DMI Inc., Wharton, NJ, USA

Effect of electrolytes on the partition coefficient of irbesartan

C. J. MBAH

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Dr. C. J. Mbah, DMI Inc., 86 N. Main Street, Wharton, NJ 07885-1600, USA

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The effect of various electrolytes namely monovalent, divalent and trivalent on the partition coefficient of irbesartan between *n*-octanol and water systems was investigated at room temperature. It was found that all the electrolytes increase the partition coefficient of irbesartan. The uptake of irbesartan by the organic phase from the aqueous phase is increased with increasing salt concentration except for potassium iodide and aluminum chloride. The effect was found to depend on the size and charge of the ions present in solution.

1. Introduction

Irbesartan is a potent, long-acting, non-peptide A II receptor antagonist with high specificity for the AT1 subtype (Waber 2001; Gillis and Markham 1997). Clinically, it is used in the treatment of hypertension. Irbesartan solubility in water is very limited, thus its pharmacokinetics depends largely on its solubility in the lipoidal membrane of the body. Numerous reports have appeared in the literature concerning the effects of partition coefficient on the pharmacological activity of chemical substances (Hansch and Dunn 1972; Hansch and Lien 1971; Bawden et al. 1983). Reports have also found that positive correlations have been observed between partition coefficient and *in-vivo* absorption and distribution (Martin et al. 1973), renal tubular reabsorption (Knoefel et al. 1961), psychotomimetic activity (Barfknecht et al. 1975). Another report has shown that partition characteristics of compounds between plasma and tissue is one of the factors that control the uptake of compounds into the tissues (Riegelman et al. 1968). Furthermore, it has been found that the incorporation of various additives into the aqueous phase may affect the partition coefficient and preservative availability (Miyawaki et al. 1959). Electrolytes have been reported to affect the partition coefficient of chemical substances. Gadalla et al. (1974) found that the partition coefficient of chlorocresol in chloroform-water systems is increased in the presence of electrolytes. Conversely, these electrolytes were found to decrease the partition coefficient of sulphadiazine in the same chloroform-water systems. As the partition coefficient of chemical substances into various tissues is affected by many factors such as pH and complexation with blood constituents, this investigation was undertaken to determine how different electrolytes affect the partition coefficient of irbesartan. Such a knowledge could provide better management of hypertensive patients on irbesartan who are afflicted with various disease states arising from abnormal physiological levels of electrolytes. Literature search has shown that no such study on the effect of electrolytes on the partition coefficient of irbesartan has been reported, and in this paper, we report the effect of eletrolytes on the partition coefficient of irbesartan between n-octanol and water systems.

2. Investigations, results and discussion

The effect of electrolytes on the partition coefficient of irbesartan was studied in *n*-octanol-water systems at room temperature and the results obtained are presented in Tables 1 and 2. The results in Table 1 show that all the monovalent electrolytes increase the partition coefficient. This effect is increased as the concentration of the electrolyte is increased except for potassium iodide where the effect seemed to be independent of molar concentrations. It was found with some salts that the effect was higher, the higher the molecular weight of the monovalent cation. The partition coefficient of irbesartan in 1 M NaCl for example, is 100.8, while that obtained for the drug in the

Table 1: Effect of monovalent electrolytes on the partition coefficient of irbesartan between distilled water (pH 7.40) and n-octanol

Concentration of electrolyte (mol/L)	Partition coefficient					
	LiCl	NaF	NaCl	NaBr	KCl	Kl
0.00	10.3	10.3	10.3	10.3	10.3	10.3
0.05	50.1	37.4	39.2	37.9	42.1	48.6
0.10	62.1	40.9	47.5	42.3	54.7	47.2
0.20	75.2	46.5	63.2	48.1	68.6	45.4
0.40	84.7	51.4	80.5	80.1	81.4	45.0
1.00	110.0	78.9	100.8	95.0	124.6	43.9

Table 2: Effect of divalent and trivalent electrolytes on the partition coefficient of irbesartan between distilled water (pH 7.40) and n-octanol

Concentration of electrolyte (mol/L)	Partition coefficient			
	Na_2SO_4	$MgCl_2$	$CaCl_2$	$AlCl_3$
0.00	10.3	10.3	10.3	10.3
0.50	64.5	39.2	39.8	100.0
0.10	100.1	48.7	50.2	86.3
0.20	114.7	50.6	70.8	68.1
0.40	646.6	60.0	86.8	60.1
1.00	–	117.4	126.1	40.3

same concentration of KCl is 124.6. The same observation was noted for monovalent anion. For example, at 1 M NaF the partition coefficient of irbesartan is 78.9, while at 1 M NaCl the partition coefficient of irbesartan is 100.8. No significant difference was observed between the effect of NaCl and NaBr on the partition coefficient of irbesartan at higher molar concentrations. The increased partition coefficient of irbesartan may be related to the dehydrating effect of the salts on the organic phase, increasing its tendency for irbesartan molecules. Salting-out effects could also explain the effect of the electrolytes on the partition coefficient of irbesartan. The observation that the partition coefficient of irbesartan in 1 M LiCl is 110.0, higher than in 1 M NaCl (100.8), indicates that lithium chloride has a greater salting-out effect than sodium chloride. The results in Table 2, indicate that divalent and trivalent electrolytes increase the partition coefficient of irbesartan. This effect is increased as the concentration of the divalent electrolytes is increased. The results also show that the increase in the partition coefficient of irbesartan by divalent electrolytes was higher the higher the molecular weight of the cation. For example, the partition coefficient of irbesartan in 1 M $MgCl_2$ is 117.4, while that obtained for the drug in the same concentration of $CaCl_2$ is 126.1. The study also indicates that, a decrease in partition coefficient of irbesartan was observed with the trivalent electrolyte ($AlCl_3$) as its molar concentration is increased. For example, at 0.05 M $AlCl_3$, the partition coefficient of irbesartan is 100.0, while at 1.0 M $AlCl_3$, the partition coefficient for the drug is 40.3. A plausible mechanism of action is that as a Lewis acid, its potential to form a complex by accepting electron pair on oxygen atom in the carbonyl functional group of the lactam ring contained in the irbesartan molecule tends to predominate at higher concentration, resulting in increase in the aqueous solubility of the drug. However, at a lower concentration, it tends to decrease the aqueous solubility of irbesartan which has a pK_a of 4.5 (Chang et al. 1997), hence higher partition coefficient. It can be seen from Tables 1 and 2 that sodium sulfate produced the greatest increase in the partition coefficient of irbesartan at 0.40 m concentration level. At 1 M concentration of sodium sulfate solution, the amount of irbesartan in the aqueous phase although detectable, was not quantifiable indicating that the uptake of irbesartan by the organic phase from the aqueous phase was nearly complete. This effect of sodium sulfate may be due to the greater charge on the sulfate anion and also on the intrinsic property of sodium sulfate as a drying agent for organic liquids. The study also shows a reasonable linear relationship between the molar concentration of the electrolytes and their effect on the partition coefficient of irbesartan.

The results obtained indicate that all the electrolytes studied increase the partition coefficient of irbesartan. The effect was found to increase as the salt concentration increases except for potassium iodide and aluminum chloride. Dehydrating of organic solvent, salting-out and complexation are all considered to be plausible reaction mechanism of the electrolytes. Finally, the study suggests that the dosage regimen of irbesartan may need to be adjusted in hypertensive patients afflicted with abnormal levels of these electrolytes and that these patients should take precautionary measures while taking antacids or nutritional supplements that contain ions of these electrolytes.

3. Experimental

3.1. Materials

Irbesartan was obtained from Bristol-Meyers Squibb (USA) and benzoic acid (internal standard) was purchased from Fisher Scientific (USA). Salts and *n*-octanol were of analytical grade (Aldrich, USA).

3.2. Apparatus

All separatons were caried out with Hitachi LC 6200 pump and LC Organizer injector, Kratos spectroflow 783 detector. A zorbax analytical column C18, 150 mm × 4.6 mm, 3.5 μm was used. pH measurement was performed with a ThermoOrion pH meter, model 330. Flask shaker is from Barnstead/Lab-line.

3.3. Chromatographic procedure

The mobile phase consisted of 1% aqueous acetic acid in methanol. The flow rate was 1 ml/min at room temperature. The injection volume was 10 μl and detection was effected at 254 nm.

3.4. Standard Solution

Stock solutions of irbesartan (500.0 ppm) and internal standard (400.0 ppm) were prepared in methanol. Aliquots (10.0–50.0 ppm) of the standard stock solution were pipetted into a 50 ml flask. A 5-ml aliquot of the internal standard soluton was added to each flask and diluted to volume with methanol.

3.5. Partition coefficient measurement

The partition coefficient of irbesartan was determined in *n*-octanol-water systems. Aqueous solutions of different molar concentration of electrolytes were prepared each containing 10 mg of irbesartan in 20 ml. To the aqueous phase 20 ml of *n*-octanol was added. The flasks were stoppered and agitated at room temperature for 2 h to achieve complete equilibration. The aqueous phase was analysed by a chromatographic method for irbesartan content and its concentration was calculated from a preconstructed calibration curve. The partition coefficient of irbesartan was calculated using the following equation (Johansen and Bundgaard 1980),

$$P = \frac{C_o V_w}{C_w V_o} = \left(\frac{C_l - C_w}{C_w}\right)\frac{V_w}{V_o}$$

where P = Partition coefficient, C_o = Concentration of irbesaratn in the organic phase, C_l = Initial concentration of irbesartan in the aqueous phase, C_w = Concentration of irbesartan in the aqueous phase, V_w = Volume of the aqueous phase, V_o = Volume of the organic phase.

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