J. Pharm. Pharmacol. 1998, 50 (Supplement): 122

An analytical study of the interaction of low levels of formaldehyde with active pharmaceuticals

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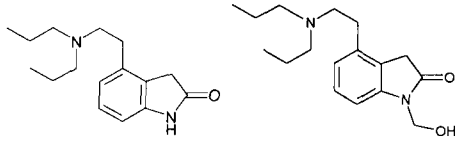
Formaldehyde is a low molecular weight, volatile and reactive organic compound which has been shown to interact with pharmaceutical products (Desai et al 1994) and is a known contaminant of packaging materials (Encycl. of Polymer Science & Engineering 1989). For these reasons, it has the potential to be in contact with and react with active compounds in pharmaceutical formulations. Formulation and preformulation studies need to be designed accordingly. In this work we placed formaldehyde as solid paraformaldehyde (polymerised formaldehyde) in contact with dosage forms containing ropinirole a non-ergoline dopamine D2 agonist. The resulting interaction gave rise to a hydroxymethyl adduct, (SB270341), as detected by LC/MS experiments.

Figure 1 - Structure of ropinirole and SB 270341



Ropinirole SB270341

Separate experiments were performed on solutions of drug substance into which an aliquot of paraformaldehyde was dispersed. These were stored at room temperature and at 40°C and examined for the presence of the adduct using HPLC analysis. The adduct increased in parallel with a loss of the main drug peak. After 48 hours at room temperature the adduct rose to 5.9% normalised peak area (NPA) and the main ropinirole peak fell by 7.4%NPA. SB 270341 was synthesised and its isomeric structure was elucidated using a combination of spectroscopic techniques. The adduct was analysed by LC/MS and was shown to have a molecular weight of 290Da (ropinirole molecular weight = 260Da). The LC/MS/MS and proton and carbon NMR data are consistent with ropinirole substituted with a hydroxymethyl group on the oxindole nitrogen.

The findings suggest that the technique of using paraformaldehyde to interact with drug substances can provide a useful "preformulation screen" to determine the propensity of drugs to interact with formaldehyde. Findings can then be used to aid the selection of excipients for formulations and components for packaging.

Desai, D.S., Rubitski, B.A., Bergum, J.S., Varia, S.A. (1994) Int. J. Pharm 110, 257–265

Vinylidene Chloride Polymers (1989) in Encyclopedia of Polymer Science & Engineering 2nd Edition Wiley Interscience Vol 17, p494