ijcrr
Vol 03 issue 05
Category: Research
Received on:29/01/11
Revised on:20 /02/11
Accepted on:08/03/11

STUDY ON THE EFFECT OF GLYCEROL, PROPYLENE GLYCOL AND POLYSORBATE 80 ON THE LIPOPHILIC BEHAVIOUR OF TRANDOLAPRIL

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ABSTRACT

The present study examines the lipophilic behaviour of trandolapril by partitioning the drug in a chloroform-water system at room temperature. The aqueous vehicles investigated are glycerol-water, propylene glycol-water and polysorbate 80-water systems. The results show that both the binary combinations and the surfactant solution decreased the lipophilicity of trandolapril. The order of decrease is: polysorbate 80> propylene glycol> glycerol. The findings suggest that none of the vehicles investigated, has the potential of enhancing the vehicle-skin partition coefficient and therefore might not be considered as potential dermal enhancers for trandolapril.

Keywords: Trandolapril, partition coefficient, spectrophotometry.

INTRODUCTION

The desire to use transdermal routes for potent drugs or to avoid certain unsuitable characteristics of oral administered drugs has empowered formulation scientists to employ various formulation approaches with the view of enhancing transdermal drug absorptions. Some of such approaches involve the use of ethosomes, liposomes, microemulsions, nanoemulsions, solid-lipid nanoparticles and transferosomes[1,2,3,4]. These nanotechnology-based solutions are lipid-based systems employed to improve drug solubility and bioavailability of poorly soluble compounds. The formulations could contain glycerol, propylene glycol and polysorbate 80 either as co-vehicles or dermal permeation enhancers. For example, propylene glycol has been reported to enhance the dermal permeability of diazepam and midazolam maleate[5], estradiol[6] and naloxone[7]. Trandolapril (2S,3aR,7As)-1-[(2S)-2-{[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino}-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid is a potent nonsulphydryl angiotensin converting enzyme inhibitor. Clinically, it used in the treatment of patients with congestive heart failure, hypertension and myocardial infarction[8,9]. Commercially, trandolapril exists only in pharmaceutical solid dosage forms (tablets or capsules), however, the potential of formulating it into transdermal pharmaceutical products exists, if appropriate vehicles (or co-vehicles) and chemical dermal enhancers could be selected. The purpose of this investigation therefore, was to examine the lipophilic behaviour of trandolapril in these vehicles (or co-vehicles) by partitioning the drug between them and chloroform. It is hoped that such information, could provide an

insight into its potential dermal absorption. Previous studies[10,11.12] have shown that linear correlation exists between permeability coefficient and partition coefficient. Another report[13] has also shown dermal permeability coefficient to depend on the partition coefficient and molecular weight of chemical compounds. However, as literature survey has shown little or no study on the lipophilicity of trandolapril in the studied vehicles (or co-vehicles), in this paper, we report the partitioning of the drug between these vehicles (or co-vehicles) and chloroform.

MATERIALS AND METHODS

Materials

Trandolapril (Abbot Laboratories, USA), glycerol, propylene glycol and polysorbate 80 were purchased from Sigma-Aldrich (USA). Chloroform was purchased from Fisher Scientific (USA).

Standard solution

Stock solution of trandolapril (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 trandolapril was determined in a chloroform-water system. To 5 ml of saturated chloroform solution containing 1 mg of trandolapril, 10 ml of saturated aqueous solution of different concentrations of glycerol, propylene glycol and polysorbate 80 were 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 trandolapril content at a maximum wavelength of 210 nm and its concentration was calculated from a pre-constructed graph.

The partition coefficient of trandolapril was calculated using the following equation[14]:

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

where, P = partition coefficient, C_1 = total concentration of trandolapril, C_w = concentration of trandolapril 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 calibration graph of trandolapril gave correlation coefficient of 0.9997. The results of the partition coefficient and estimated permeability parameters are presented in Table 1. The results show that all the vehicles or (co-vehicles) decreased the partition coefficient of trandolapril. The decreasing effect was observed with increasing concentration of each vehicle (or co-vehicle). Polysorbate 80-water system was noted to show the highest decreasing effect on the partition coefficient of the drug. The difference between the effect of glycerol and propylene glycol on the partition coefficient of trandolapril could be attributed to decrease in the ability of water molecules to squeeze out the drug molecules from the aqueous environment, resulting in less drug molecules moving into the organic phase. This phenomenon is applicable more to propylene glycol-water system than glycerol-water system. Furthermore, differences in the dielectric constant of the binary systems could also have contributed to the observed difference in the partition coefficient. However, with polysorbate 80-water system, the decrease in the partition coefficient could be as a result of micellar complexation or

entrapment of trandolapril in micelles. A plot of logarithm of the observed partition coefficient versus the concentration of vehicle (or co-vehicle) gave linear relationships with correlation coefficients of –0.9501, –0.9498 for glycerol-water and propylene-water systems respectively and –0.9399 polysorbate 80-water system. The graphs are shown in figure1 for the binary systems and figure 2 for polysorbate 80-water system. As an earlier report[15] has shown that permeability coefficient is a useful parameter in evaluating percutaneous absorption, the potential permeability coefficient of trandolapril through the skin was estimated using the observed partition coefficient. The estimation was done by the application of previously reported dermal permeability equation[13]:

$\log k_p$ (cm/h) = -2.7 + 0.71 log P – 0.0061 MW, where k_p is the dermal permeability coefficient, P is the observed partition coefficient of trandolapril, MW is the molecular weight of trandolapril. The estimated permeability coefficients were used to calculate the potential fluxes at steady-state using the following equation[16]:

$k_p = J_{ss}/C$, where J_{ss} is the flux at steady-state, C is the concentration (μg / ml) of the test compound. A comparison of the k_p values of trandolapril in glycerol-water; propylene glycol-water system and polysorbate 80-water systems at a concentration level of 5 % w/v, showed glycerol-water system (1.3527×10^{-4} cm/h) with factors of about 1.2 and 3.9 much greater than propylene glycol-water system (11.460×10^{-5} cm/h) and polysorbate 80-water system (3.5070×10^{-5} cm/h) respectively.

CONCLUSION

The investigation shows that the studied vehicles (or co-vehicles) decreased the partition coefficient of trandolapril. Polysorbate 80-water system was observed to produce the highest decrease in the lipophilicity (defined by the partition coefficient) of trandolapril. As permeability through the skin depends partly on the partition coefficient of the drug, the study suggests that none of the vehicles (or co-vehicles) could enhance the transdermal absorption of trandolapril through vehicle/skin partition coefficient mechanism.

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Table 1 Effect of glycerol and propylene glycol on the partition coefficient of trandolapril and the estimated permeability parameters.

Vehicle or (co-vehicle) conc. % w/v	Glycerol			Propylene glycol		
	log P	$k_p \times 10^{-4}$ (cm/h)	J_{ss} ($\mu g/cm^2/h$)	log P	$k_p \times 10^{-5}$ (cm/h)	J_{ss} ($\mu g/cm^2/h$)
0.0	2.1799	1.6651	0.0167	2.1799	16.6510	0.0167
5.0	2.0528	1.3527	0.0135	1.9514	11.4600	0.0115
10.0	1.9938	1.2283	0.0123	1.8716	10.0590	0.0101
15.0	1.9646	1.1710	0.0117	1.7945	8.8674	0.0089
20.0	1.9542	1.1513	0.0115	1.7448	8.1754	0.0082
25.0	1.8760	1.0131	0.0101	1.6925	7.5054	0.0075

k_p = Permeability coefficient; J_{ss} = Flux at steady-state.

Table 2 Effect of polysorbate 80 on the partition coefficient of trandolapril and the estimated permeability parameters.

Vehicle or (co-vehicle) conc. % w/v	Polysorbate 80		
	log P	$k_p \times 10^{-5}$ (cm/h)	J_{ss} ($\mu g/cm^2/h$)
0.05	1.4998	6.2425	0.0062
0.1	1.4589	5.1229	0.0051
0.5	1.4244	4.8420	0.0048
1.0	1.3617	4.3703	0.0044
2.0	1.3112	4.0239	0.0040
5.0	1.2271	3.5070	0.0035

k_p = Permeability coefficient; J_{ss} = Flux at steady-state

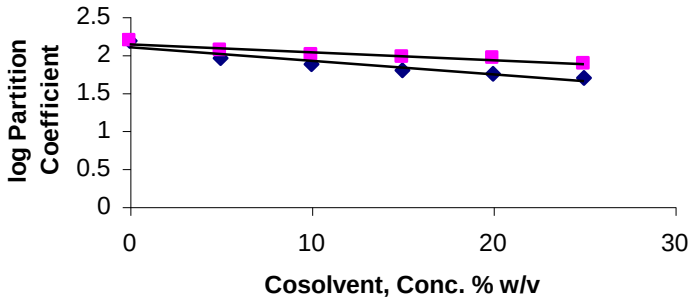

Figure 1: Effect of glycerol-water and propylene-water systems on the partition coefficient of trandolapril.

Key: (▪) Propylene glycol-water system; (■) Glycerol-water system.

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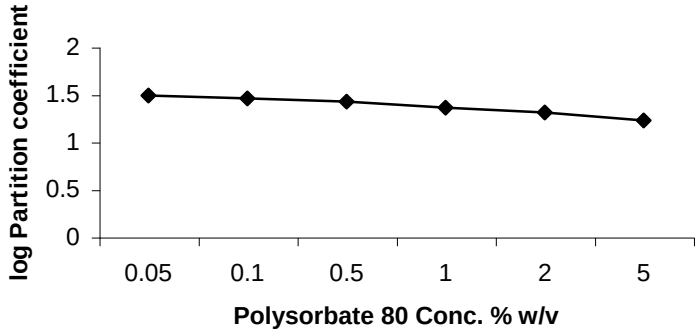

Figure 2: Effect of polysorbate 80-water system on the partition coefficient of trandolapril.

Key: (▪) Polysorbate-water system.

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