

1. Introduction

Salbutamol [2-*t*-butylamino)-1-(4-hydroxy-3-hydroxymethylphenyl) ethanol] is a β_2 -agonist agent widely used in the therapeutic control of bronchial asthma. It has one asymmetric carbon atom and is administered as a racemic mixture despite the therapeutic activity residing dominantly in the R-(-)-isomer with no activity being attributed to the S-(+)-isomer (Pesola and Walle, 1992). In addition, there is evidence that S-salbutamol produced hyper-responsiveness and may explain the adverse effect of regular racemic salbutamol on asthmatic disease control (Morley et al., 1991; Chapman et al., 1992). Whereas, the R-isomer dilated the bronchial airway more effectively when given alone than when administered as the racemates (Pesola and Walle, 1992). Not only S-salbutamol produced unwanted response but also it has longer half-life compared to that of the R-isomer due to greater clearance of R-isomer (Boulton, and Fawcett, 1997). These phenomena may explain why the administration of racemic mixture of salbutamol causes some patients with chronic asthma too worse.

One of the key aspects in the formulation of the drug product is the nature and quality of the excipients. The choice of excipient can impact on the bioavailability of the drug substance, control the site of release and affect the release rate. Thus excipients are not necessarily inert additions to a pharmaceutical formulation. They often interact with the drug substance forming complexes that can change the physicochemical properties of the target compound. A number of pharmaceutical excipients in general use are

chiral. For example, chiral polymers constitute an important category of excipient including compounds such as starch, celluloses both in natural or derivatised forms and cyclodextrins, etc. When enantiomeric compounds and chiral excipients are combined in a formulation, interaction between the individual enantiomers and the chiral excipient may alter stability, solubility and rate of release. Consequently, the use of chiral excipient in a formulation can potentially result in an enantioselective difference in bioavailability.

Numerous publications have been reported into investigations of stereoselectivity in the formulation of chiral drugs with chiral excipients (Aubry and Wainer, 1993; Vakily and Jamali, 1992 and 1994; Carr et al., 1993, Duddu et al., 1993; Maggi et al., 1996; Suedee and Heard, 1997). Modest stereoselective release has been reported from formulations of racemic propranolol with either the film-forming excipient hydroxypropyl cellulose (Duddu et al., 1993) or phenylcarbamate derivatives of cellulose (Suedee and Heard, 1997). Greater stereoselective release of the enantiomers of tiaprofenic acid, both in vitro and in vivo, was recently reported from drug/derivatised β -cyclodextrin mixtures (Vakily et al., 1995).

Chiral excipients embedded in the formulations of racemic salbutamol to control the delivery of the drug are listed in Table 1. These excipients have possibility to provide enantioselectivity for the release of salbutamol. This is believed because the fact that some of the polymers used as excipients have also been used as chiral selectors for enantioselective separations. For example, CDs and derivatives were found to exhibit an excellent ability of

chiral recognition as a stationary phase for liquid chromatography and some of the chiral phases are commercially available and extensively utilised for the purpose of analysis and laboratory chiral separation (Szejtli, 1982). Egg white protein has been also developed as chiral stationary phases to resolve enantiomers in HPLC (Miwa et al., 1987; Oda et al., 1991a and 1991b). In addition, cellulose derivatives such as HPMC is used to perform different functions in pharmaceutical formulations such as binders, fillers, disintegrants and dissolution rate modifiers, many of which also possess intrinsic chirality.

Although several chiral excipients (see Table 1) have been intensively employed in the formulated racemate of salbutamol, but the enantioselective dissolution has been discerned solely with the formulation containing HPMC (Esquisabel et al. 1997). Thus it is our aim to prepare five tablet formulations composed of racemic salbutamol and chiral excipient such as native CD and derivatives (γ -CD, DM- β -CD, SBE- β -CD), egg albumin as well as HPMC, and to evaluate in the enantioselective dissolution from such formulations. For this purpose, we also investigated with a commercial controlled-release salbutamol 4 mg tablet Volmax[®] (Glaxo-Wellcome). In case of chiral excipient CDs, the inclusion complexes of the drug with CD were prepared and subsequently determined in the properties before incorporating in the tablets. The amounts of R-and S-salbutamol released from the formulations were measured by stereospecific high performance liquid chromatography (HPLC) using chiral column.