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CONTROLLED TRANSDERMAL MUCOLYTIC DELIVERY SYSTEM

Deepak Thassu and S.P. Vyas

Pharmaceutics Laboratory
Department of Pharmaceutical Sciences,
Doctor Harisingh Gour Vishwavidyalaya,
Sagar - 470 003 (M.P.) INDIA

ABSTRACT

Bromhexine a mucolytic agent was studied to explore for dermal route of administration. The formulations were based on commercial eudragit polymers and polyvinyl pyrrolidone.

Two systems i.e., Matrix and Pseudolatex were studied for their comparative performance evaluation in in vitro. The various combinations of hydrophobic (Eudragit RL-100) and hydrophilic (PVP 40,000) polymers were used to prepare the both matrix and pseudolatex topical systems. The prepared systems were studied for in vitro diffusion using a Franz diffusion cell. Study revealed that the relative concentration of hydrophobic to hydrophilic polymers determines the drug diffusion and across the skin permeation of the drug. Both the systems were noted to be stable, however, the drug release and across the skin permeability of drug from pseudolatex system recorded to be better and uniform. Preliminary studies on bromhexine are indicative of its potentiality for transdermal preparation and establish the need for in vivo evaluation.

INTRODUCTION

In the last few years, the trend of topical delivery system has markedly increased. The various transdermal therapeutic systems containing drugs to achieve systemic pharmacological effects exemplify a new level of technological involvement (1).

Controlled drug delivery can be achieved with the transdermal formulation basically by vehicles determined delivery and the skin controlled systemic input that meters the percutaneous absorption. The former situation is always preferred and under this system controlled input has been achieved by membrane moderated, adhesive diffusion controlled, Matrix dispersion and Microreservoir devices (2).

Inadequacy of current topical vehicles create need to develop better systems for delivery of topical agents in proper amount to appropriate layers of skin at a defined and required rate (3). Many of the current vehicles are marginally effective in delivering their active ingredients to proper tissue sites. Pseudolatex systems initially developed for tablet film coating were studied and found to produce highly substantive, clear and virtually invisible water resistant and protective film on the skin (4). The crystallographic analysis of pseudolatex films indicate the absence of crystalline drug. In vitro diffusion was prompted from this new topical delivery system in comparison to release of the model drug from other commercially marketed products (5).

The object of mucolytic treatment is to achieve liquification of viscous sputum which in turn results in easier expectoration (6,7). Bromhexine hydrochloride is a potent mucolytic agent. The electronic microscopic studies suggest that it acts upon mucus producing cells of respiratory tract (8,9). The drug also causes highly significant reduction in the A.M.P.S. fibre content (10,11). The drug is to be given 0.6 to 0.8 mg/kg body weight three times a day minimum for one week to achieve the therapeutic effect (12,13). Bromhexine hydrochloride when administered orally the most frequent complaint is gastric irrita-

tion and its bitter taste. Similarly through inhalation route administration the transient coughing is the main problem (14).

Considering the above parameters the drug was choosen for transdermal system. After making preliminary investigation on drug nature and its permeation behaviour across the skin, an attempt was made to prepare such polymeric system that would release the drug to the skin at a slower rate than its across skin transportation rate. Thus the mode of therapy could be made independent of age and sex. The polymeric film type and pseudo-latex submicroscopic dispersion type systems were selected for transdermal patches.

MATERIALS AND METHODS

Bromhexine hydrochloride (IPCA Laboratories, Bombay, India) Polyethyleneglycol (PEG 400), Polyvinylpyrrolidone (PVP) Polystyrene, supplied (Sigma Chemical Company, St. Louis, MO, USA), Eudragit RL-100 (Rohm Pharma, West Germany). All the solvents and chemicals used were of Analar grade as supplied by E. Merck India Ltd.

Characterization of Drug

(a) Partition Coefficient : Octanol/water system was used to determine partition coefficient of the drug. The system was kept at room temperature at $37^{o}\pm1^{o}C$ for 36 hours and the drug concentration in aqueous and organic phases was determined (Table I).

(b) Drug Solubility in Skin : A piece of freshly excised skin (100 mg) was put into a tube containing 10 ml of 10 mcg/ml drug in 40% P.E.G. 400 solution and equilibrated for 36 hrs. at $37\pm1^{o}C$. The solubility of the drug in the whole skin C_s was then calculated (Table 1).

(c) Drug Permeation : The Franz diffusion cell was used for skin permeation investigation. The freshly excised abdominal skin of male hairless mouse (6-7 weeks old; source- Scientific

TABLE I

Characterization of Bromhexine hydrochloride

Partition coefficient of drug (Km)	Drug solubility in skin (C_S) mg/ml	Drug permeation rate mg/cm^2/hr
8.9 ± (0.13)	0.40 ± (0.08)	0.048 ± (0.002)

Values in parenthesis indicate ±S.D. from an average.

Stores, Agra, India) in full thickness of skin was used. The saturated solution of bromhexine hydrochloride was prepared by suspending excess amount of drug in 40% v/v aqueous P.E.G. 400 solution. The same solution with no drug in receptor compartment was used. The temperature was maintained at 37±1°C. The samples were estimated by U.V. Spectrophotometry using Schimadzu Double Beam Spectrophotometer (16).

(d) Drug Analysis : Concentration of drug in each solution was measured by U.V. spectrophotometry at 317 nm using Shimadzu Double Beam Spectrophotometer (16).

Preparation of Delivery System

The controlled release devices studied were consisted of four formulations belonging two type of systems i.e. the pseudolatex system with peripheral adhesive (T.P.S.) (Fig 1) and film system with face adhesive (T.F.S.) (Fig 2) with two polymeric composition to variation in each type.

Preparation of Pseudolatex and Film type Matrices

(a) Casting of Films : For the preparation of film matrices, 10% polymer was selected in different ratio as mentioned in Table II. The films were casted using the method described by Iyer (17). Dibutyl phthalate was used as a plasticizer

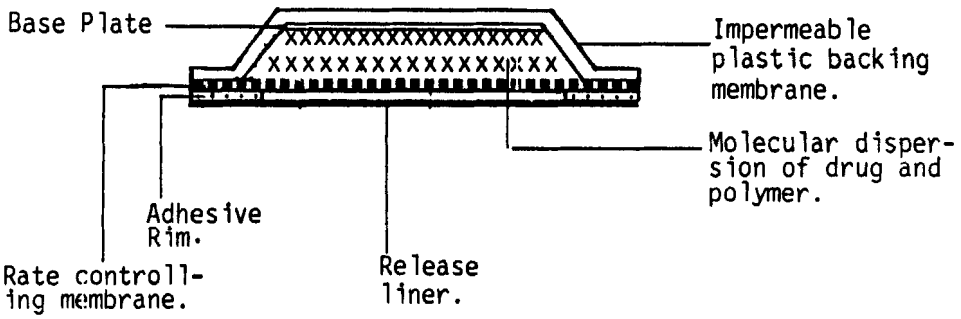

Fig 1 : Transdermal Pseudolatex System (T.P.S.)

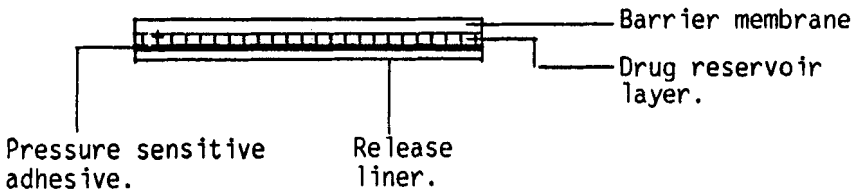

Fig 2 : Transdermal Film System (T.F.S.)

TABLE II

Formulation Composition of Polymeric Composites of Bromhexine Hydrochloride Transdermal Systems.

Product Name	Polymer Description* and Drug Rato
Product A	Eu.RL-100 + P.V.P. + Drug :: 20 : 80 : 0.15
Product B	Eu.RL-100 + P.V.P. + Drug :: 40 : 60 : 0.15
Product C	Eu.RL-100 + P.V.P. + Drug :: 60 : 40 : 0.15
Product D	Eu.RL-100 + P.V.P. + Drug :: 80 : 20 : 0.15

* (i) for pseudolatex preparation 8% w/w surfactant was used.

(ii) Dibutyl phthalate (2% w/w) used as plasticizer in film matrix systems.

in 2% w/w concentration. The thickness and the dimension of films (20 cm^2) were controlled by pouring the constant volume in the rings of the same diameter and dimensions. The prepared films after drying were stored under controlled humidity (below 30% RH) at room temperature.

(b) Preparation of Pseudolatex : The pseudolatices were prepared using the same combination and concentration of polymers as were used for matrix type system. The method developed by Vander hoff and coworkers for the preparation of these colloidal dispersions from already formed polymers was choosen (18). Pseudolatices were prepared by emulsion solvent removal method. This method involves the emulsification of an organic solution of drug and polymer with an aqueous solution of surfactant. The 8% w/w surfactant was used. The prepared emulsion was kept for partial evaporation. The total organic solvent was evaporated under the reduced pressure whilst water was evaporated partially that transformed the preparation into thin paste like base. The final formulation was stored under controlled humidity (below 30% RH) at room temperature.

(c) Preparation of Drug Matrix System : The delivery system with peripheral adhesive system was composed of a impermeable membrane of plastic and the base plate of polystyrene. The rate controlling membrane was prepared of cellulose triacetate (microporous). The formulation was protected using the release liner (Fig 1). The face adhesive system was prepared using Backing membrane of polyurethane + polystyrene. Release liner was used to protect the formulation (Fig 2). The specifications and further details are given in Table III.

Bromhexine Hydrochloride Release Kinetics

The release of drug from two delivery systems of four different polymeric combinations were monitored using continuously perfused in vitro Franz diffusion cell system. The formulations were placed between the upper and lower halves of vertical diffu-

TABLE III

Formulation Specifications and Components of Transdermal Systems of Bromhexine Hydrochloride.

COMPONENTS	Transdermal Peripheral adhesive patch (T.P.S.)			Transdermal Face adhesive patch (T.F.S.)		
	Type of Polymers	Thick-ness (mcm)	Drug content (mg/ml)	Type of Polymers	Thick-ness (mcm)	Drug content (mg/cm^2)
Backing membrane	Plastic moulded	75.0	-	Polyura-thane + Polysty-rene	69.0	-
Reservoir*	Eudragit RL-100 + P.V.P.	60.5	3.5	Eudragit RL-100 + P.V.P.	59.8	3.5
Rate con-trolling membrane	Cellulose triacetate	39.3	-	--	-	-
Adhesive	Pressure sensitive adhesive	30.5	-	Pressure sensitive adhesive	30.5	-

* Area of reservoir 20 cm^2. Dichloromethane:methanol (20:80) was used as a solvent for polymers.

P.V.P.- Polyvinyl pyrrolidone.

sion cell. The buffer was continuously perfused via a peristaltic pump at 10 ml/hr, perfusate was collected hourly for 24 hours. The content of receptor compartment was stirred with a film coated magnetic bar. A thermostating jacket of water (at 37°C) provided isothermal conditions for the release process. For each polymeric system four replicates were run and the data provided cumulative amount of Bromhexine hydrochloride released per unit time. The results have been expressed in terms of percentage of the total amount of drug contained in the system at the begining of the experiment (Table IV).

TABLE IV

Cumulative amount of Bromhexine Hydrochloride expressed as mean percent dose (±S.D.) released in 24 hours from different preparations into buffer at 37°C.

PRODUCTS	Percent Dose Released in 24 hours		
	Device T.P.S.	Device T.F.S.	Pseudolatex System (P.S.)
A	63.95±4.10	57.80±3.80	74.12±4.73
B	50.50±2.95	44.14±2.30	60.68±3.55
C	41.69±2.01	36.90±1.80	53.94±3.14
D	38.05±1.82	33.14±1.68	48.34±2.32

T.P.S.- Transdermal Pseudolatex System.
T.F.S.- Transdermal Film System.

Transdermal Delivery of Bromhexine Hydrochloride

The transdermal transport of the drug has been estimated using the same *in vitro* diffusion cell apparatus in which fresh excised skin from a hairless mouse (Scientific Stores, Agra, India) was interposed between delivery system and receptor compartment. The skin membrane of full thickness, aged 6 to 7 weeks was used. The experiments were performed in triplicate (Table V).

RESULTS AND DISCUSSION

The relationship between partitioning and the drug permeability across the skin is well established. Durrheim *et al.*(19) found that for the homologus n-alkanol, permeability coefficient through hairless mouse skin is parallel to the partition coefficient, hence, partition coefficient of Bromhexine hydrochloride was determined in n-octanol and water system. Bromhexine hydrochloride with a partition coefficient Km 8.9 $^{oct}/_{water}$ may be characterized as a lipophilic drug.

TABLE V

Characterization of Transdermal Drug Delivery Systems

Pseudolatex delivery system (T.P.S.)					Film matrix delivery system (T.F.S.)				
Product	Patch area (cm^2)	Drug content (mg/ml)	Release flux ($mg/cm^2/day$)	Skin permeation ($mg/cm^2/day$)	Product	Patch area (cm^2)	Drug content (mg/ml)	Release flux ($mg/cm^2/day$)	Skin permeation $mg/cm^2/day$)
$T.P.S._0$	20	3.5	2.238±0.143	1.893±0.096	$T.F.S._0$	20	3.5	2.023±0.133	0.984±0.059
$T.P.S._1$	20	3.5	1.754±0.103	0.879±0.048	$T.F.S._1$	20	3.5	1.544±0.080	0.701±0.038
$T.P.S._2$	20	3.5	1.454±0.070	0.786±0.039	$T.F.S._2$	20	3.5	1.291±0.066	0.542±0.026
$T.P.S._3$	20	3.5	1.331±0.063	0.614±0.028	$T.F.S._3$	20	3.5	1.159±0.058	0.419±0.021

T.P.S.- Transdermal Pseudolatex System T.F.S.- Transdermal Film System.

On the basis of the pharmacokinetic parameters of bromhexine hydrochloride (15), the required release rate of the drug 11.28 mcg/hr was calculated. The formula cp x vd x ke (cp = effective plasma concentration, vd = volume of distribution, Ke is Rate of Elimination) was used for the calculation. The calculated delivery rate was taken as desired rate assuming that the drug elimination rate equals the drug permeation rate. To characterize the drug nature, the solubility of drug C_s in the skin was determined and calculated 0.40 mg/ml. The drug permeation nature was studied and the permeation rate was found to be 0.048±0.002 $mg/cm^2/hr$.

An attempt was made to prepare different blends of lipophilic and hydrophilic polymers to achieve the desired rate (11.28 mcg/hr) of drug delivery. Eu.RL-100 was used as polymeric matrix containing different concentration of P.V.P. from 80% to 20% (Table II).

The release kinetics of Bromhexine hydrochloride from various formulated products are shown in Fig 3 & 4. The hydrophilic hydrophobic polymers combination that corresponds to product A showed highest release in both the systems i.e., matrix and the pseudolatices. In the case of pseudolatex system (P.S.) a linear correlation could established between cumulative percent drug released vs $t^{\frac{1}{2}}$ that is indicative of matrix release mechanism. The release was appreciably fast from pseudolatex system. In 24 hours approximately 75% of the drug was released from the product A (a pseudolatex based system) whereas, in the case of matrix system 63% of the incorporated drug was released whilst the polymeric composition in both systems used was the same.

The rate controlling membrane was used to control the release of drug from the pseudolatex system. All the rate controlling membrane based matrix system showed zero order release initially and followed by a matrix diffusion release kinetics. The higher percentage of hydrophilic polymer (P.V.P.) facilitated the drug permeation across the membrane. The noted effect

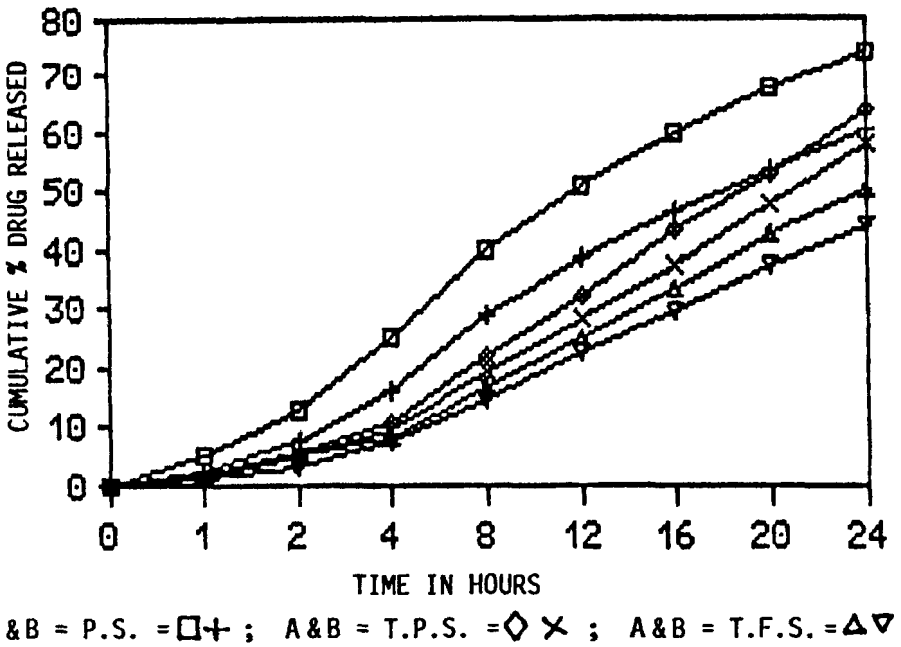

FIG 3- The time course for the in vitro release of Bromhexine hydrochloride from Pseudolatex System (P.S.), Transdermal Pseudolatex System (T.P.S.) and Transdermal Film System (T.F.S.) of Product A with release flux T.P.S. 2.238±0.143 mg/cm^2/day; T.F.S. 2.023±0.133 mg/cm^2/day and Product B with release flux T.P.S. 1.754±0.103 mg/cm^2/day; T.F.S. 1.544±0.080 mg/cm^2/day.

is indicative of an appreciable affinity of bromhexine salt form towards the lipid phase. The recorded lipophilic nature of drug could be accounted for a release that approximated a zero-order kinetics.

The bar diagram shown in Fig 5 & 6 gives the picture of the effect of product designing and different blend of polymers on the release kinetics.

The rate of appearance of drug in the receptor compartment of Franz diffusion cell delivered across the hairless mouse skin

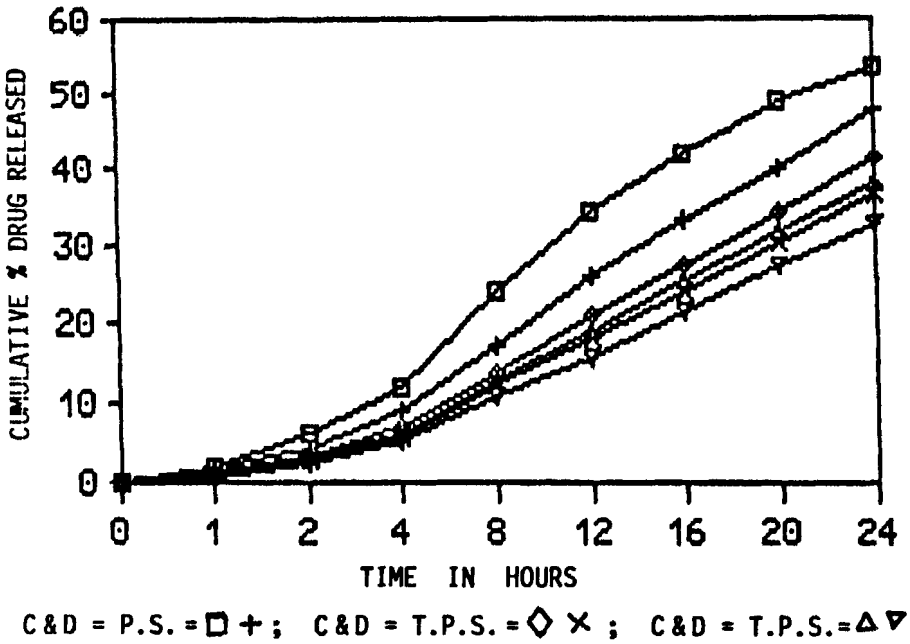

FIG 4- The time course for the in vitro release of Bromhexine hydrochloride from Pseudolatex System (P.S.), Transdermal Pseudolatex System (T.P.S.) and Transdermal Film System (T.F.S.) of Product C with release flux T.P.S. 1.454 0.070 mg/cm^2/day; T.F.S. 1.291±0.066 mg/cm^2/day and Product D with release flux T.P.S. 1.331±0.063 mg/cm^2/day; T.F.S. 1.159±0.058 mg/cm^2/day.

from different formulation was studied for 24 hours. Product A of T.P.S. and T.F.S. showed higher rate of permeation (1.893 0.096 and 0.984 0.059 mg/cm^2/day respectively). The pseudolatex system was noted to increase the delivery of drug more than one order of magnitude, almost in all the four formulations. The observations suggest that evenly drug distribution, surfactants and crystal appearance and crystal size could have regulated the permeation of drug. Initially in the case of pseudolatex system the skin permeation was slower than the film

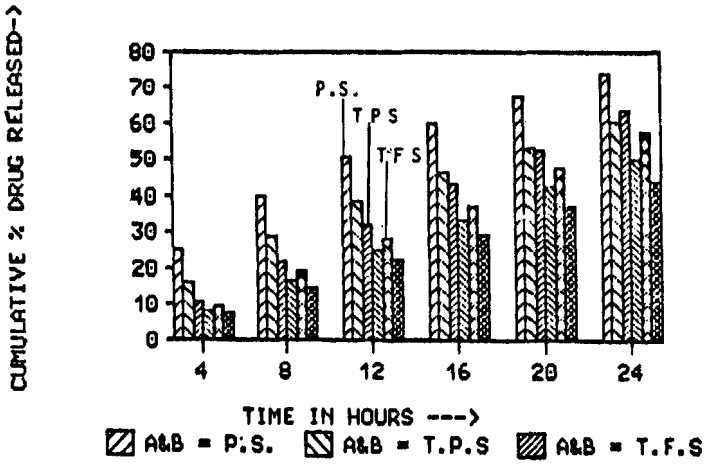

FIG 5

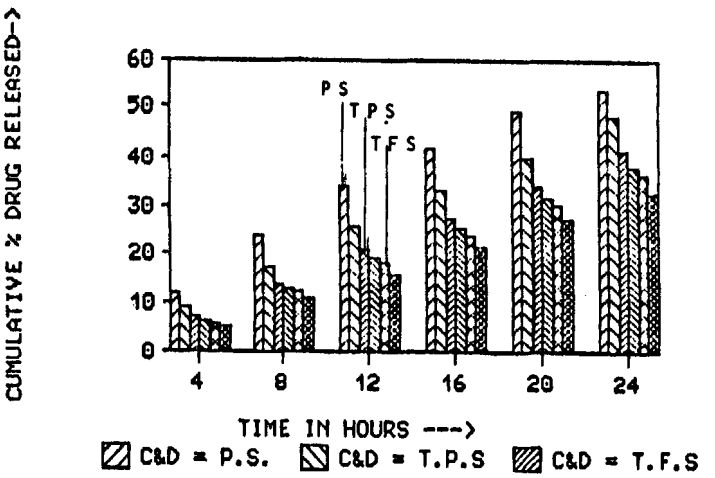

FIG 6

Amount of drug released in 24 hours from P.S. T.P.S. and T.F.S. of Product A & B (Fig 5); Product C & D (Fig 6).

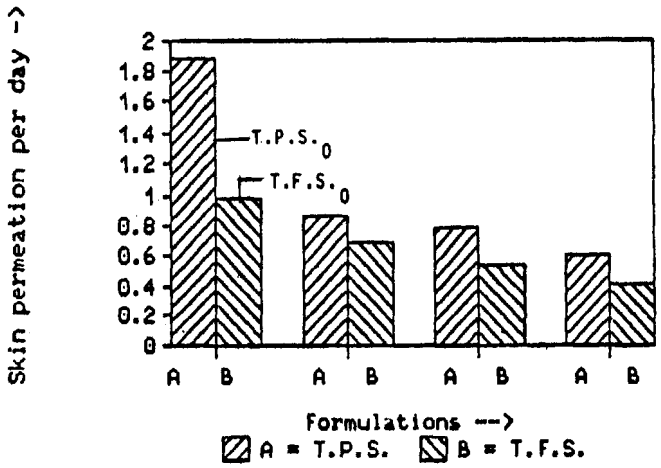

FIG 7- Bromhexine hydrochloride permeation across the skin in 24 hours from T.P.S. (with a rate controlling membrane) and T.F.S. (without rate controlling membrane) of product A = $T.P.S._0$- 1.893±0.096 mg/cm^2/day; & $T.F.S._0$- 0.984±0.059 mg/cm^2/day; product B = $T.P.S._1$- 0.879±0.048 mg/cm^2/day & $T.F.S._1$- 0.701±0.038 mg/cm^2/day; product C = $T.P.S._2$- 0.786±0.039 mg/cm^2/day & $T.F.S._2$- 0.542±0.026 mg/cm^2/day; and product D = $T.P.S._3$- 0.614±0.028 mg/cm^2/day & $T.F.S._3$- 0.419±0.021 mg/cm^2/day.

system but after 7 to 8 hours the rate increases, it can be attributed to the rate controlling membrane that avoids an immediate intimate contact of drug with skin prior to the hydration.

The bar diagram (Fig 7) shows the effect of different blends of polymers and the designing of the formulation on the skin permeation. The rate controlling membrane although considerably reduces the release flux as well as the skin permeation but still the system performs better than the film system.

Thus, it is concluded that the pseudolatex system is best suited for transdermal controlled drug delivery of bromhexine,

to avoid dose dumping and to extend the duration of action of drug. The developed pseudolatex system holds promise for further studies.

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