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INFLUENCE OF GLYCEROL, PROPYLENE GLYCOL, POLYSORBATE-80 AND SODIUM LAURYL SULFATE ON THE PARTITION COEFFICIENT OF QUETIAPINE FUMARATE

*C. J. Mbah and C. E. Chigozie
Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, NIGERIA.
*Email: cjmbah123@yahoo.com

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ABSTRACT
The objective of the present study was to investigate the effects of glycerol, propylene glycol, polysorbate-80 and sodium lauryl sulfate on the lipophilic character of quetiapine fumarate by studying their effects on the partition coefficient of the drug. The partition coefficient was evaluated in n-hexane-water system at room temperature. Of the vehicles investigated, it was found that glycerol, propylene glycol, polysorbate-80 decreased the partition coefficient of quetiapine fumarate, while an increase in partition coefficient of the drug was observed with sodium lauryl sulfate. The findings suggest that sodium lauryl sulfate in contrast to glycerol, propylene glycol, polysorbate-80 has the potential of enhancing absorption and pharmacological activity of quetiapine fumarate.
KEYWORDRS: Quetiapine fumarate, Partition coefficient, Cosolvents, Surfactants.

INTRODUCTION

Quetiapine fumarate, 2-{2-(4-dibenzo [b, f] [1,4]thiazinepine-11-yl-1-piperazinyl)ethoxy}ethanol fumaric acid is an atypical antipsychotic agent belonging to the class of benzisoxazole derivatives. Clinically, it is used in the treatment of schizophrenia. Its mechanism of action involves selective antagonism of 5-HT_2 and D_2 receptors[1,2]. Commercially, only pharmaceutical solid dosage form (tablets) is available, however, there could be need for pharmaceutical liquid dosage forms especially in the therapy of geriatric patients. Glycerol or propylene glycol is very often found in pharmaceutical liquid dosage forms as co-vehicles[3].

Polysorbate-80 or sodium lauryl sulfate is contained in pharmaceutical liquid dosage forms as stabilizing agent or as membrane permeability enhancer for highly hydrophilic substances[4,5]. In order to explore the potential effects of these vehicles on the biological activity of quetiapine fumarate when present in pharmaceutical liquid dosage forms, the present study examined their effects on the partition coefficient of the drug. Previous reports have shown partition coefficient of drugs to have sufficient effect on pharmacological activity[6,7]. Reports have also shown that these vehicles could alter the partition coefficients of chemical substances[8,9]. However, as literature review has shown no such study on the effects of cosolvency or micellization on the partition coefficient of quetiapine fumarate, the present study investigated the effects of two cosolvent systems (glycerol-water and propylene glycol-water system, respectively) and two micellar solutions (polysorbate-80 and sodium lauryl sulfate solution, respectively) on the partition coefficient of quetiapine fumarate.

MATERIALS AND METHODS

Materials

Quetiapine fumarate (Astra Zeneca, Canada), glycerol, propylene glycol and polysorbate 80 were purchased from Sigma-Aldrich (USA). N-hexane was purchased from BDH Chemicals Ltd (England).

Standard solution

Stock solution of quetiapine fumate (100 µg/ml) was prepared in methanol. Aliquots (10.0-50.0 µg/m) of the standard stock solution were pipetted into a 10 ml volumetric flask, diluted to volume with methanol.

Partition coefficient determination

The partition coefficient of quetiapine fumarate was determined in n-hexane-water system. To 5 ml of n-hexane, 5ml of aqueous solution of different concentrations of glycerol, propylene glycol and polysorbate-80 and sodium lauryl sulfate respectively, containing 250 mg of quetiapine fumarate each was added. The flasks were stoppered and agitated at room temperature for 2 h to achieve complete equilibration. The aqueous phase was analyzed by a spectrophotometric method for quetiapine fumarate content at a maximum wavelength of 252 nm and its concentration was calculated from a pre-constructed graph. The partition coefficient of quetiapine fumarate was calculated using the following equation[10]:

$$P = \frac{(C_1 - C_w)V_w}{C_w V_o}$$

where, P = partition coefficient, C_1 = total concentration of quetiapine fumarate, C_w = concentration of quetiapine fumarate in the aqueous phase, V_w = volume of the aqueous phase, V_o = volume of the organic phase.

RESULTS AND DISCUSSION

The regression analysis of the Beer's plot for quetiapine fumarate gave correlation coefficient of 0.9996. Absorbance versus concentration relationship is described by the regression equation: A = 0.00612C + 0.0024. The results of the partition coefficient study are shown in Table I. The results show that glycerol, propylene glycol and polysorbate-80 decreased the partition coefficient of quetiapine fumarate, however, an increasing effect was observed with sodium lauryl sulfate. With the cosolvent systems investigated, glycerol-water system exhibited stronger decreasing effect on the partition coefficient of the drug than propylene glycol-water system at the same concentration level. The decreasing effect was noted as the concentration of the vehicle was being increased. For instance, at the maximum concentration investigated (25 % v/v), the logarithm partition coefficient of quetiapine fumarate produced by glycerol-water system and propylene glycol-water system are 0.2352 and 0.2474 respectively. The difference in the partition coefficient values observed between glycerol and propylene glycol could be attributed to the polarity difference between both vehicles. Glycerol being more polar than propylene glycol, the glycerol-water system would tend to have more affinity for quetiapine fumarate, thus decreasing the ability of the

cosolvent system to squeeze out the hydrophilic drug into the organic phase. In addition, the increase in dielectric constant of glycerol-water system when compared to propylene glycol-water system could also account for the observed difference in the partition coefficient of the drug. With the micellar solutions studied, polysorbate-80 decreased the partition coefficient of the drug while an increase in the partition coefficient of the drug was observed by sodium lauryl sulfate. The decrease in the partition coefficient of quetiapine fumarate observed with polysorbate-80 could be due to the entrapment of the drug in the micelles, thus retarding the partitioning of the drug out of micellar solution into the organic phase (n-hexane). However, the increase in the partition coefficient of the drug observed with sodium lauryl sulfate could be explained not in terms of micellar entrapment, but rather by pH effect. In this micellar solution, the drug would be in its basic form and tend to be more unionized and therefore greater affinity for the organic layer than the aqueous layer.

CONCLUSION

The study shows that all the vehicles investigated except sodium lauryl sulfate solution decreased the partition coefficient of quetiapine fumarate. The strongest decrease in the partition coefficient of the drug was observed with polysorbate-80. Finally, the study suggests that if pharmaceutical liquid dosage forms of the drug are to be formulated with glycerol or propylene glycol (serving as co-vehicles); polysorbate-80 or sodium lauryl sulfate (serving as stabilizing agent or membrane permeability enhancer), it is only sodium lauryl sulfate that has the potential of enhancing the pharmacological activity of the drug.

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Table 1. Effect of glycerol, propylene glycol, polysorbate 80 and sodium lauryl sulfate on the partition coefficient of quetiapine fumarate. (Mean ± SD, n=3)

Concentration of cosolvents (%v/v)	Logarithm of partition coefficient		Concentration of micellar solutions (% w/v)	Logarithm of partition coefficient	
	Glycerol	Propylene glycol		Polysorbate-80	Sodium lauryl sulfate
0.00	0.5079± 0.0038	0.5079 ±0.0038	0.00	0.5079 ±0.0055	0.5079 ±0.0077
5.00	0.4958±0.0061	0.4883 ±0.0058	0.05	0.4516 ±0.0052	0.5272 ±0.0029
10.0	0.4734±0.0074	0.4661 ±0.0065	0.10	0.3286 ±0.0033	0.5765 ±0.064
15.0	0.4516±0.0021	0.4258±0.0076	0.20	0.2476 ±0.0075	0.6108 ±0.0057
20.0	0.2530±0.0068	0.2658 ±0.0032	0.50	0.2056 ±0.0083	0.7267 ±0.0034
25.0	0.2352±0.0047	0.2474 ±0.0065	1.00	0.1935 ±0.0047	0.8052 ±0.0068