# RELEASE OF SALBUTAMOL ENANTIOMERS FROM HPMC MATRICES ELABORATED BY WET GRANULATION

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## Introduction

In the last decade, attention has been paid to the release of enantiomers of different drugs from formulations containing the racemate. These studies are based on the hypothesis put forward by Duddu et al in 1993 (1) which assumes that chiral excipients may interact preferentially with one enantiomer leading to stereoselective release from a formulation containing a racemate. In previous studies, we considered the release of salbutamol (2,3) and ketoprofen (3,4) enantiomers from matrices elaborated by direct compression with hidroxypropylmethyl cellulose (HPMC) K100M, a chiral excipient commonly used in pharmaceutical technology. In these studies we observed a small stereoselective release for ketoprofen but not for salbutamol sulphate. However, diffusion tests (5) confirmed the existence of a chiral interaction between salbutamol and HPMC K100M.

The objective of this study was to investigate if the use of wet granulation techniques, will allow a major interaction drug-excipient and will yield systems showing stereoselectivity in the release profile.

## Materials and Methods

Racemic salbutamol sulphate was obtained from Vencaser S.A. (Bilbao, Spain). Hydroxypropylmethylcellulose (HPMC) K100M was a gift from Colorcon (Kent, UK). The purity of all other reagents was analytical grade or equivalent.

Table 1 shows the composition of the matrices elaborated. All materials, with the exception of lubricants (talc and magnesium stearate), were thoroughly mixed in a mortar and then wetted with 20% polyvinylpyrrolidone in ethanol. The wet mass was then passed through a 1mm mesh sieve and dried at 37ºC for 1 hour. The dried granules were then rescreened and a range between 0.7 and 1mm was collected, lubricated and compressed with a reciprocating tablet press machine (BONALS) equipped with cylindrical punches of 12 mm in diameter and biconvex profile.

***Table 1**. Formulation composition (mg).*

| | SG1 | SG2 |
|---|---|---|
| Salbutamol | 9.6 | 9.6 |
| HPMC K100M | 156.8 | 336 |
| Mannitol | 179.2 | - |
| PVP | 37.6 | 37.6 |
| Talc | 14 | 14 |
| Magnesium stearate. | 2.8 | 2.8 |

The dissolution studies were performed in 500 mL of Milli-Q water at 37°C and 100 rpm, using the rotating basket (USP 25 apparatus I) (six replicates). The concentrations of R- and S-salbutamol were analyzed with a Capillary Zone Electrophoresis (CZE) technique (6).

In order to characterize the drug release mode from the matrices, the data were fitted to the following power law equation (7):

$M_t/M_\infty = K \cdot t^n$ where $M_t/M_\infty$ 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. The mean dissolution time (MDT) was also calculated. MDT is the mean ratio of the first to zero moments of the dissolution rate-time curve. MDT calculations and the fitting to the equation were performed by using the WINNONLIN program (8). The paired Student's t-test was used to compare the kinetics parameters and the release of the two enantiomers in every experiment by using the statistical program SPSS® 10.0 (9). The significance level was set at $p<0.05$.

## Results and Discussion

Figure 1 shows the dissolution profiles of salbutamol for the formulations SG1 and SG2. Both formulations provide an extended release of the drug.

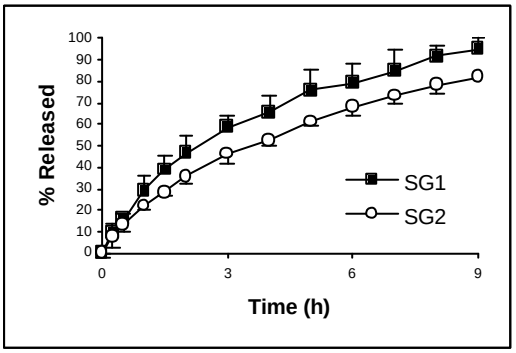


***Figure 1:*** *Plots of cumulative percentage of dissolved RS-salbutamol vs time for formulations SG1 and SG2.*

The values of the kinetic parameters of salbutamol enantiomers and MDT are listed in table 2. The exponent n is indicative of the release mechanism. When *n* takes a value of 0.5, the drug is released following a quasi-Fickian diffusion. Values of *n* between 0.5 and 1, suggest that the drug release is controlled by both diffusion of the drug in the hydrated matrix and the erosion of the matrix itself. Formulation SG2 shows a bigger value of *n* and hence the erosion mechanism plays a more important role on the release of salbutamol. The difference in the release mechanism and in the percentage released can be due to the absence of mannitol in the SG2 composition, because this excipient is a hydrophilic polymer that favours the HPMC K100M hydration and influences the polymer swelling, the gel barrier formation and, subsequently, the dissolution of the drug in the hydrated matrix, favoring the release by diffusion. The presence of mannitol in composition of the formulation SG1 and its influence on the matrix hydration is the cause that this formulation presents a lower value of MDT and a bigger percentage released.

***Table 2:*** *Values of the kinetic parameters (mean ± S.D.). * Statistical significant differences (p<0.05) between enantiomers.*

| | | *K* (% $h^{-n}$) | *n* | MDT (h) |
|---|---|---|---|---|
| **SG1** | **R** | 29.8±4.9 | 0.56±0.06* | 2.96±0.32 |
| | **S** | 31.4±3.7 | 0.52±0.04* | 2.84±0.34 |
| **SG2** | **R** | 22.7±2.0 | 0.61±0.04* | 3.25±0.14* |
| | **S** | 23.5±1.5 | 0.57±0.02* | 3.06±0.16* |

Figure 2 shows the R/S ratio of salbutamol enantiomers released *vs* time. This ratio is practically close to unity, although both formulations show significant differences in the percentage released between enantiomers in some times, concretely, formulation SG1 at 7 and 9 hours and formulation SG2 from 6 to 9 hours. Moreover, the R/S values are over the unity, which means that HPMC interacts preferably with S-salbutamol. This result is in agreement with the obtained in the diffusion studies of salbutamol from HPMC K100M gels (5).

The results show that both formulations confirm the stereoselective interaction observed between salbutamol and HPMC in the diffusion studies, however this enantioselectivity was not found from formulations elaborated by direct compression (2), therefore, the use of wet granulation techniques allows a major interaction drug-excipient and favors the chiral interaction.

Both formulations show significant differences ($p<0.05$) between enantiomers in the value of *n*, although formulation SG2 also shows differences in the value of MDT and its R/S ratio is superior. These results show that formulation SG2 provides a bigger stereoselectivity, although we have already mentioned that the erosion

mechanism plays a more important role on the release of salbutamol from this formulation, and the stereoselective release depends presumably only on diffusion process (1). The explanation to this fact is that the formulation SG2 contains a bigger amount of HPMC K100M, the stereoselectivity is dependent upon the amount of chiral excipient in the formulation (2-5). For this reason, formulation SG2 shows a bigger enantioselectivity in spite of the fact that the erosion mechanism (non stereoselective process) is implicated in the release of salbutamol from these matrices.

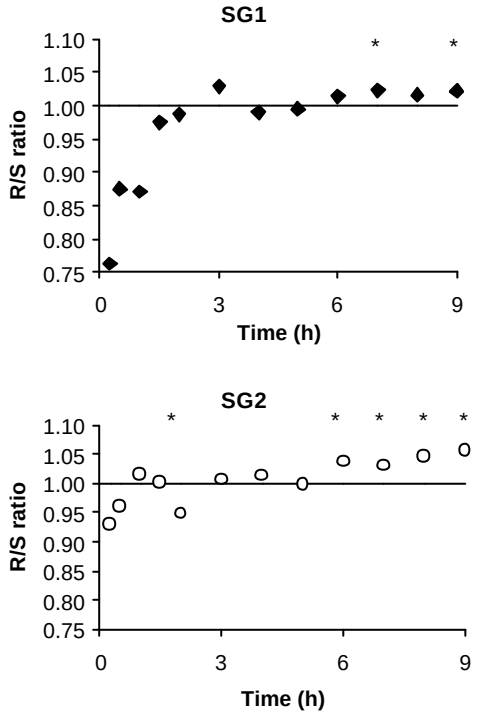


***Figure 2:*** *R/S ratio of salbutamol enantiomers released* vs *time. * Statistical significant differences (p<0.05) between enantiomers.*

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## Acknowledgements

We would like to thank the Basque Government for the research grants to M.A. Solinís and Y. de la Cruz.

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