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Research Article

EFFECT OF ALUMINUM HYDROXIDE ON PERMEATION OF ACECLOFENAC IN ABSENCE AND PRESENCE OF HYDROXYPROPYL-B-CYCLODEXTRIN THROUGH GOAT INTESTINE: EVALUATION OF THERMODYNAMIC PARAMETERS OF PERMEABILITY

BRAJA B PANDA[1],TAPAN PATEL[2],SUBRATA MALLICK[1,2*]

[1]Department of Pharmaceutics, [2] Department of Pharmaceutical Technology, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan University, Kalinganagar, Bhubaneswar-751003, Orissa, India. Email: s_mallickin@yahoo.com; profsmallick@gmail.com

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ABSTRACT

Doctor generally advises to take antacid like aluminium hydroxide to combat gastrointestinal complications during long term oral use of aceclofenac. The purpose of this study was to examine the intestinal permeability potential of aceclofenac upon concomitant use with aluminum hydroxide. Effect of aluminum hydroxide on intestinal permeation of aceclofenac in different ratios in absence and presence of hydroxypropyl-β-cyclodextrin (HBC) has been evaluated. The time-dependent permeation of the drug from aluminium hydroxide dispersion was measured across the isolated goat intestine using organ bath. Thermodynamic parameters such as activation energy (E_a) and the enthalpy (ΔH), entropy (ΔS) and free energy (ΔG) of activation for the intestinal transport of aceclofenac were evaluated. Permeation of aceclofenac from drug-aluminum hydroxide dispersion increased exponentially with increasing temperature. Permeability of aceclofenac from aluminum hydroxide dispersion in 1: 4 ratio has been significantly affected and the same value was also decreased after 1h incubation of the dispersion at 37° C. HBC remarkably improved permeation by protecting the drug through inclusion complexation.

Keywords: Permeability, Drug transport, Aluminum hydroxide, Hydroxypropyl-β-cyclodextrin, Thermodynamic parameters.

INTRODUCTION

Aceclofenac, a phenyl acetic acid derivative non-steroidal anti-inflammatory drug displays good efficacy and tolerability not only in the topical treatment of inflammation in periodontitis[1] but also in the systemic therapy for rheumatic disorders[2,3]. But the long term oral use leads to gastrointestinal complications like ulceration, perforation and obstruction[4]. To combat these adverse effects of aceclofenac, doctor generally advises to take antacid like aluminium hydroxide.

Aluminium hydroxide interacts with the carboxy and carboxy groups of quinolone irreversibly and reduces bioavailability of the drug significantly[5-7]. This is an important factor affecting the intestinal absorption and bioavailability of gatifloxacin upon concomitant use of aluminum hydroxide with gatifloxacin[7]. It is understood from the report that permeation of gatifloxacin was significantly affected in presence of aluminum hydroxide.

An effort has been made here to examine the intestinal permeability potential of concomitant use of carboxyl group containing aceclofenac and aluminum hydroxide which has not been studied earlier. The pharmaceutical industry requires rapid and accurate methods for intestinal permeability potential in the early stages of drug discovery[8,9] and its formulation development[10]. In this report, we examined the effect of aluminum hydroxide on permeability of aceclofenac in their different ratios through goat intestine ex vivo. Thermodynamic behavior for intestinal permeability was determined to reveal mechanisms of intestinal transport of drug molecules. Mechanisms of corneal drug penetration have been studied by several researchers using thermodynamic approach[11-13]. The time-dependent permeation of the drug from aluminium hydroxide dispersion was measured across the isolated goat intestine using organ bath at different temperatures. Considerable interest has been generated in the use of cyclodextrins for improvement of chemical stability and bioavailability and also reducing the side effects and toxicity of the drugs[14-17]. As concomitant use of aluminum hydroxide with aceclophenac supposed to affect drug transport, permeability of the drug from aluminium hydroxide dispersion in presence of hydroxypropyl-β-cyclodextrin (HBC) was also determined to examine any improvement. The activation energy and the enthalpy, entropy and free energy of activation for the movement of aceclofenac have been evaluated.

MATERIALS AND METHODS

Aceclofenac was obtained as a gift sample from Aristo Pharma Pvt. Ltd., Mandideep, India. Aluminium hydroxide was procured from CDH, New Delhi, India (minimum assay 47% (Al_2O_3); pH of solution not more than 10.0; maximum limits of impurities chloride 0.5%, sulfate 0.25%, arsenic 0.0005%).

Krebs Ringer buffer solution

Krebs Ringer buffer solution of pH 7.4 was prepared fresh in distilled water using Analytical Grade Chemicals (containing in mmol/l: 118 NaCl, 4.7 KCl, 2.5 $CaCl_2.2H_2O$, 1.2 $MgSO_4.7H_2O$, 1.2 KH_2PO_4, 25 $NaHCO_3$ and 8.3 D-glucose). Calcium chloride was added last in the form of solution in order to prevent the precipitation of bicarbonate. Long time survival of isolated tissue in cloudy physiological solution may be in question and may give an erratic response with drugs.

Tissue preparation

Isolated tissue of the duodenal part of small intestine of goat was collected from slaughter house not later than 1 h[18] and immediately immersed in standard Krebs Ringer buffer solution. The tissue was washed gently with Krebs Ringer solution to remove the mucous and lumen contents and oxygenated continuously (95% O_2 - 5% CO_2) to maintain (at 37^{0}C) the homeostasis of the intestine cells. The tissue was cut into two 8 cm pieces and used for permeation study (one blank without drug and other test with drug)

Ex vivo intestinal permeability studies

The methods employed were modified from experimental procedures as described in the literature[19,20]. Accurately weighed amount of aceclofenac was dissolved in Krebs solution. The resultant drug solution sample (4mL of 1 mg/mL) was injected into the lumen of the duodenum (6cm length exposed for permeation) using a syringe, and the two sides of the intestine were tightly closed. Then the tissue was placed in a chamber of organ bath having accurate temperature regulator and aeration was continued. The receiver compartment was filled with 40 mL of Krebs solution. Samples were withdrawn at regular time interval from the receiver compartment and filtered through a 0.45 µm membrane filter (Whatman Puradisc 25 Nylon, India). Absorbance data were recorded at 273 nm using UV–vis spectrophotometer (JASCO V-630 spectrophotometer, Software: Spectra Manager). Same amount of fresh Ringer solution was replaced to the donor compartment after each sampling. The mean of at least three determinations was used to calculate the cumulative amount of drug permeated using standard calibration curve and the error expressed as standard deviation (mean ± sd, n =

3). The cumulative amount of drug permeated vs. time was plotted on a graph. Detail of run of permeation experiment of aceclofenac from drug-aluminum hydroxide dispersion (1:1, 1:2 and 1:4 w/w) in absence and presence of hydroxypropyl-β- cyclodextrin (1:1 drug-HBC molar ratio) without and with 1h incubation at 37° C is tabulated in Table 1. The permeation experiment has also been repeated at temperatures 23, 30 and 45°C for calculation of thermodynamic parameters of permeation.

Table 1: Experimental set of permeation of aceclofenac from drug - aluminum hydroxide dispersion in absence and presence of hydroxypropyl β cyclodextrin (HBC)

Run of experiment	Code	Drug: Aluminum Hydroxide ratio (w/w)	Incubation[a] before permeation (h)	Temperature of permeation (°C)
Set I	Ac	Aceclofenac alone	no incubation	37
	Ac:AH(1:1)	1:1	no incubation	37
	Ac:AH(1:2)	1:2	no incubation	37
	Ac:AH(1:4)	1:4	no incubation	37
	Ac:AH(1:4)HBC	1:4[b]	no incubation	37
Set II	Ac:AH(1:1)1h	1:1	1.0	37
	Ac:AH(1:2)1h	1:2	1.0	37
	Ac:AH(1:4)1h	1:4	1.0	37
Set III	Ac:AH(1:4)23	1:4	1.0	23
	Ac:AH(1:4)30	1:4	1.0	30
	Ac:AH(1:4)37	1:4	1.0	37
	Ac:AH(1:4)45	1:4	1.0	45
Set IV	Ac:AH(1:4)HBC23	1:4[b]	1.0	23
	Ac:AH(1:4)HBC30	1:4[b]	1.0	30
	Ac:AH(1:4)HBC37	1:4[b]	1.0	37
	Ac:AH(1:4)HBC45	1:4[b]	1.0	45

[a] Incubation temperature of drug-aluminium hydroxide dispersion in absence and presence of hydroxypropyl β cyclodextrin (HBC) was 37 °C

[b] Aluminum hydroxide was dispersed in aceclofenac and hydroxypropyl-β-cyclodextrin (1:1 molar ratio) solution.

Analysis of experimental data

Calculation of the Apparent Permeability Coefficients

Apparent permeability coefficients (P_{app}) were calculated according to Eq. 1:[21]

$$P_{app} = \frac{dQ}{dt} \times \frac{1}{AC_0} \text{.....(1)}$$

Where P_{app} (cm/s) is the apparent permeability coefficient, $dQ/A.dt$ (µg.cm^{-2}.s^{-1}) the amount of drug permeated per unit surface area and per unit of time calculated from the regression line of time points of sampling, A (cm^2) the surface area available for permeation, and C_0 (µg/ml) the initial drug concentration in the donor compartment.

Activation energy (E_a) was determined from the regression line of Arrhenius equation:

$$P_{app} = A \exp^{\left(\frac{-E_a}{RT}\right)} \text{.....(2)}$$

$$Ln\, P_{app} = Ln\, A - \frac{E_a}{RT} \text{.....(3)}$$

Arrhenius plot of $Ln\ P_{app}$ versus $1/T$ was constructed where T is absolute temperature.

Other useful thermodynamic relationships are:

$$E_a = \Delta H + RT \text{.....(4)}$$

$$\Delta G = \Delta H - T\Delta S \text{.....(5)}$$

$$\Delta G = -RT.LnP_{app} \text{.....(6)}$$

Where, ΔH and ΔS are the enthalpy and entropy of activation, respectively. ΔG is the free energy of activation. Using above equations all the parameters was determined.

Statistical analysis

The data are presented as mean ± standard deviation of the mean. The statistical significance was determined by the paired t-test. Significant differences were judged at the $p < 0.05$ level.

RESULTS

Intestinal permeability

The cumulative amount of aceclofenac permeated as a function of time in presence of aluminum hydroxide in different ratios (1:1, 1:2 and 1:4 w/w) at 37° C with zero time incubation before permeation for the transport through goat intestine [Ac:AH(1:1); Ac:AH(1:2); Ac:AH(1:4) respectively] has been depicted in Fig. 1. The profiles of aceclofenac alone [Aceclo] and drug-aluminum hydroxide dispersion in presence of hydroxypropyl β cyclodextrin [Ac:AH(1:4)HBC] have been included in the figure to examine the effect of inhibition and recovery in permeation if any. The linear appearance rate dQ/dt (µg.cm^{-2}.s^{-1}) of aceclofenac in the receiver side was determined from slope of this plot and used to calculate the P_{app} (mean ± sd, n = 3). The permeation of aceclofenac has been decreased with the increased amount of aluminium hydroxide. The plot shows a remarkably inhibited effect of permeation in Ac:AH(1:4) and recovery has been noticed in presence of HBC (Ac:AH(1:4)HBC).

Amount of aceclofenac permeated versus time in presence of aluminum hydroxide in different ratios after 1h incubation at 37° C has been presented in Fig. 2.

The profiles of aceclofenac alone and drug-aluminum hydroxide dispersion in presence of hydroxypropyl β cyclodextrin (HBC) have also presented to get a comparative view [Aceclo; Ac:AH(1:1)1h; Ac:AH(1:2)1h; Ac:AH(1:4)1h; Ac:AH(1:4)HBC1h]. The $dQ/A.dt$ (µg.cm^{-2}.s^{-1}) was determined from slope of this plot and P_{app} (mean ± sd, n = 3) calculated. The plot shows a remarkably inhibited effect (p<0.05) of permeation in Ac:AH(1:4)1h and a remarkable effect of recovery (p<0.05) in presence of HBC [Ac:AH(1:4)HBC1h].

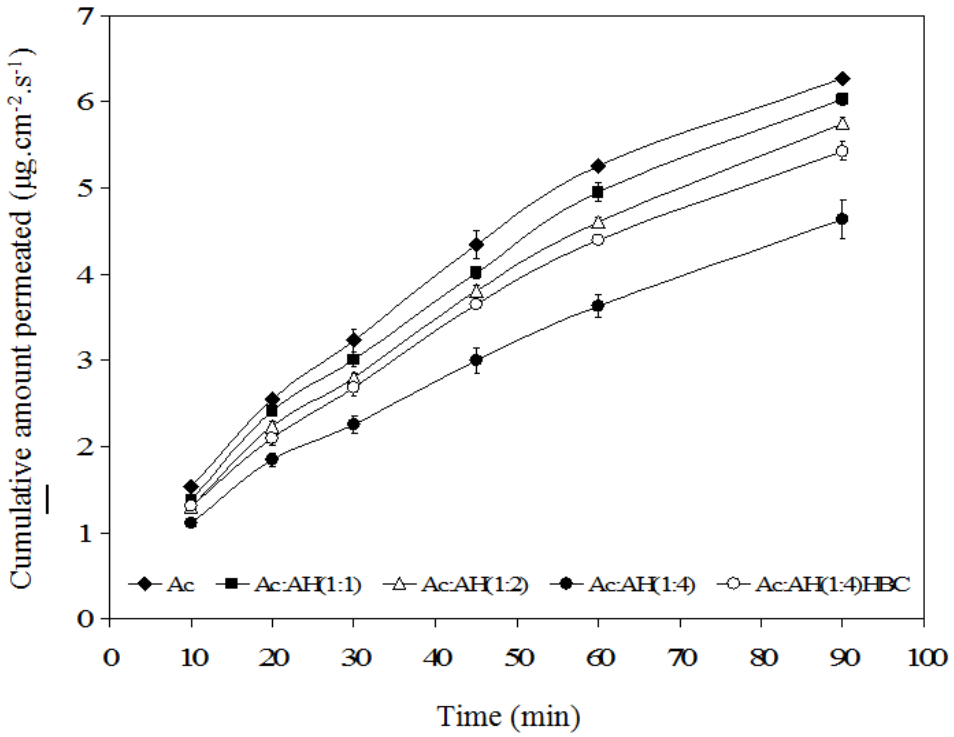

Fig. 1: Plot of the cumulative amount of aceclofenac permeated versus time in presence of aluminum hydroxide in different ratios for the transport through goat intestine *ex vivo* without incubation before permeation. The profiles of aceclofenac alone and drug-aluminum hydroxide dispersion in presence of hydroxypropyl-β-cyclodextrin (HBC) have presented to get a comparative view (Ac; Ac:AH(1:1); Ac:AH(1:2); Ac:AH(1:4) and Ac:AH(1:4)HBC). The linear appearance rate *dQ/A.dt* (µg.cm^{-2}.s^{-1}) of aceclofenac on the receiver side was determined from slope of this plot and used to calculate the P_{app} (mean ± sd, n = 3). The plot shows a remarkable inhibition effect of permeation in Ac:AH(1:4) and a remarkable recovery found also in presence of HBC (Ac:AH(1:4)HBC).

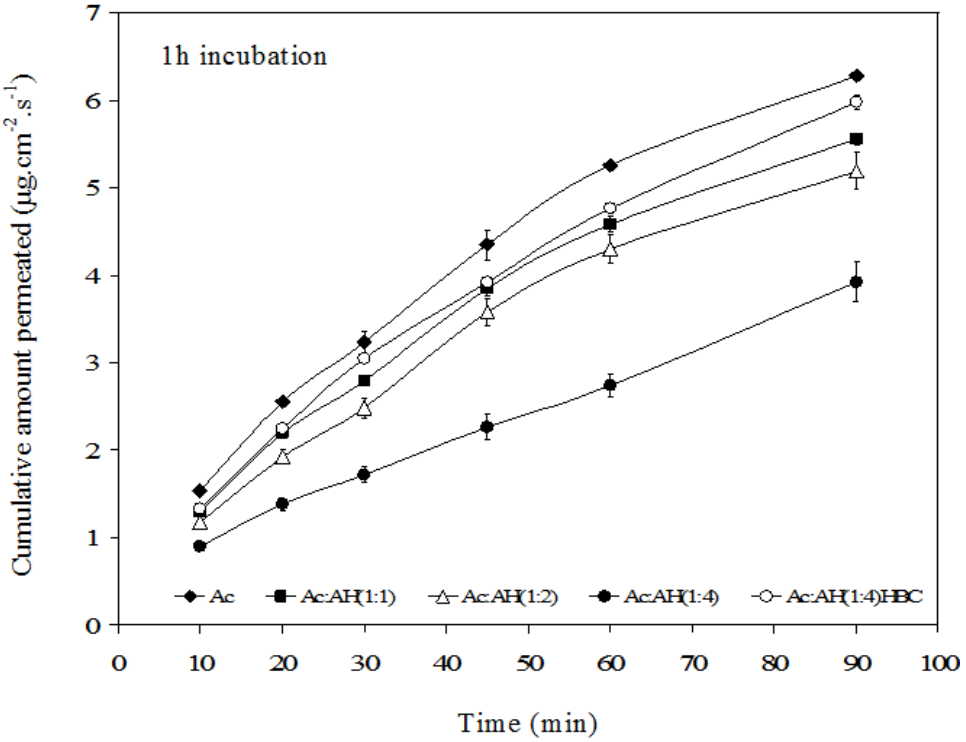

Fig. 2: Plot of the cumulative amount of aceclofenac permeated versus time in presence of aluminum hydroxide in different ratios for the transport through goat intestine *ex vivo* with 1 h incubation before permeation. The profiles of aceclofenac alone and drug-aluminum hydroxide dispersion in presence of hydroxypropyl-β-cyclodextrin (HBC) have presented to get a comparative view (Ac; Ac:AH(1:1); Ac:AH(1:2); Ac:AH(1:4) and Ac:AH(1:4)HBC). The *dQ/A.dt* (µg.cm^{-2}.s^{-1}) of aceclofenac was determined from slope of this plot and used to calculate the P_{app} (mean ± sd, n = 3). The plot shows a remarkable inhibition effect of permeation in Ac:AH(1:4) and remarkable effect of recovery also in presence of HBC (Ac:AH(1:4)HBC).

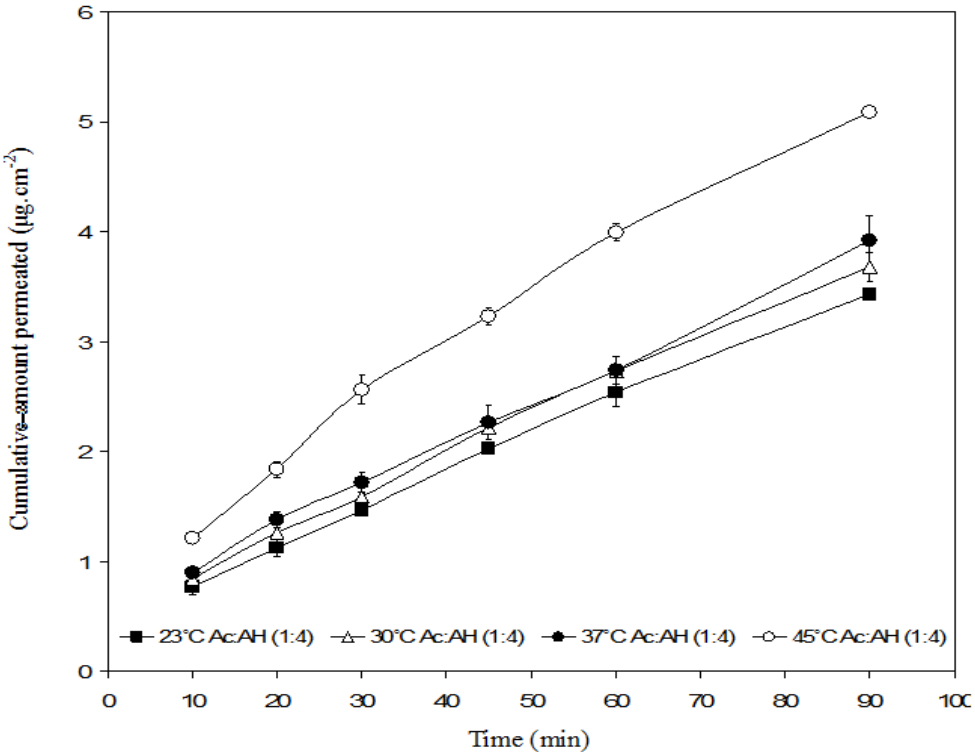

Fig. 3: The time-dependent permeation of aceclofenac at temperatures 23, 30, 37 and 45° C from drug-aluminium hydroxide dispersion (1: 4 ratio) after 1 h incubation at 37° C in absence of hydroxypropyl-β-cyclodextrin. The amount of permeation of aceclofenac was enhanced gradually by the rise of temperature.

The time-dependent permeation of aceclofenac from drug-aluminum hydroxide dispersion (1: 4 ratio) with 1 h incubation before permeation in absence and presence of hydroxypropyl-β-cyclodextrin (1: 1 molar ratio with drug) at temperatures 23, 30, 37 and 45°C is presented in Fig. 3 and Fig. 4 respectively.

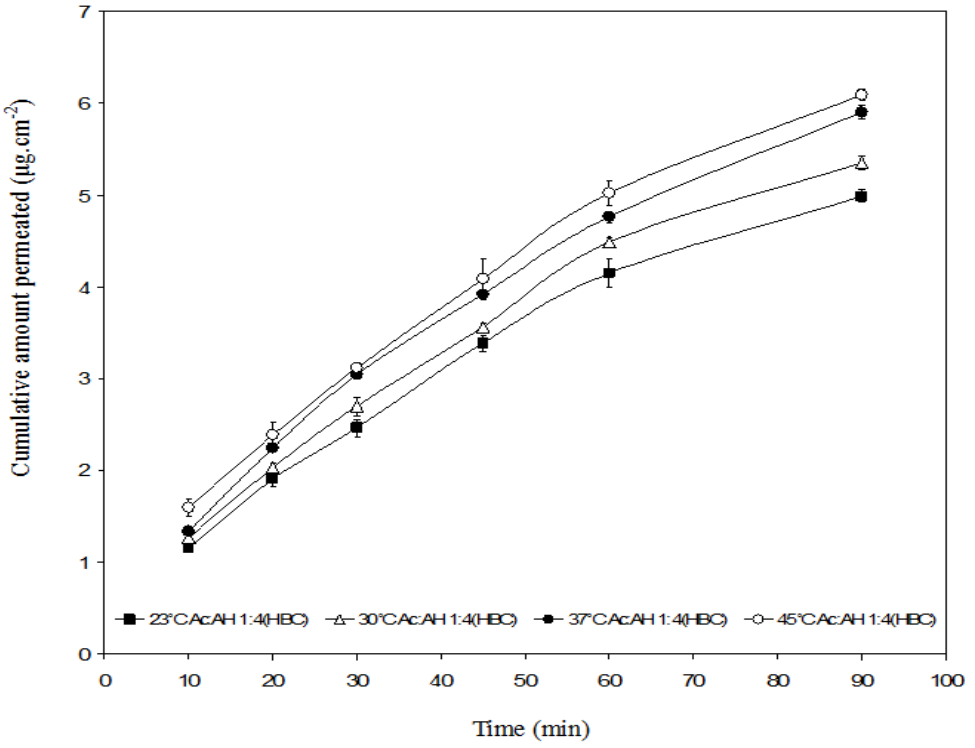

Fig. 4: The time-dependent permeation of aceclofenac at temperatures 23, 30, 37 and 45° C from drug-aluminium hydroxide dispersion (1:4 ratio) after 1 h incubation at 37° C in presence of hydroxypropyl-β-cyclodextrin (1:1 molar ratio with drug). Here also the amount of permeation of aceclofenac was enhanced gradually by the rise of temperature.

In both the cases the permeation of aceclofenac was enhanced gradually by the rise of temperature.

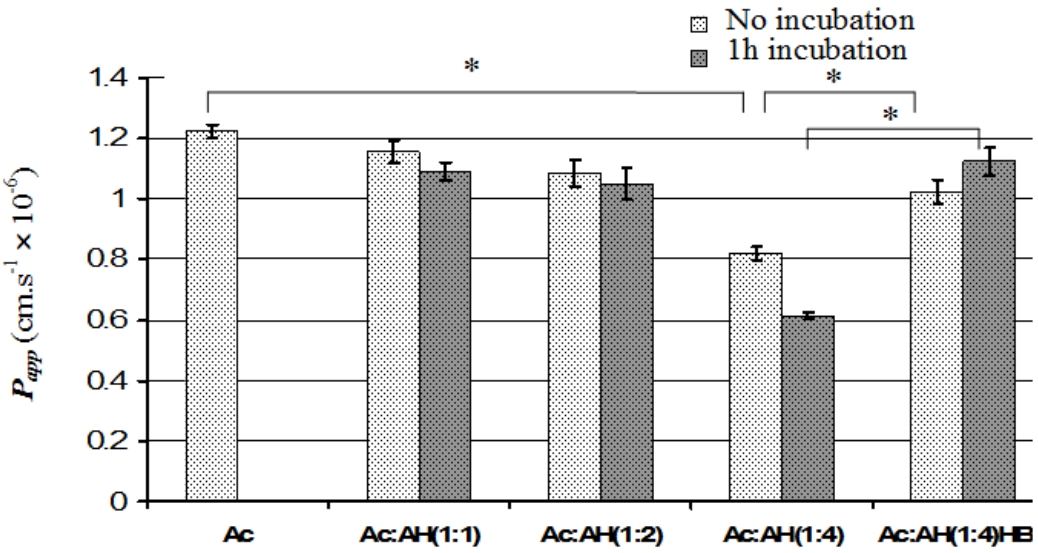

Fig. 5: Permeability of aceclofenac through goat intestine from drug-aluminium hydroxide dispersion at different ratios before and after 1 h of incubation at 37° C. Significantly decreased permeability has been observed in presence of maximal amount of aluminium hydroxide [shown bracketed between Ac and Ac:AH(1:4); *p*<0.05] and significant improvement was also possible in presence of HBC in Ac:AH(1:4)HBC when compared with Ac:AH(1:4) [shown bracketed; *p*<0.05]. Permeability in presence of HBC after 1h of incubation improved significantly (between Ac:AH(1:4)1h and Ac:AH(1:4)HBC37; p<0.05) and the same has been decreased only slightly in comparison to drug alone (no significant difference between Ac and Ac:AH(1:4)HBC37; *p*<0.05).

Fig. 5 shows the permeability of drug through goat intestine from Aceclo, Ac:AH(1:1), Ac:AH(1:2), Ac:AH(1:4), Ac:AH(1:4)HBC. In set I run of experiment, permeability value (cm/sec × 10^{-6}) of Aceclo [1.22 ± 0.021] has been decreased in presence of aluminium hydroxide with zero time of incubation before permeation [1.156 ± 0.036, 1.085 ± 0.045 and 0.818 ± 0.022 in Ac:AH(1:1), Ac:AH(1:2) and Ac:AH(1:4) respectively]. Significantly decreased permeability has been observed in presence of maximal amount of aluminium hydroxide [between Aceclo and Ac:AH(1:4); *p*<0.05] and significant improvement was also possible in presence of HBC [1.023 ± 0.041 in Ac:AH(1:4)HBC; when compared with Ac:AH(1:4) *p*<0.05]. In Set II run of experiment after 1h of incubation at 37° C permeation value (cm/sec × 10^{-6}) decreased to 1.090 ± 0.033, 1.050 ± 0.052, and 0.613 ± 0.012 [in Ac:AH(1:1)1h, Ac:AH(1:2)1h and Ac:AH(1:4)1h respectively]. Permeability (cm/sec × 10^{-6}) in presence of HBC after 1h of incubation (1.123 ± 0.045) improved significantly [between Ac:AH(1:4)1h and Ac:AH(1:4)HBC37; p<0.05] and the same has been decreased only slightly in comparison to drug alone (no significant difference between Aceclo and Ac:AH(1:4)HBC37; *p*<0.05). The permeability (cm/sec × 10^{-6}) of aceclofenac from drug-aluminium hydroxide dispersion at temperatures 23, 30, 37 and 45°C in absence and presence of hydroxypropyl-β-cyclodextrin with 1 h incubation before permeation [(0.558 ± 0.022) to (0.628 ± 0.018) and (0.992 ± 0.031) to (1.135 ± 0.039) respectively] is presented in Fig. 6. It has been noticed that permeability of aceclofenac was significantly enhanced (*p*<0.05) in presence of HBC at all the temperatures.

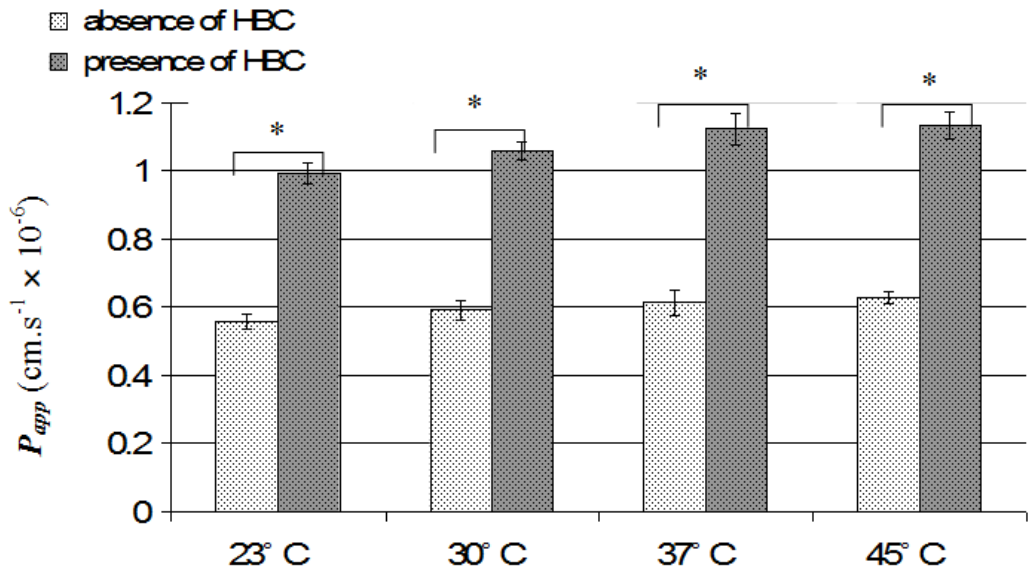

Fig. 6: The permeability (cm/sec × 10^{-6}) of aceclofenac from drug-aluminium hydroxide dispersion of Ac:AH(1:4) at temperatures 23, 30, 37 and 45° C in absence and presence of hydroxypropyl-β-cyclodextrin with 1 h incubation at 37° C before permeation. It has been noticed that permeability of aceclofenac was significantly enhanced (*; *p*<0.05) in presence of HBC at all the temperatures.

Evaluation of thermodynamic parameters

Fig. 7 shows Arrhenius plot for the permeability against the inverse of temperature. The permeability increased exponentially with increasing the temperature[11,22,23] and the activation energy (E_a, kJ mol^{-1}) determined for Ac:AH(1:4)HBC has been increased significantly in comparison to Ac:AH(1:4) after 1h of incubation (4.96 ± 0.18 and 4.18 ± 0.21 respectively; p<0.05). That means increasing degree of permeability of drug for Ac:AH(1:4)HBC was significantly more than that for Ac:AH(1:4) with increasing the temperature.

Enthalpy, entropy and free energy of activation (ΔH, ΔS and ΔG respectively) for the movement of aceclofenac from drug-aluminium hydroxide dispersion in absence and presence of HBC across the isolated intestine at respective temperature were estimated using above thermodynamic relationships. The positive values of enthalpy of activation (ΔH; kJ mol^{-1}) indicated that the heat is absorbed by the system (endothermic) and it is temperature dependant. As understood from Eq.(4) ΔH was decreased with elevation of temperature 23, 30, 37 to 45°C (1.72 to 1.53 for Ac:AH(1:4) and 2.50 to 2.32 for Ac:AH(1:4)HBC) with 1 h incubation before permeation. At particular temperature more heat absorption for Ac:AH(1:4)HBC compared to Ac:AH(1:4) indicated accelerated permeation for Ac:AH(1:4)HBC at that temperature. The lower the transfer free energy (ΔG; kJ mol^{-1}), higher will be the permeability coefficient and vice versa[24]. At particular temperature ΔG (kJ mol^{-1}) has been decreased for Ac:AH(1:4)HBC compared to Ac:AH(1:4) which indicated increased permeability for Ac:AH(1:4)HBC at that temperature (35.43 to 37.75 for Ac:AH(1:4) and 34.02 to 36.19 for Ac:AH(1:4)HBC) with 1 h incubation before permeation. It is also temperature dependant. As understood from Eq.(4) ΔG was increased with increase of temperature 23, 30, 37 to 45°C.

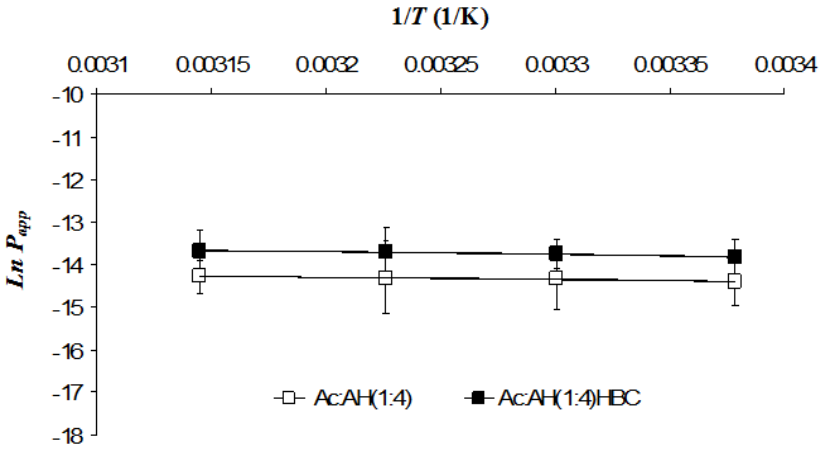

Fig. 7: Plot of *Ln* permeability (mean ± sd) versus the reciprocal of absolute temperature. Activation energy (E_a) of permeability of aceclofenac from drug-aluminium hydroxide dispersion in absence and presence of HBC with 1 h incubation at 37° C before permeation was determined from the regression line (R^2 values 0.960 and 0.921 respectively) of Arrhenius equation. Significant difference of the slope between lines has been noticed indicating remarkable difference in E_a.

Entropy is related to the dispersal of a system's energy and the freedom of motion of its particles at a specific temperature. The increase in entropy of activation (ΔS; J mol^{-1} K^{-1}) for permeation is the value for amount permeated minus the value for the amount to be permeated at a specific temperature. We found entropy of activation (ΔS; J mol^{-1} K^{-1}) a negative value of -114 for Ac:AH(1:4) and -106 for Ac:AH(1:4)HBC) with 1 h incubation before permeation. A negative entropy change contributes to making the free energy change positive for the forward process of permeation and thereby tends to make that process occur spontaneously. No major change in ΔS was observed with the elevation of temperature. The free energy change (ΔG; kJ mol^{-1}) for Ac:AH(1:4) and Ac:AH(1:4)HBC) with 1 h incubation before permeation was positive (35.43 to 37.75 and 34.02 to 36.19 respectively). ΔG increased slightly in both the systems with the increase of temperature. This is an example of the universal tendency toward randomization or disorder[25]. As for example, for polyethylene entropy change for fusion (ΔS_f) and entropy change for crystallization (ΔS_{cr}) are +18.8 and -18.8 J mol mar^{-1} K^{-1} respectively. Here, the reverse process of ordering or crystallization is opposed by freedom of rotation through fusion and its increase in entropy. In the study of mechanism of ionization of pilocarpine Mitra et al.,[26] (1988) explained that the increase in standard entropy (a positive value) provides a force for the reaction of pilocarpine ions to form pilocarpine and pilocarpine ions were held in a more orderly arrangement than the predominantly nonionic pilocarpine in the aqueous environment. Here also the dissociation of pilocarpine into ions will give a negative value of standard entropy change.

DISCUSSIONS

Poor bioavailability of drug may result because of erratic gastrointestinal absorption due to drug-drug interaction. The reduced enteral absorption of quinolones in presence of antacids containing polyvalent cations is thought to be due to chelation of antibiotics by the ions [7,27-29]. In the present study permeation of aceclofenac has been gradually decreased as the aluminium hydroxide amount increased and the permeation has still been remarkably inhibited after 1h incubation at 37° C.

Aluminum hydroxide has an isoelectric point of 11.4[30,31] and will show an alkaline pH not more than 10 in distilled water. The surface of the aluminum hydroxide will be positively charged and aceclofenac being a weak acid is electrostatically attracted to aluminum hydroxide. The metal cation of aluminum hydroxide might have interacted to form complex through carboxyl and carbonyl groups of aceclofenac[5]. The possible assumption is also suggested by some literatures that the interaction between antacids containing polyvalent cations and fluoroquinolones is due to chelation of the antibiotic by the ions [27-29] and aluminum in particular, forms a very stable complex which is not easily soluble[32]. Inclusion complexation with beta cyclodextrins can improve chemical stability, bioavailability and also reduce side effects and toxicity of the drugs[14-17]. Similarly, presence of HBC remarkably improved permeation due to protection of drug by inclusion complexation. Drug-aluminum hydroxide interaction became rate limited compared to permeation rate in presence of HBC.

In this study, we applied a thermodynamic approach by determining individual parameters like activation energy, enthalpy, entropy and free energy of activation of permeability. Significant increase of E_a for Ac:AH(1:4)HBC proved significant improvement of drug permeability facilitated by HBC in comparison to Ac:AH(1:4) after 1h of incubation. Significant increase of positive values of ΔH at a particular temperature for Ac:AH(1:4)HBC indicated more heat was absorption and accelerated permeation compared to Ac:AH(1:4). The lower transfer free energy (ΔG) proved higher permeability

coefficient in presence of HBC at respective temperature. Negative value of entropy of activation (Δ*S*) contributed the free energy change positive for the forward process of spontaneous permeation and negative value of -114 for Ac:AH(1:4) and -106 for Ac:AH(1:4)HBC) again proved improved permeability in presence of HBC.

Permeability potential of aceclofenac from aluminum hydroxide dispersion in different ratios in absence and presence of HBC has been examined through isolated goat intestine. Permeability of aceclofenac has been significantly affected from aluminum hydroxide dispersion in 1: 4 ratio and the permeability value was also decreased after 1h incubation of the dispersion at 37° C. Aluminum hydroxide might have interacted with aceclofenac to form a stable complex which was not easily soluble and affected permeation. The time-dependent permeation of aceclofenac from drug-aluminum hydroxide dispersion increased exponentially with increasing the temperature. Presence of HBC remarkably improved permeation by protecting the drug through inclusion complexation and drug-aluminum hydroxide interaction became rate limited. Thermodynamic parameters such as activation energy, enthalpy, entropy and free energy of activation of permeability have been evaluated to understand mechanisms of intestinal transport of drug molecules when it was particularly affected by aluminum hydroxide.

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