

Figure 18.10.

tions. It should be noted that the scale of operation is dependent on the column size and can lead to a range from tens of grams to tons of separated isomers. Clearly, the larger quantities separated imply that this technology has industrial applications.

The enantiomers of aminoglutethimide (27) (Fig. 18.10) have been separated using an SMB approach (48) (see also Section 3, Fig. 18.11 for more information on aminoglutethimide). A set of 16 columns (6×1.6 cm) containing Chiralcel OJ were used. The feed concentration was 1.63% in a mixture of hexane:ethanol (15:85), which was used as the mobile phase. A feed rate of 0.45 ml/min and a mobile phase rate of 6 ml/min gave rise to a production of 5.27 g of each enantiomer per day. The *S*-(-)-enantiomer was obtained as the extract in solution, in a 99.8% purity, while the *R*-(+)-enantiomer also in solution as the raffinate, achieved a 99.9% purity. This would lead to a productivity of 59.9 g of each enantiomer per kilogram of CSP per day. It should be noted that one big advantage of SMB over preparative chromatography are the vast savings on mobile phase consumption; this is generally coupled to thin film evaporators that allow for very high levels of

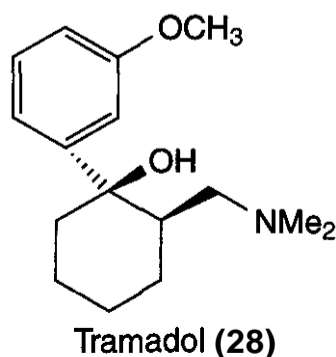


Figure 18.11.

recovery of the solvent. This becomes even more evident when a poorly soluble compound is used.

The two isomers of the racemic analgesic drug Tramadol (28) (Fig. 18.11) display differing affinities for various receptors. (-)-Tramadol mainly inhibits the reuptake of noradrenaline, whereas the (+)-isomer inhibits the reuptake of serotonin. In addition, the (+)-isomer and its primary metabolite, the *O*-desmethyl derivative, are selective agonists of μ opiate receptors (54). Tramadol has been efficiently separated using SMB; in addition, the resolution by crystallization is given in Section 3 of this chapter (55). Comparison between batch chromatography and SMB for the separation of tramadol was made. Use of 12 columns (100×21.2 mm ID), each packed with 20 g of Chiralpak AD 20-pm phase, and using a mobile phase composition of 2-propanol/light petroleum/diethylamine (5:95:0.1 v/v/v) with feed concentration of 20 g/L, obtained a very high productivity. Thus, 680 g of racemic tramadol could be separated per liter of stationary phase (which equates to 1.2 kg of racemate per kilogram of stationary phase per day). The solvent consumption of 144 L/kg of racemate should also be noted. This gives both (+)- and (-)-enantiomers of high optical purity, with the extract of 6.33 g/L and the raffinate of 7.69 g/L. Typically, the solvent (mobile phase) is readily recycled by the use of thin film evaporators, which further extends the economic practicality of the process.

2.4 Conclusions

It should be noted that all the techniques described in this chapter can be inter-linked. In other words, if one technique, i.e., asymmetric synthesis, failed to deliver enantiopure material, then another technique such as crystallization can be used to push through the product to the desired purity. As an example of this "double" approach, the application of SMB and crystallization to the separation of mandelic acid is noteworthy (56). When very high levels of enantiopurity are required, the efficiency and cost effectiveness of SMB may not be economical. However, if for example, a lower enantiomeric excess can be coupled with an enhancement by crystallization, then the