solid dispersion resulted in the dissolution kinetics being almost pH independent. The amount released at 30 min approached 100% in both cases.

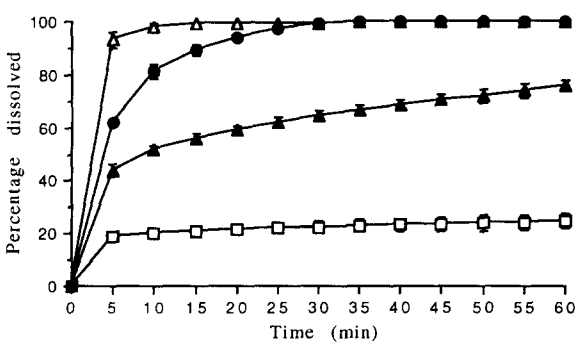

Fig. 3. Dissolution kinetics of SR 33557 alone and solid dispersion containing 70% w/w PEG 6000 at pH 1.2 and 4.5. (□) SR 33557 alone (pH 1.2), (△) SD 70% PEG 6000 (pH 1.2), (▲) SR 33557 alone (pH 4.5), (●) SD 70% PEG 6000 (pH 4.5).

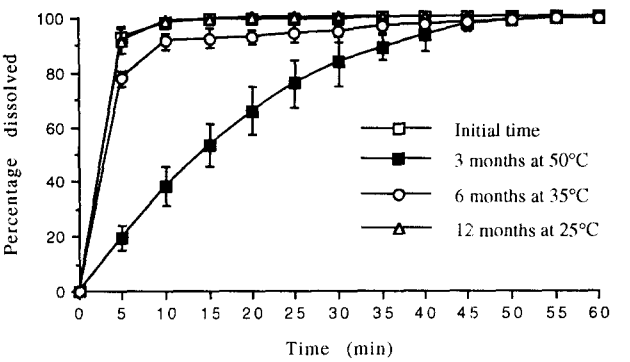

Fig. 4. Dissolution kinetics of the 70% w/w PEG 6000 solid dispersion at pH 1.2 according to time and storage temperature.

3.4. Storage study

The dissolution kinetics of the 70% w/w PEG 6000 solid dispersion as determined in pH 1.2 medium according to time and storage temperature are presented in Fig. 4. It was observed that the temperature had an influence on the dissolution kinetics. This was characterized by a slower release of the drug substance, especially so after 3 months at 50° C. In fact, at 50° C the powder becomes softer, and hence is more slowly dispersed in the dissolution medium. After 6 months at 35° C, although it was slightly slower, 90% of the drug substance was released in 10 min. However, the dissolution profile of the solid dispersion at ambient temperature (25° C) after 12 months storage was identical to that obtained initially as seen on the curves which are superimposed.

3.5. X-ray diffraction

X-ray spectra are presented in Fig. 5. The main spectral lines of the drug substance and those of PEG 6000 were found in that of the 70% w/w PEG 6000 solid dispersion; however, the relative intensity of most of the lines corresponding to SR 33557 in the solid dispersion was less as compared to that of SR 33557 alone. The reflec-

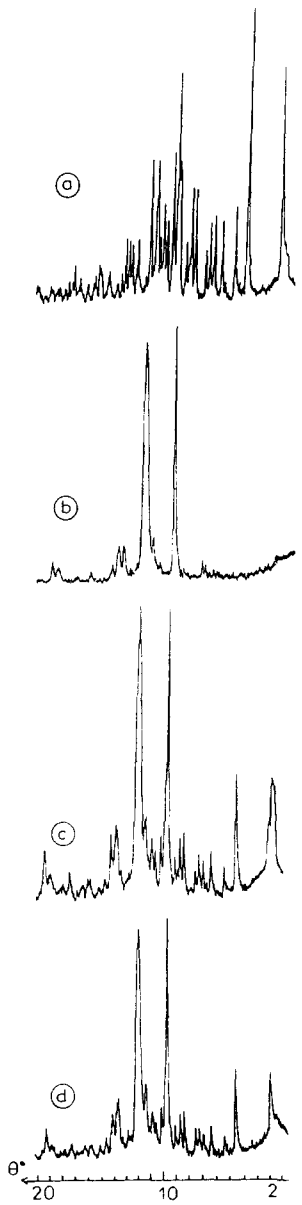

Fig. 5. X-ray diffraction spectra: (a) SR33557; (b) PEG 6000; (c) freshly prepared solid dispersion containing 70% w/w PEG 6000; (d) solid dispersion containing 70% w/w PEG 6000 after 3 months storage at 50° C.

tions corresponding to d values of 4.64, 4.03, 3.81, 3.39, 3.31 and 3.19 Å for the drug substance and for PEG 6000 were also found in the solid dispersion spectrum, with greater intensity. This can be explained by the relative proportions of the constituents in the solid dispersion. No significant difference in the reflections corresponding to the two solid dispersion spectra (at the initial time point and after 3 months at 50° C) was observed, therefore, there is no crystalline modification of the solid dispersion with time when submitted to our accelerated ageing conditions.

4. Conclusion

From this study, it can be concluded that the type of drug/carrier association plays a considerable role in the dissolution of the drug, in either the form of physical mixtures or solid dispersions, the latter showing the best results, and more especially, the eutectic mixture. Furthermore, in the case of solid dispersions, it was shown that the dispersion of the particles of drug substance and improvement of the wettability were two important factors for the dissolution of the drug substance. The influence of solid dispersions on the reduction of the contact angle was also displayed with a minimum value for the eutectic mixture. The stability study performed on the solid dispersions containing 70% w/w PEG 6000 demonstrated an effect of the temperature, mainly at 50° C on the dissolution kinetics. However, good reproducibility of the dissolution kinetics was seen on samples stored at 25° C. The X-ray spectra did not show any modification of the solid dispersion containing 70% w/w PEG 6000 when kept for 3 months at 50° C.

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