Preparation and characterization of naratriptan base from the hydrochloride salt

Abstract

Naratriptan (NAR), a 5-Hydroxy tryptamine agonist, is an indole derivative currently used in the treatment of acute phase migraine as the hydrochloride salt. The drug is administered as a tablet taken orally. Unfortunately current oral formulations for migraine are not associated with good patient compliance because of the related nausea and vomiting associated with migraine. There is a need for alternative routes of administration of this molecule. Transdermal drug delivery system may offer another possibility for migraine therapy. However, the skin permeability of the base form of the drug is expected to be higher than the salt. The aim of this project was to investigate the preparation and characterisation of naratriptan base (NAR) from its hydrochloride salt (NAR.HCl). NAR was precipitated from an aqueous solution of NAR.HCl by pH adjustment with sodium hydroxide. The solid material was identified using a range of analytical procedures including ultraviolet spectroscopy, high pressure liquid chromatography (HPLC), differential scanning calorimetry (DSC), and liquid chromatography-mass spectroscopy (LC-MS). In addition, the octanol-water partition coefficient was determined as well as the solubility and stability in a range of vehicles were studied. The results confirmed that the formed precipitate was pure NAR base with a total recovery of ~78%. The purity was confirmed by the presence of a single peak in the

DSC and LC-MS analyses. The partition coefficient was calculated as 0.63 ± 0.10. NAR solubility was in the following rank: Transcutol P® (TC) > dipropylene glycol (DPG) > ethanol > propylene glycol (PG) > oleic acid (OA) > octanol > phosphate buffer saline (PBS) > labrafac PG® > labrafac WI® > miglyol (MG) > water. NAR was unstable in isopropyl myristate (IPM), polyethylene glycol 200 (PEG 200) and polyethylene glycol 400 (PEG 400) as more than one peak were noticed in the HPLC chromatogram. The nature of instability and the degradation products are currently being investigated. These data serve as a starting point for further development of transdermal dosage form of NAR.