Studies on the Effects of Electrolytes and pH Control on the Lipophilicity of Fexofenadine Hydrochloride

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Abstract

The effects of electrolytes and pH control on the lipophilic character of fexofenadine hydrochloride was investigated at room temperature. The study was performed by partitioning the drug between 1-octanol and water system. The water system consists of either electrolyte solution of varying concentrations or water adjusted to varying pH values. The most lipophilic effect was observed with aluminum chloride while the least drug lipophilicity was seen with sodium fluoride. The study also showed that pH control had no significant effect on the lipophilicity of fexofenadine hydrochloride.

Introduction

Fexofenadine hydrochloride, (+) 4-{1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl}-1′,1′-dimethylbenzene acetic acid hydrochloride is a nonsedating long-acting HI-receptor antagonist (Lagow, 2005). Clinically, it is administered in tablets or capsules for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. The purpose of this study was to investigate the effects of electrolytes (salts) and pH control on the lipophilic character (determined by partition coefficient) of fexofenadine hydrochloride. It is envisaged that the study could provide some knowledge on the pharmacokinetic changes that might occur following concomitant administration of the drug with preparations containing electrolytes, acidifying or alkalinizing agents. Previous studies have shown partition characteristics of chemical substances to have sufficient effect on pharmacokinetics (Martin *et al* 1973), pharmacological activity (Hansch and Dunn 1972; Hansch and Lien 1971; Bawden *et al* 1983), renal tubular reabsorption (Knoefel *et al* 1961), tissue uptake (Riegelman et al 1968).

Another report (Mbah 2005) also showed that electrolytes affect the partition coefficient of medicinal agents. A review of the literature has shown little or no report on how electrolytes or pH control affect the lipophilicity of fexofenadine hydrochloride and in this paper, we investigated the partitioning of fexofenadine hydrochloride between 1-octanol and salt solutions or aqueous solutions of varying pH values.

Materials and Methods

Materials: Fexofenadine hydrochloride (Aventis Pharmaceuticals, USA), benzoic acid (Fisher Scientic, USA), salts, hydrochloric acid, sodium hydroxide and 1-octanol (Sigma-Aldrich, USA).

Apparatus: All separations were carried out with Hitachi LC 6200 pump and AS 2000 autosampler, Kratos spectroflow 783 detector. A zorbax analytical column SB-CN, 150 mm x 4.6 mm, 3.5μm was used. The pH measurement was done with ThermoOrion pH meter model 330 (USA) equipped with a combination electrode.

High performance liquid chromatographic procedure: The mobile phase consisted of phosphate buffer (pH 3.0), methanol and acetonitrile. The flow rate was 1 ml/min at room temperature. The injection volume was 10 μl and detection was effected at 254 nm.

Standard solution: The stock solutions of fexofenadine hydrochloride (1486.40 μg/ml) and benzoic acid (400.0 μg/ml) were prepared in methanol. Aliquots (148.64-743.20 μg/ml) of the standard stock solution were pipetted into a 50-ml flask. A 5-ml aliquot of internal standard (benzoic acid solution) was added to each flask and diluted to volume with methanol.

Partition coefficient measurement: The partition coefficient of fexofenadine hydrochloride was determined in 1-octanol-water system. Aqueous solutions of different molar concentration of electrolytes and varying pH values were prepared each containing 60 mg of fexofenadine hydrochloride in 20 ml. To the aqueous phase was added 20 ml of 1-octanol. The flasks were stoppered and agitated at room temperature for 2 h to achieve complete equilibration. The content of fexofenadine hydrochloride in the aqueous phase was analysed by a HPLC method and its concentration was calculated from a preconstructed calibration curve. The partition coefficient was obtained using the equation below (Johansen and Bundgaard 1980), $P = CoVw / CwVo = (C_I - Cw)/(Cw) \times (Vw) / (Vo)$. Where P = partition coefficient, Co = concentration of fexofenadine hydrochloride in the organic phase. C_I = initial concentration of fexofenadine hydrochloride in the aqueous phase, Cw = concentration of fexofenadine hydrochloride in the aqueous phase, Vw = volume of aqueous phase, Vo = volume of the organic phase.

Results and Discussion

The effect of electrolytes, pH control on the lipophilicity of fexofenadine hydrochloride was investigated and the results are presented in Tables 1-3. The results in the Table 1 show that the monovalent salts increased the lipophilicity of the drug. The increase was observed with increasing salt concentration except potassium iodide that decreased the lipophilic character of the drug with increasing salt concentration. It was noted that with

some electrolytes, the increase was a function of the formula weight of the monovalent cation. For instance, the partition coefficient of the drug in 1 M LiCl was 18.9 while its partition coefficient at the same concentration level in NaCl and KCl were 21.7 and 24.0 respectively. The same findings were observed with monovalent anions. For example, bromide ion increased the lipophilicity of fexofenadine hydrochloride more than the chloride and fluoride ions at the same molar concentration.

Table 1: Effect of monovalent electrolytes on the partitioning of fexofenadine hydrochloride between distilled water and 1-octanol

Concentration of electrolyte (mol/L)	Partition coefficient of fexofenadine HCl					
	LiCl	NaF	NaCl	NaBr	KCl	KI
0.00	0.83	0.83	0.83	0.83	0.83	0.83
0.05	6.8	4.4	8.0	10.0	9.1	20.4
0.10	10.3	5.1	11.1	12.9	12.7	17.3
0.20	13.1	5.3	13.6	15.6	13.8	15.8
0.40	15.3	5.6	16.8	17.9	17.0	14.0
1.00	18.9	6.5	21.7	19.1	24.0	11.7

The results as presented in Table 2 show that divalent and trivalent electrolyte increased the lipophilicity of the drug. The increase was proportional to increasing electrolyte concentration and was also a function of the formula weight of the cation or anion.

Table 2: Effect of divalent and trivalent electrolytes on the partitioning of fexofenadine hydrochloride between distilled water and 1-octanol

Concentration of electrolyte (mol/L)	Partition coefficient of fexofenadine HCl				
	Na_2SO_4	$MgCl_2$	$CaCl_2$	$BaCl_2$	$AlCl_3$
0.0	0.83	0.83	0.83	0.83	0.83
0.05	4.7	11.4	11.0	12.5	14.3
0.10	5.4	12.7	12.1	13.8	22.4
0.20	5.8	14.3	13.6	15.3	45.0
0.40	9.4	16.9	14.5	17.5	95.1
1.00	27.6	18.6	17.5	19.0	-

Table 3: Effect of pH control on the partitioning of fexofenadine hydrochloride between distilled water and 1-octanol

pH	Partition coefficient of fexofenadine HCl
0.0	0.830
2.20	0.943
3.11	0.890
4.00	0.848
5.35	0.837
6.24	0.802
7.03	0.750
8.00	0.837
9.02	0.852
10.04	0.901

For example, the partition coefficients of the drug in a molar solution of $CaCl_2$ and $BaCl_2$ were 17.5 and 19.0 respectively. Common ion and dehydrating effects are plausible mechanisms of action of the electrolytes on the lipophilicity of fexofenadine hydrochloride. The results in table 3 show the pH effect on the lipophilic character of the drug. The results indicate that at low and high pH values, the lipophilicity of fexofenadine hydrochloride was slightly increased. Protonation and ionization of the carboxylic acid group as well as common ion effect are the probable mechanisms of the pH effect.

Conclusion: All the electrolytes investigated increased the lipophilic character of fexofenadine hydrochloride. Trivalent electrolyte (aluminum chloride) exhibited the greatest influence on the drug's lipophilicity. The pH control was found to have no significant effect on the lipophilicity of the drug. Finally, the study suggests that the pharmacokinetics of fexofenadine hydrochloride could be potentially altered following concomitant administration of the drug with preparations containing electrolytes but not with acidifying or alkalinizing agents.

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