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Release of salbutamol sulfate enantiomers from hydroxypropylmethylcellulose matrices

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Abstract

The in vitro dissolution profiles of nine sustained-release formulations of (±)-salbutamol were determined. The formulations contained chiral pharmaceutical excipients, such as hydroxypropylmethylcellulose (HPMC) and heptakis (2,6-di-*O*-methyl)-β-cyclodextrin (DMCD). The influence of the degree of ionization was studied in six formulations that were buffered at different pH values. The quantitative determination of salbutamol enantiomers released by the matrices was carried out using a stereospecific capillary electrophoresis method. The release of salbutamol enantiomers from all formulations was found to be non-enantioselective. Likewise, the addition of buffering agents to the formulation did not provide an enantioselective release of salbutamol enantiomers from the matrices under the conditions established. © 1998 Elsevier Science B.V.

Keywords: Stereoselective dissolution; Chiral excipient; Hydroxypropylmethylcellulose; Cyclodextrin; Salbutamol sulfate enantiomers; Sustained release

1. Introduction

Recently many attempts have been made to investigate the implications of pharmaceutical formulations of chiral drugs (Aubry and Wainer, 1993; Maggi et al., 1996). Although much work has been done on the pharmacokinetic, pharmacodynamic, and toxicological aspects of chirality, its implications on physical pharmacy have been poorly established.

A wide variety of chiral excipients, such as cellulose polymers and cyclodextrins, are used as excipients in pharmaceutical formulations. The interaction of the enantiomers of a chiral drug with these chiral excipients may lead to the formation of diastereomers with different physical and chemical properties. It has been hypothesized that chiral excipients may interact preferentially with one enantiomer leading to a stereoselective disso-

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Table 1
Tablet composition (mg)

	Formulation no.								
	1	2	3	4	5	6	7	8	9
Salbutamol sulfate	9.6			9.6			9.6		
Freeze-dried mixture		54			54			54	
Physical mixture			54			54			54
HPMC	156.8	156.8	156.8	156.8	156.8	156.8	156.8	156.8	156.8
Mannitol	230.8	186.4	186.4	190.8	146.4	146.4	190.8	146.4	146.4
Magnesium stearate	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Sodium carbonate				32.34	32.34	32.34			
Sodium bicarbonate				7.66	7.66	7.66			
Citric acid							37.4	37.4	37.4
Disodium phosphate							2.6	2.6	2.6

lution from a formulation containing a racemate (Duddu et al., 1993).

Previous studies have shown the possibility of obtaining sustained release formulations of salbutamol sulfate by using chiral excipients in the composition of hydrophilic matrices (Bonferoni et al., 1992, 1993). In this work the effect of chiral excipients, hydroxypropylmethylcellulose (HPMC) and heptakis (2,6-di-*O*-methyl)-β-cyclodextrin (DMCD), on the release from matrix tablets of the enantiomers of a chiral drug molecule, salbutamol sulfate, has been studied, and the reasons for stereoselectivity of release, or lack of it, were examined.

Drug release from a formulation can be modified by controlling the pH immediately surrounding the dissolving solid formulation, as shown by Doherty and York (1989). For this reason, the second objective of this work has been to study the influence of formulation pH on the in vitro release profiles of salbutamol enantiomers.

2. Materials and methods

2.1. Materials

Racemic salbutamol sulfate was obtained from Vencaser S.A. (Bilbao, Spain), HPMC (Methocel K100M) was kindly provided by Colorcon Limited (Orpington, Kent, UK) and DMCD was obtained from Sigma Chemical Company (Madrid, Spain). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of tablets

Three types of tablets were prepared: the first one contained racemic salbutamol; the second type was formed by a freeze-dried mixture of salbutamol with DMCD (1:1), prepared according to the method used by Kurozumi et al. (1975), although slightly modified; and for the third type a physical mixture of salbutamol with DMCD (1:1) was used. The composition of each formulation is listed in Table 1. The drug or the mixture were mixed with HPMC and the remaining additives (mannitol, magnesium stearate and buffering agents). Three formulations were unbuffered (nos. 1, 2, and 3), their pH was around 6, and six formulations were internally buffered, three at pH 2.5 (with citric acid and disodium phosphate) (nos. 7, 8, and 9) and three at pH 10 (with sodium carbonate and disodium bicarbonate) (nos. 4, 5, and 6). The mixture was tabletted by direct compression with a reciprocating tablet press machine (BONALS).

2.2.2. Dissolution test

The dissolution tests were performed in 500 ml of milli-Q water, at 37°C and 100 rpm, using the rotating basket (USP XXIII Apparatus 1) (six replicates). The samples (2 ml) were collected at

30, 60, 120, 180, 240, 360, and 540 min, and immediately stored at −20°C until quantification by capillary zone electrophoresis (CZE).

2.2.3. Analytical procedure

The samples collected during the dissolution tests were analyzed with a previously described CZE technique (Equisabel et al., 1997). The apparatus was a Hewlett-Packard capillary electrophoresis system equipped with a diode-array detector. CZE was performed in a fused-silica capillary (40 cm effective length, and 50 μm i.d.). Separation was carried out in a constant voltage mode (15 kV) at 20°C (capillary temperature). Samples were introduced by hydrodynamic injection at 50 mbar for 5 s. Electrophoresis buffers were prepared by dissolving 40 mM Tris-base in water and adjusting the pH with phosphoric acid to 2.5. DMCD was dissolved in Tris–phosphate buffer. The calibration solutions of salbutamol sulfate were prepared dissolving different concentrations of drug (2, 5, 10, 20, and 40 μg/ml). This technique proved to be a sensitive, selective, accurate and reproducible method for the determination of the salbutamol enantiomers under the conditions described.

2.2.4. Kinetic analysis

In order to understand the drug release mode from the matrices, the data were fitted by using the WINNONLIN program (Scientific Consulting, Inc., PCNonlin, 1995) to the following power law equation: $M_t/M_\infty = K \cdot t^n$ where M_t/M_∞ is the fraction of drug released up to time t, K is the kinetic constant and n is the release exponent indicative of the release mechanism (Peppas, 1985). The mean dissolution time (MDT) and the percentage of the drug released after 9 h were also calculated. MDT is the mean ratio of the first to zero moments of the dissolution rate–time curve and it is expressed by the following equation: $\mathrm{MDT} = \mathrm{ACC}/M_\infty$, where ACC is the complementary area under the accumulated dissolution curve and M_∞ is the maximum accumulated dissolution amount. This parameter was calculated by using the PKCALC program (Schumaker, 1986). The paired Student's t-test was used to compare the kinetic parameters of the enantiomer release. The significance level was set at $p < 0.05$.

3. Results and discussion

Differential rates of release of drug enantiomers from a finished product are theoretically possible and the lack thereof should be confirmed. Salbutamol is one of the most widely used β_2-agonists. All marketed formulations of the drug contain racemic salbutamol, with *R*-salbutamol as the enantiomer responsible for the therapeutic activity. It was thought that the *S*-enantiomer of salbutamol was inactive, but it is not. In fact, it has been shown that this enantiomer enhances inflammatory responses and increases airway hyper-reactivity to spasmogens and allergens in both animals and humans (Perrin-Fayolle et al., 1996). Therefore, the attainment of different patterns in the release of salbutamol enantiomers from tablets containing chiral excipients could contribute to the modification of the profile of activity, and/or adverse effects of racemic formulations of salbutamol.

Fig. 1 shows the dissolution profiles of racemic salbutamol and its enantiomers for each formulation. As can be seen, all formulations show an extended release of the drug during the study period and a typical diffusion-dependent dissolution profile. This finding was already shown in previous studies in which the release of enantiomers from tablets with similar characteristics was evaluated (Hernández et al., 1996). Both enantiomers present an asymptotic profile, and their dissolution curves are practically superimposable in all cases. Significant stereoselectivity in the dissolution profiles of the enantiomers is not observed.

The values of the parameters obtained for all formulations from the data fitting to the power law equation and MDT are listed in Table 2. The kinetic constant, K, ranged from 1.71 to 2.88% min^{-n} for the *R*-enantiomer ($2.31 \pm 0.44\%\ \mathrm{min}^{-n}$) and from 1.57 to 2.80% min^{-n} for the *S*-enantiomer ($2.30 \pm 0.45\%\ \mathrm{min}^{-n}$). There were no significant statistical differences ($p > 0.05$) in the K value between both enantiomers for each formulation. The MDT values of the formulations ranged between 165.24 and 195.24 min (178.58 ± 11.18 min) (*R*-enantiomer) and between 164.25 and 215.87 min (181.97 ± 15.24 min) (*S*-enan-

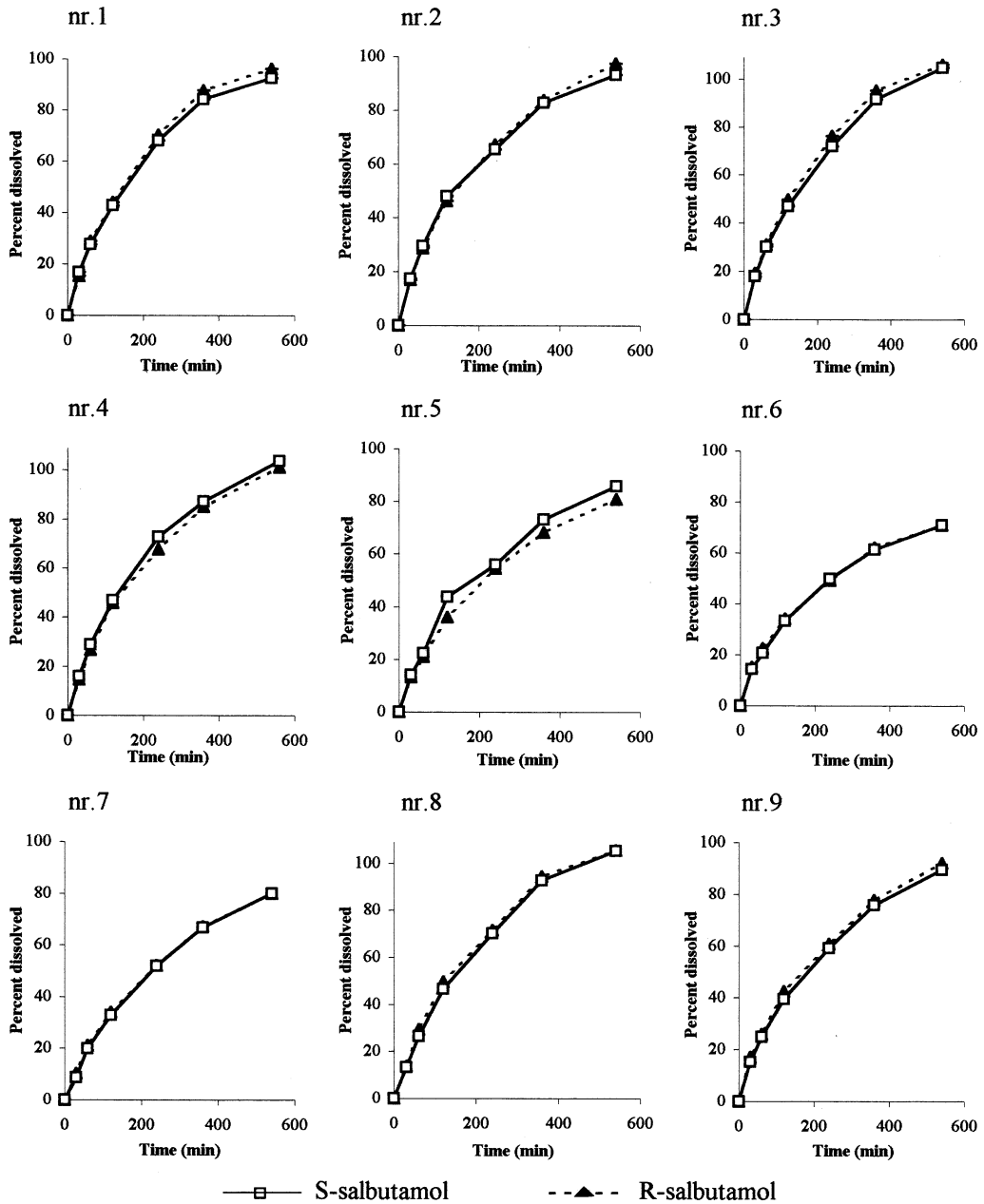

Fig. 1. Plots of cumulative percentage of dissolved (*R*)- and (*S*)-salbutamol vs. time for the nine formulations.

tiomer). Neither were there significant statistical differences ($p > 0.05$) in this parameter between both enantiomers.

The values of n ranged between 0.52 and 0.70, suggesting that salbutamol release is controlled by both diffusion of the drug in the hydrated matrix and the erosion of the matrix itself (Peppas, 1985). HPMC is one of the most widely used materials in sustained release matrix formulations. The release of a hydrophilic drug from this kind

Table 2
Values of the kinetic parameters obtained (mean ± S.D.)

Formulation no.		K (% min^{-n})	n	MDT (min)
1	*R*-Salbutamol	2.04 ± 0.64	0.65 ± 0.06	165.24 ± 16.25
	S-Salbutamol	2.16 ± 0.67	0.63 ± 0.05	164.25 ± 15.22
2	*R*-Salbutamol	2.73 ± 0.53	0.60 ± 0.02	176.97 ± 11.43
	S-Salbutamol	2.80 ± 1.01	0.58 ± 0.05	164.30 ± 11.67
3	*R*-Salbutamol	2.48 ± 0.40	0.62 ± 0.03	167.32 ± 18.61
	S-Salbutamol	2.30 ± 0.43	0.63 ± 0.04	174.95 ± 16.76
4	*R*-Salbutamol	2.03 ± 0.12	0.64 ± 0.02	195.24 ± 13.95
	S-Salbutamol	2.59 ± 0.68	0.62 ± 0.04	183.35 ± 15.20
5	*R*-Salbutamol	2.23 ± 0.62	0.58 ± 0.04	185.88 ± 10.12
	S-Salbutamol	2.58 ± 0.51	0.56 ± 0.04	186.02 ± 19.99
6	*R*-Salbutamol	2.88 ± 0.40	0.52 ± 0.03	166.43 ± 12.75
	S-Salbutamol	2.55 ± 0.44	0.54 ± 0.03	181.66 ± 16.60
7	*R*-Salbutamol	1.86 ± 0.39	0.61 ± 0.03	191.52 ± 13.95
	S-Salbutamol	1.58 ± 0.15	0.63 ± 0.01	215.87 ± 42.65
8	*R*-Salbutamol	1.71 ± 0.46	0.69 ± 0.06	174.54 ± 26.09
	S-Salbutamol	1.57 ± 0.47	0.70 ± 0.06	181.49 ± 26.27
9	*R*-Salbutamol	2.87 ± 0.40	0.56 ± 0.02	184.15 ± 5.76
	S-Salbutamol	2.55 ± 0.68	0.57 ± 0.04	185.85 ± 12.51

of formulation depends on: (a) water diffusion through the matrix (nonstereoselective process); (b) diffusion of enantiomers through the hydrated matrix (presumably an enantioselective process); (c) erosion of the hydrated matrix (nonstereoselective) (Duddu et al., 1993). Fig. 2 shows the S/R ratio of salbutamol released from the matrices after 9 h. As can be observed, this ratio is close to unity for all formulations, and does not show statistically significant differences ($p > 0.05$) from unity in any case. Therefore, there is no enantioselective release under the tested conditions. For this reason we conclude that the only process that could be enantioselective for these formulations

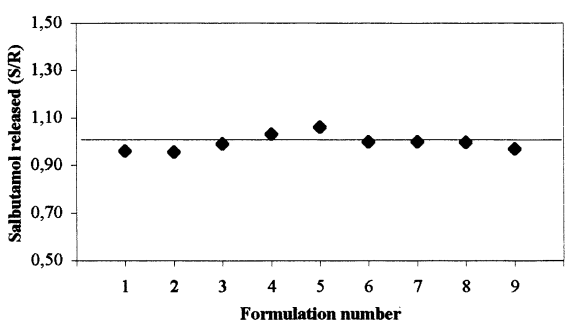

Fig. 2. S/R ratio of salbutamol released from the matrices.

(i.e. the diffusion process) is not, in fact, such a process.

As suggested by Carr et al. (1993), the vigorous dissolution procedure (e.g. 100 rpm stirring speeds) may contribute to the practically equivalent release rates of salbutamol enantiomers by promoting drug release through erosion mechanisms. A dissolution test more reliant on diffusion through the chiral matrix may accentuate enantiomeric differences in release rates. Nevertheless, in our opinion the method used in this study more closely reflects the physiological conditions that the tablets will undergo after their administration.

Other chiral polymers were used in combination with HPMC, in order to test their influence on enantioselectivity. Such is the case of six formulations incorporating DMCD as chiral additive. The presence of at least one aromatic ring in the racemic guest molecule structure greatly increases the possibility of stereoselective interaction between the enantiomers and the β-cyclodextrin. Since salbutamol has this structural feature, it would be a potential candidate for enantioselective interactions. If cyclodextrins are used in the formulation of orally administered racemic pharmaceuticals, stereoselective release and subsequent absorption of the enantiomers may result. The use

of hydrophobic derivatives of cyclodextrins, such as DMCD, may provide suitable conditions for stereoselective intermolecular interactions and/or release. In fact, stereoselective release has been reported for tiaprofenic acid from sustained release formulations containing DMCD under certain conditions (Vakily and Jamali, 1992; Vakily et al., 1995). Several authors have shown that salbutamol can form inclusion complexes with β-cyclodextrin, ethylated-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, and DMCD. DMCD possesses the advantage of having a higher aqueous solubility and forms a slightly stronger complex with salbutamol (Marques et al., 1990a,b).

Cyclodextrin tends to dissolve quickly and disintegrate the matrix, but the HPMC gels and preserves the matrix integrity, which makes it possible to modulate the release rate. The results obtained show that the inclusion of DMCD does not carry an enantioselective release of salbutamol enantiomers, as can be inferred from Fig. 1 and from the K values in Table 2 for these formulations.

Although the inclusion of cyclodextrin in the composition of the formulations does not carry any chiral interaction, this is observed under the conditions used in the analytical technique, as can be seen in Fig. 3. The addition of DMCD to the buffer permits one to resolve the enantiomers of salbutamol by capillary electrophoresis.

The last phase of this work consisted of the study of the influence of the pH-formulation on the dissolution of the enantiomers. It would be advantageous to control the pH immediately surrounding a dissolving solid formulation, and transfer dissolution control from a patient-controlled pH variable to a pharmaceutical formulation variable. Doherty and York (1989) proposed that formulation buffers can be incorporated to modify the microenvironmental pH in order to control the solubility of the drug in the diffusion layer and hence the concentration gradient with subsequent effects on the dissolution rate. Thus, through composition modification, it would be possible to obtain the desired absorption profile. Levy et al. (1965) used aluminium glycinate or magnesium carbonate in aspirin formulations,

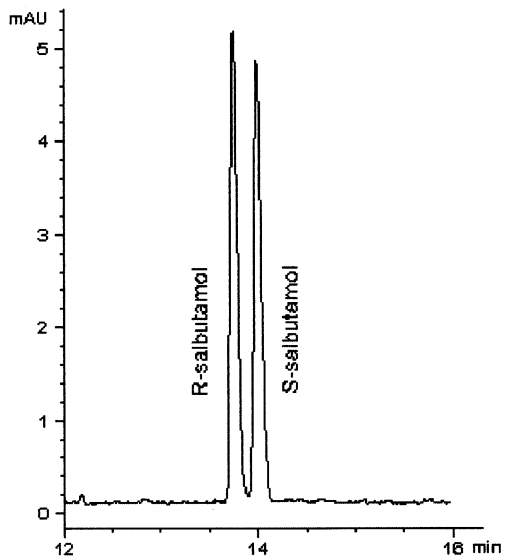

Fig. 3. Electropherogram obtained for a solution containing (R)- and (S)-salbutamol.

and Dwight (1972) used glycine, sodium bicarbonate, sodium carbonate or sodium citrate in penicillin formulations. For this reason, in this study pharmaceutical additives have been included in formulations in order to modify the microenvironmental pH.

Six of formulations in this study contained buffering agents, three of them were buffered at pH 10, and the other three at pH 2.5. The remaining formulations did not contain buffers and their pH was around 6. Significant differences in release of racemic salbutamol have been found among the formulations ($p < 0.05$), and the percentage of dissolved of racemic salbutamol after 9 h ranged from 70% for formulation no. 6 to 105% for formulation nos. 3 and 8. These differences could be attributed to the higher ionization and, therefore, solubility of salbutamol (which is a base) at lower pH. K and MDT values did not show significant differences between the enantiomers ($p > 0.05$) in any of these formulations. Therefore, we can conclude that drug ionization does not determine the interaction with chiral additives and, for this reason, does not cause the release of salbutamol sulfate from these matrices, to be an enantioselective process.

4. Conclusion

The results obtained show that there are no enantioselective interactions between salbutamol sulfate enantiomers and HPMC that can influence its release. The addition of other chiral compounds such as DMCD and the modification of pH of the tablets do not provide an enantioselective release of salbutamol sulfate for these formulations in the assayed conditions.

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