STABILISATION OF CIRAZOLINE BY ANIONIC SURFACTANTS

R.C. Fedynec, G.A. Lewis and H.N.E. Stevens
Pharmacotechnie, LERS, Synthelabo, 58, rue de la Glacière, 75013 PARIS

Cirazoline, 2(2' cyclopropylphenoxy-methyl)-2-imidazoline hydrochloride, is a potent nasal decongestant which undergoes rapid base catalysed hydrolysis in aqueous solution to N-(2-aminoethyl)2-(2-cyclopropylphenoxy)-acetamide by opening of the imidazoline ring. Complexation and subsequent solubilisation of the drug with sodium dodecyl sulphate (SDS) leads to improve stability (Davies et al 1980); however SDS irritates the nasal mucosa to an unacceptable degree.

The effect of the structure and concentration of better tolerated anionic surfactants, eg sodium dodecylpolyoxyethylene sulphate (SDPS) and dioctyl sodium sulphosuccinate (DOSS), was investigated in accelerated tests performed above the pH of maximum Cirazoline stability; however increasing the temperature above 60°C leads to destruction of the micelles and loss of stability.

The stability of Cirazoline (4×10^{-4}M) in the presence of SDPS (1.2×10^{-2}M) at pH 7 and a range of temperatures up to 50°C has been studied using reversed phase HPLC. The results are shown below.

Degradation is first order in spite of the fact that the apparent first order rate constant is known to depend on the initial concentration of drug as well as the surfactant. The ratio of the rate constant without surfactant to that with surfactant gives the degree of stabilisation by the micelle. These data together with knowledge of the pH-stability profile allow predictions to be made for shelf lives at ambient temperature and lower pH.

Table 1. Effect of temperature on the stabilisation of Cirazoline by sodium dodecylpolyoxyethylene sulphate (SDPS)

Temperature	Rate constants (hr^{-1}) with SDPS	Rate constants (hr^{-1}) without SDPS	Surfactant Effect Ratio
22°	7.51×10^{-4}	2.84×10^{-3}	3.78
30°	1.82×10^{-3}	8.31×10^{-3}	4.57
40°	8.19×10^{-3}	3.48×10^{-2}	4.25
50°	5.89×10^{-2}	2.07×10^{-1}	3.51

SDPS which is a mixture of species having the typical structure $C_{12}H_{25}(OC_2H_4)_4\ OSO_3Na$ is not as effective at stabilising Cirazoline as is SDS, either as a result of weaker complexation or some hydrolysis within the micelles themselves. It is also rather less effective than DOSS, at an equimolar concentrations. Nonionic surfactants although better tolerated are not effective in stabilising Cirazoline either alone, or when used to solubilise the 1:1 complex formed between the drug and hydrophobic anions.

Davies, D.J.G. et al (1980) Proc. APGI Conf. Paris 2 : 217-223

0022-3573/81/120103P-01$02.50/0