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A Thermodynamical Approach to the Diffusion of Terbutaline Sulphate from the Transdermal Films

NARASIMHA MURTHY, S* AND SHOBHA RANI R. HIREMATH[1]
*M.S. Ramaiah College of Pharmacy, M.S.R.I.T. Post, Bangalore : 560054
[1]Al-Ameen College of Pharmacy, Hosur Road, Bangalore : 560027

The transdermal films of terbutaline sulphate were formulated using the hydroxy propyl methyl cellulose for achieving controlled release of the drug for the treatment of asthma. The films were subjected to *in vitro* diffusion studies using a static diffusion cell of Keshary-Chein type at two different temperatures such as 37° and 40° to observe the effect of the temperature on the diffusion of the drug and to calculate the molar enthalpy of diffusion. The drug release increased with increasing temperature. It appears that the process being endothermic, it can be spontaneous only if it proceeds towards maximum randomness. Therefore, the entropy change associated with changes in the state and free energy were determined.

Transdermal drug delivery systems are fabricated to achieve controlled release of drugs and these systems were found to follow a specific thermodynamical rule, though the reasons for the expected performance may be explained by several other logics and fundamental principles. The present work is an illustration to study various thermodynamical parameters associated with the spontaneity of the process, the influence of change in the formulation composition and their influence on the results. Transdermal films of terbutaline sulphate, formulated using various cellulose polymers have already been reported[1]. The transdermal formulations containing hydroxy propyl methyl cellulose as the polymer matrix were found to give reproducible and desired release profile[2] and therefore it was selected for the present study.

EXPERIMENTAL

The films were prepared using a 2% w/v aqueous solution containing 20,30,40%w/w of plasticiser by mercury casting method. The *in vitro* release studies were carried out in the static diffusion cell of Keshary-Chein at two different temperatures such as 37° and 40°. Rat abdominal skin was prepared as reported earlier[3]. Phosphate buffer of pH 7.2 was used as the receptor medium. Samples were withdrawn at hourly intervals and the drug content was estimated spectrophotometrically at 450 nm[4].

*For Correspondence

RESULTS AND DISCUSSION

For a process to be spontaneous, it has to tend to acquire a state of minimum energy or a state of maximum randomness, i.e., the process should be associated with the dissipation of energy or the process should lead to a state of maximum entropy[5]. The factor $T\Delta S$ is a quantitative measure of randomness of a system at T on absolute scale. As the rise in temperature tends to increase the molecular motion and hence the randomness of a system, T is always associated with ΔS, or to quantitatively measure the randomness at a particular temperature. The energy factor is measured by ΔH, i.e. Enthalpy change of a system. The driving force which is defined as the overall tendency for a process to occur is resultant of these two factors and is designated as ΔG. This is called as the free energy change of the process and is given by the equation, $\Delta G=\Delta H-T\Delta S$. It is this ΔG, the free energy change and not ΔH, the potential energy change which determines the spontaneity of a process.

Table I - Diffusion of terbutaline sulphate from transdermal films

Plasticiser %w/w	Flux 37°	Flux 40°	ΔH_d cal/mole	ΔG calories	ΔS cal/mol.K
20	0.053±0.0022	0.057±0.0010	5236.7	-334.4	18.27
30	0.067±0.0014	0.072±0.0005	5580.5	-465.4	19.82
40	0.071±0.0007	0.077±0.0011	5840.5	-508.8	20.82

All values are means of three experiments along with standard deviation of the mean.

Therefore, for a process such as diffusion, the $T\Delta S$ must be positive and the term ΔG should have a negative sign as an indication of passive forward process.

The present study involving diffusion of drug from transdermal formulations has been found to be an endothermic process since the rate of release increased with increasing in temperature. Therefore, the process must be leading towards attainment of maximum randomness, as it is spontaneous. The thermodynamical parameters associated with such a process are very difficult to determine practically. Therefore, a modified equation of Clausis-Clapeyron[6] was framed so as to determine the molar heat of diffusion, according to which the process should be carried out at two different temperatures, with a minimum difference and noting the drug diffusion as rate or flux.

$$\text{Log } R_2/R_1 = \Delta H_d/2.303 \{T_2-T_1/T_1T_2\}$$

where R_1 and R_2 are the the molar rates of diffusion or molar flux. ΔH_d is the molar heat of diffusion, and T_1 and T_2 are the temperatures on the absolute scale.

The extent of spontaneity of the process can be explained only on the basis of the ΔS and ΔG values which can be calculated at a surrounding temperature of 37° by the equations as comparing factor between the formulations. The results are given in Table 1.

$$\Delta G = RT \text{ ln } C_2/C_1$$

Where C_2 and C_1 are the final (amount of drug undiffused) and initial concentrations of the drug respectively and R is the gas constant.

$$\Delta S = \frac{\Delta H - \Delta G}{T}$$

The free energy change, the enthalpy change and the entropy change associated with the drug diffusion are given in the table. The increase in the concentration of the plasticiser has led to an increase in the flux of terbutaline sulphate. This may be due to increased binding of drug with PEG-400 and polymer due to attractive forces, electrostatic interactions, H-bonding and thus leading to a decrease in $S_{initial}$ ($\Delta S = S_{final}-S_{initial}$) or due to alteration of the barrier properties, thus resulting the increased S_{final} of drug in the barrier. Therefore ΔS has increased with the increase in the plasticiser concentration leading to an enhanced driving force. Though the values of ΔG is not a measure of extent of spontaneity or rate or mechanism of a process, In the present case, the ΔG was found to increase indicating an increased driving force.

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