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A DIFFUSION CONTROLLED DRUG DELIVERY SYSTEM FOR THEOPHYLLINE

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SUMMARY

The goal of achieving ideal attributes of a drug delivery system including reliability and predictability has led investigators to design controlled release (CR) systems based on the principles of microporous coatings, diffusion controlled coatings and various hydrogel type systems.

In this study, the critical role of "water content fraction" of a polymer in deciding its diffusion characteristics has been ascertained and the correlation between molecular size/shape, membrane thickness, pore radii and drug diffusion has also been demonstrated. The theoretical considerations, designing and engineering of a *"barrier coated-reservoir"* type of a delivery system for theophylline using poly (vinyl alcohol) [PVA] as the coating material are discussed. After realizing the desired theoretical *in-vitro* release profile, *in-vivo* studies were carried out on a dog model. The potential of poly (vinyl alcohol) as a barrier coating material in developing a CR system is interestingly observed.

INTRODUCTION

Excellent physico-chemical properties and satisfactory performances have precipitated wide areas of applications for hydrogels[1]. The water swelling behavior of an

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hydrogel allows for the understanding of diffusional properties of a large number of solutes and the development and applications in novel drug delivery systems[2-8]. Literature reviews in the past have often emphatically highlighted the importance and applications of membrane transport principles[9,10]. The phenomenon is not solely restricted to biological areas but also is potentially useful in the development of formulations that deliver predetermined metered doses on exact schedule to the intended surfaces of absorption.

Theophylline, a dimethylated xanthine derivative has been a drug of choice for the treatment of asthma. The pharmacokinetic and pharmacodynamic profiles of this drug have been extensively discussed in standard text[11-16]. A narrow therapeutic index further warrants the need for a precisely controlled zero (near zero) order long acting delivery system. In this work, an attempt had been made to design a suitable system for theophylline utilizing PVA membranes of adequate thickness to control the release rate powered by a driving force built inside the core upon dissolution.

MATERIALS AND METHODS

Materials: Poly(vinyl acetate), [PVAc], Sap.value=260-270, density=1.177 g/cc; poly(vinyl alcohol), [PVA], hot water soluble grade (CELLACEL® 279), viscosity of a 2% aq.soln @ 20°C=20-30 cps, density =1.05 g/cc were received as gift samples from Cellulose Products of India Ltd., Ahmedabad; acetone and methyl ethyl ketone [MEK] were of analytical reagent grade and purchased from the local market. All the drugs used in this study were of pharmacopeial grade and procured from local market. The sodium salts of theophylline and mefenamic acid were prepared in this laboratory. A specially designed and fabricated stainless steel diffusion cell was used to investigate the diffusion behavior of all the drug molecules.

Method for casting free films of PVAc: A 3% w/v solution of PVAc in acetone+MEK (1:1) was prepared and 3 ml poured on clear mercury surface in Anumbra® petri dish (4" dia). The solvent was allowed to evaporate by placing the dish at a distance of 6 inches from an infra-red lamp (Phillips, India) in a non-turbulent area for about 10-12 minutes. The free films so obtained (average thickness = 30 μ) were kept in polythene bags and preserved in desiccators over activated silica gel until use.

Method for casting free films of PVA : On similar lines as above free films of PVA (35 μ) were cast from a 3% w/v solution of PVA in a mixture of water+acetone+MEK (6:1:1). The solvent was evaporated by placing the dish in a hot air oven at 40°C.

Determination of water content fraction (wcf) of free films: Uniform strips (1 x 5 cm) were cut from the free films and soaked in distiled water in separate glass stoppered flasks

for 24 hours at room temperature (about 30±2°C). The films were then carefully removed with the help of forceps and gently wiped with filter paper on both sides and weighed accurately. These were then dried to a constant weight under reduced pressure. The wcf was calculated as follows:

$$wcf\ (\%) = \frac{\text{wet membrane wt. - dry membrane wt.}}{\text{wet membrane wt.}} \times 100 \qquad \text{---------(I)}$$

Diffusion studies: A specially designed stainless steel diffusion cell described in an earlier publication[17] was used to study the molecular transport across the polymeric films. The cell was designed to have a high diffusional area to volume ratio.[18] To avoid any interferences in the rate of transport by ionic impurities, the medium used was deionized water (conductivity = 10^{-7} mhos). The water was made free from any dissolved CO_2 by boiling for 30 minutes and using the same within 24 hours. Preliminary diffusion studies on PVAc and PVA films were carried out using 30 ml of sodium salicylate solution (1.5 mg/ml). The same volume of the medium was filled into the receptor cell. Samples were withdrawn at regular intervals upto 24 hrs and the drug content analyzed.

On the basis of the results obtained, PVAc films were found to be totally unsuitable. Therefore, detailed diffusion studies using six different drug molecules were carried out only on PVA films.

Effect of film thickness on drug diffusion:

For this study, PVA films with thicknesses of 45, 65 and 95 μ were used. Aqueous solution of theophylline sodium salt (0.5 mg/ml) was used as the feed solution in the donor cell.

Calculation of diffusion parameters:

The membrane diffusion coefficient (P_2) was calculated as per the following method reported by Tumara *et al* [19]:

$$P_2 = \frac{1}{A}\left\{\frac{-1}{t(1/V_1 + 1/V_2)} \ln \frac{1 - (C_2/C_1)}{1 + (C_2/C_1)(V_2/V_1)}\right\} \qquad \text{----------(II)}$$

Where, C_1, V_1 and C_2, V_2 are the concentration (moles/cc) and the volume (ml) of the donor and the receptor cells respectively at any time 't' and 'l' is the membrane thickness (cm); 'A' is the area of the exposed film (sq.cm). P_2 can be expressed either as sq.cm/sec or sq cm/h.

The solute flux (J_s), was calculated as follows [19]:

$$J_s = \frac{(P_2)\ (\Delta C)}{l} \qquad \text{[moles/sq cm/sec]}$$

----(III)

Where, ΔC is the concentration difference across the cell at any time 't' secs and 'l' is the membrane thickness in cm.

Calculation of molecular size: Two parameters indicating the size of the drug molecule were calculated theoretically as follows:

(i) The molecular volume [MV] was calculated using the following relationship[20]:

$$MV = \frac{\text{Molecular weight}}{\text{Density x Avogadro Number}} \qquad \text{----------(IV)}$$

(ii) The partial molal volume [pmv] was calculated by adding up the individual pmv(s) of various atoms or groups constituting the molecule[21,22]. Assuming the molecules to be spherical, the molecular diameter and the partial molal diameters were calculated.

Calculation of membrane pore radius from diffusion data: The pore radius of the PVA films was calculated using the following methods:

(i) Calculation of the equivalent pore radius based on the '***hindered diffusion theory***' of Flynn *et al* Eqn. (V)[23] :

$$\frac{D_p}{D_f} = (1- (r_s/r_p)^2 \ [1- 2.104(r_s/r_p) + 2.09(r_s/r_p)^3 - 0.905(r_s/r_p)^5] \qquad \text{----(V)}$$

Where D_p and D_f are the diffusivities through pores and the free solution (water) respectively. 'r_s' is the spherical solute radius and 'r_p' is the equivalent membrane pore radius.

(ii) The pore radius was also calculated using the "Hagen-Poiseulli" equation[19] as follows:

$$r_p = \sqrt{\frac{8(n).\ (V)}{H}} \qquad \text{----------(VI)}$$

Where r_p is the pore radius of the film in cm, n the viscosity of the medium (cps), V is the permeability in ultrafiltration (sq.cm.sec/g) and H, the water content fraction.

THEORETICAL CONSIDERATIONS

The designers of a controlled release therapeutic system are required to have a good understanding of the various pharmacokinetic and pharmacodyamic parameters of the experimental drug. The following are some of the important values for theophylline:

Desired therapeutic blood levels:	10 - 20 µg/ml	(Ref. 15)
Fraction of dose absorbed:	100 %	(Ref. 15)

Volume of distribution:	0.48 L/kg	(Ref. 15)
Time to achieve peak level:	2 - 3 h	(Ref. 14)
{for slow release formulations}:	3 - 6 h	(Ref. 14)
Protein binding:	60 %	(Ref. 16)
Clearance rate:	0.04 L/h/kg	(Ref. 15)

Calculation of the zero-order release rate (k_o) for theophylline and predicting the fast and slow release drug component: If the rate of drug release from a controlled release system follows a zero or a pseudo zero-order kinetics, then the plasma drug concentration 'C_{plasma}' for a simple one-compartment, heterogeneous system is determined by[24]:

$$C_{plasma} = \frac{k_o}{k_e V_d}(1 - e^{-k_e t}) \quad \text{..... (VII)}$$

Where, k_e is the elimination rate constant, V_d is the volume of distribution (L), and 't' is the time (h).

At some time after the administration of the drug, $e^{-ke.t}$ approaches zero and a steady state plasma drug concentration as defined by:

$$C_{plasma} = \frac{k_o}{k_e.V_d} \quad \text{.....(VIII)}$$

is established and maintained as long as the drug molecules are being released at a rate constant of k_o from the delivery system.

The drug delivery system designed herein is a barrier coated reservoir device and carries only the sustained release portion of the dose. This part has to be delivered at a constant rate for a fixed period of time. The initial dose 'D_I' which attains the peak serum level concentration could be administered as a separate intravenous injection of the dose or through a rapid dissolving dosage form containing the initial dose.

Using the pharmacokinetic parameters stated earlier, one may predict the desired release rate constant k_o, for theophylline system (from equation II) to be = **28.056 mg/h**. Theoretically, such an ideal delivery system should release the drug for about 12 hours at a zero-order rate. This is not achieved practically because, after about 10 hours the solution inside the polymeric coat becomes dilute and hence the thermodynamic activity decreases resulting in an exponential fall in the release rate.

The loading dose of 100 mg was calculated from the following equation[25]:

$$\frac{D_i}{D_m} = \frac{1}{k_e.t_r}\left[1 - e^{-ke\,(\tau - tr)}\right] \quad \text{.....(IX)}$$

Where, t is the dosing interval and is fixed for per-oral applications to 12 h in consideration to the patient compliance and the normal gastro-intestinal (GI) transit time; 't_r' is the residence time of the dosage form in that region of the GI tract where absorption takes place (assumed to be 8 h).

Theoretical considerations in the fabrication of the proposed drug delivery system: In principle, it is the aim to coat a drug containing tablet (core) with a rate determining diffusional barrier to get the so called "diffusion tablets".

Water or liquid of the GI tract must be able to penetrate through the barrier. Thus, a saturated solution can be formed within the tablets and as long as the saturation concentration lasts by dissolution of the undissolved drug, a constant release rate is ensured. This type of a specially designed diffusion tablet may also be called as the "therapeutic system"[26].

Preparation of tablet cores: Since only water soluble drugs could be delivered through the proposed system [26], theophylline anhydrous was converted into its water soluble sodium salt by a reported method[27]. Sodium theophyllinate tablets containing theophylline equivalent to 350 mg were prepared by the dry compression method after obtaining granules by slugging the powder blend. The tablet weight was adjusted to about 450 mg with lactose and magnesium stearate (pharmacopoeial grades) the latter being used in the concentration of 0.5 % w/w. The 10.5 mm round, bi-convex tablets were then evaluated for various pharmacopoeial standards for tablets. Hardness of the tablets was kept between 5 - 7 kg/sq cm (determined using a Monsanto® tablet hardness tester).

Film coating of tablets: Since film coating in a pan would require a large quantity of the drug, individual tablets were "dip-coated"[28,29] to produce uniformly coated tablets, The composition of the film coating solution was :PVA (3.0 g), Acetone (12.5 ml), Methyl ethyl ketone (12.5 ml) and distilled water (75.0 ml). This mixture was refluxed at 85-90^{o}C for 10 minutes and the resultant clear solution filtered through a 100 mesh nylon cloth. Individual tablets were dipped into the above solution using a pair of forceps and transfered into a cylindrical container specially designed and fabricated in this laboratory. Tablets were dried using a hot air blower (Moulinex®, France). The thickness of the films cast on the tablets was determined using a micrometer and standardized in relation to the number of dip coats applied. Different number of coats were applied to a batch of tablets which were then evaluated for *in-vitro* release as follows.

In-vitro dissolution testing: The USP Type I dissolution testing apparatus was employed using distilled water (900 ml at 37±1^{o}C) as the medium. The basket rotational speed was 50 rpm and the drug release estimated spectrophotometrically at 271 nm.

TABLE 1
Transport of sodium salicylate molecules across PVAc and PVA films

TIME (hrs)	CONCENTRATION (μg/ml)			
	PVAc FILMS		PVA FILMS	
	Donor cell	Receptor cell	Donor cell	Receptor cell
0	1700	0	1700	0
2		nm*		308
4		nm		479
8		nm		592
24		nm	753	692

* *not measurable*

In-vivo studies: Preliminary *in-vivo* studies were done on a healthy male beagle dog weighing 18 kgs. Standard protocol[30] was observed and a sensitive HPLC method[12] was used to estimate the plasma theophylline levels. To determine the steady state serum level concentration of theophylline and to calculate the various pharmacokinetic parameters in the test animal, aminophylline intavenous injection (containing 80 % theophylline and 20% of ethylene diamine) was administered.

RESULTS AND DISCUSSION

The wcf determination showed a significant difference in the two selected film formers PVAc and PVA [0.172 and 66.21 respectively]. The results were found to be in confirmation with the study by Ratner and Hoffman[3] on hydrogels. Since, permeation across water swollen membranes has been visualized primarily by diffusion through the microscopic water saturated pore channels within the polymer structure[8,31], the wcf could be certainly expected to reflect the porosity of the membrane. This was corroborated by the results of the preliminary diffusion studies on both the materials using sodium salicylate (Table 1). The PVAc films with a negligible wcf virtually did not show any diffusion of this drug whereas, PVA a hydrogel, with a reasonably high wcf not only allowed drug diffusion through its water filled pores but also, interestingly, showed a good control over the rate of drug transport thereby, exhibiting a good potential for use as a "rate controlling membrane".

The molecular size of the drug is an important parameter that must be considered if a polymeric membrane is to be relied upon as the rate controlling material[32]. Table 2, shows the diffusion coefficients (P_2) and the solute flux for all the drug molecules subjected to diffusion studies using PVA films of thickness 35 μ. Table 3, shows the effect of molecular size on drug diffusion. The partial molal volume is not only a simpler

TABLE 2
Diffusion coefficients for drugs across PVA films

DRUG	CONCENTRATION IN DIFFUSION CELL AT THE END OF 24 HOURS mol/cc x 10^7		SOLUTE FLUX [J_s] mol/sq cm/sec x 10^{10}	DIFFUSION COEFFICIENT [P_2] sq cm/sec x 10^7
	Donor	*Receptor*		
Sodium salicylate	60.420	45.80	0.390	0.946
Sodium theophyllinate	13.700	10.04	0.087	0.840
Sodium mefenamate	10.960	8.03	0.070	0.834
Salbutamol sulfate	6.354	4.77	0.039	0.880
Cyproheptadine HCl	9.340	5.92	0.067	0.690
Tetracycline HCl	6.700	3.69	0.049	0.580

TABLE 3
Correlation between molecular size, pore size and diffusion

DRUG	Molecular radius (Å)	Partial molal radius (Å)	P2 x 10^7 Sq cm/sec	Df x 10^7 Sq cm/sec	Pore radius (Å)
Sodium salicylate	3.658	3.218	0.946	58.67	7.30
Sodium theophyllinate	3.787	3.112	0.840	56.66	7.53
Sodium mefenamate	4.430	4.166	0.834	48.43	8.98
Salbutamol sulfate	4.612	4.369	0.880	46.53	9.47
Cyproheptadine HCl	4.952	4.758	0.690	41.63	9.93
Tetracycline HCl	5.154	4.856	0.580	41.63	10.15

NOTE: The equivalent pore radius calculated using the "Hagen-Poiseulli" equation[19] was found to be = 18.62 Å.

approach to calculate the molecular size but also has been successfully used in various applications[20-22]. The diffusion coefficients registered a fall with an increase in the spherical molecular diameter. However, in the case of salbutamol sulfate, it was higher than the smaller sodium salts of mefenamic acid and theophylline. This deviation from the general behavior can be explained as residing in the shapes of these molecules. Stein and Nir[33], have stated that in polymers, the value of P_2 is more sensitive to the molecular shape than in the case of liquids. P_2, in the case of liquids decreases with deviation from spherical shape whereas, in polymers, a sphere usually has a much lower value for P_2 as compared to an ellipsoid of the same volume. In the salbutamol sulfate molecule, the linear side chain may be responsible for this behavior. The other contributing factor could be the higher aqueous solubility of this molecule resulting into a higher affinity towards the aqueous pores in the hydrogel film.

The equivalent pore radius calculated from the diffusion data is presented in Table 3. It may be observed that as the molecular size increases, the pore size increases with a

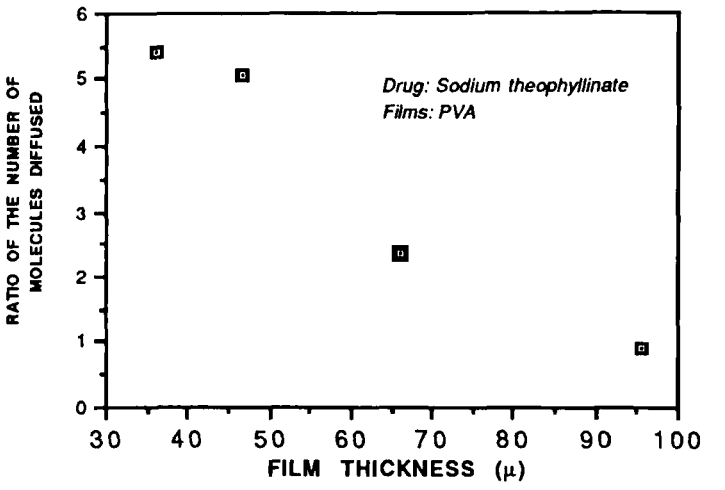

FIGURE 1

Effect of film thickness on drug transport

decrease in the P_2. This effect can be explained by visualizing the passage of a diffusant molecule between two polymer chains as in the case of the Brandt's activated state model[34]. It is clear from this mechanism that larger "holes" need to be formed in the polymer structure for the diffusion of larger molecules. This will certainly require greater energy for their formation. Hence, the activation energy will be higher resulting into lower diffusion coefficients. Crank and Park[35] have found this to be true in every case. The drug diffusivity through the pores i.e. D_p is same as the diffusion coefficient P_2. D_f, is the drug diffusivity in water.

Figure 1, shows the effect of membrane thickness on drug diffusion. As anticipated, the number of drug molecules diffusing across the PVA membranes decreased with the increase in its thickness. This has been found to be in close agreement with previous findings [36-39]. The importance of film thickness in this type of drug delivery system needs to be stressed upon as it is one of the vital rate controlling tools available to the designer. The thickness of the membrane coat may be invariant with time but the rate of drug release can be controlled at a required magnitude by coating the drug core (tablet/pellet) with different wall thickness[40].

The drug release rate has a reciprocal relationship with the film thickness. However, the basic feature of the drug delivery system, i.e., zero-order release kinetics is more or less ascertained by using such hydrogel membranes. In the diffusion controlled system designed herein, the driving force is kept constant by maintaining the

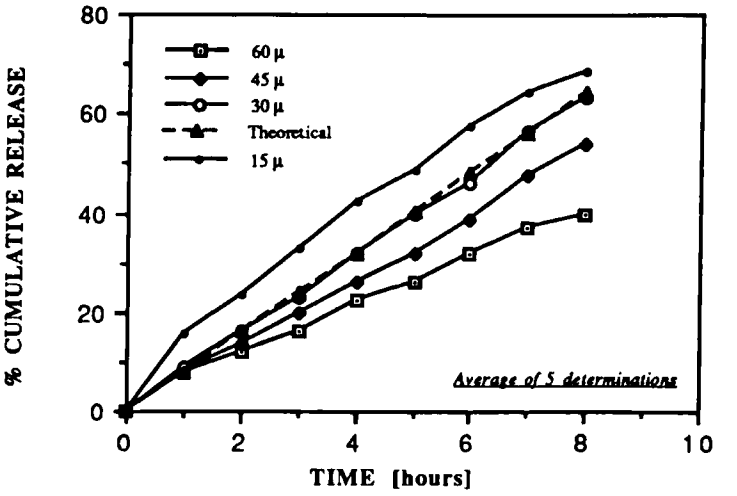

FIGURE 2
In-vitro release profiles of PVA coated theophylline diffusion tablets

hydrostatic/osmotic pressure inside the coated drug reservoir as a result of controlled drug solubility attendant to the rate of permeation of water into the drug core being eventually controlled by the membrane of a suitable thickness.

The tablet cores of sodium theophyllinate, when subjected to standard tests were found to give satisfactory results. The dip coating method was also found to produce uniform and smooth film over the tablets. Ten coats of the solution produced a film thickness of 30±3 μ.

As illustrated in Fig. 2, almost all the tablets investigated for *in-vitro* dissolution exhibited constant release profiles. Tablets with thicker films gave slower release rates confirming the suitability of the coating material. However, as far as the manufacturing process is concerned, on a large scale, conventional pan coating method may be recommended.

It was interesting to note that the release rate (28.415 mg/h) from tablets with a coat thickness of 30 μ was almost similar to the one desired theoretically (28.056 mg/h) to maintain blood level concentration of 10-20 μg/ml for a period of 12 hours. This encouraged the need for preliminary animal studies. The advantages of a dog model over others have been discussed by Kaplan[41]. The bioavailability of the delivery system was investigated taking help from the work reported by Tse *et al*[30,42].

TABLE 4
Pharmacokinetic parameters for theophylline (in beagle dog):

Parameter		value
Dose administered (I.V. route), [D], mg	:	60.0
Plasma concentration at time t=0, i.e.,FD/V_d,[C_o], mg/L	:	5.15
First order elimination constant, [k_e], h^{-1}	:	0.1574
Biological half-life, [$t_{1/2}$], h	:	4.4027
Apparent volume of distribution [V_d], L/kg	:	0.647
Correlation coefficient [r]	:	0.96
Normalized area under the curve [AUC], µg.h/ml	:	32.719
Plasma clearance [PC_l], ml/min/kg	:	1.697

Note: The above data was analyzed as per one compartment open pharmacokinetic model[43].

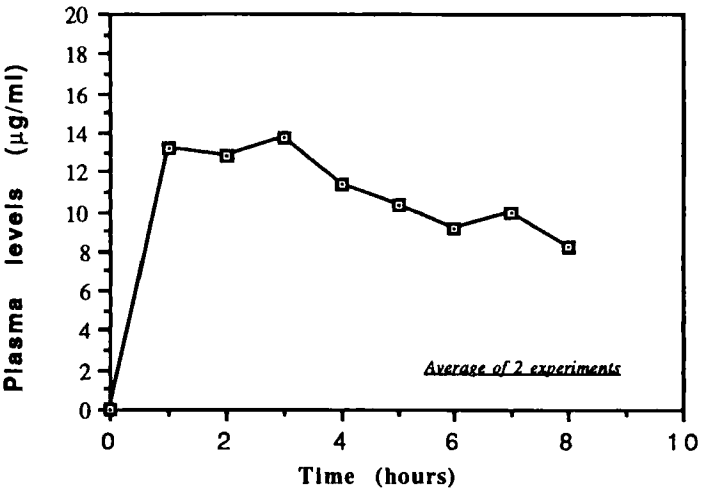

FIGURE 3
Plasma levels of theophylline from the CR diffusion tablets in beagle dog

The theophylline blood level data after intravenous and oral administration was analyzed as per the one compartment open pharmacokinetic model. The equations and symbols pertaining to this model have been described by Gibaldi and Perrier[43]. The marginal superiority of the HPLC method over others for the plasma estimation of theophylline, has also been reported[44].

The pharmacokinetic parameters calculated for the experimental animal have been presented in Table 4.

Figure 3, shows the plasma levels obtained against time for the delivery system. The maximum level (T_{max}) was found to be 13.6 µg/ml and was attained 3 hours post dosing. It was interesting to observed that the drug release rate was reasonably constant maintaining an average level of about 11.6 µg/ml for 7 hours.

Rate performance and *in-vitro:in-vivo* correlation:

To develop a drug delivery system with a controlled release and a programmed duration of therapeutic effectiveness, it is of utmost importance to establish an *in-vitro:in-vivo* correlation. It could be demonstrated with this theophylline system that the *in-vivo* release (21.27 mg/h) was slower than the *in-vitro* (28.417 mg/h). This means, an existence of a correlation factor **f= 0.7485 mg/h.**

$$\text{i.e.,} \quad k_{o\,(vivo)} = 0.7485\ k_{o\,(vitro)}$$

The decrease release *in-vivo* can be explained by the formation of thicker adherent liquid layers around the tablet in the GI tract in comparison to the *in-vitro* dissolution test.

CONCLUSIONS:

It could be concluded that, for a polymeric material to qualify for usage in a "reservoir" type of a barrier coated drug delivery system, it is highly imperative to possess good diffusional and swelling properties as found in the case of PVA. It may thus be possible to design a drug delivery based on the principles of diffusion coating for any drug and membrane combination exhibiting physico-chemical properties as observed in this study with theophylline and PVA.

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