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IN-VITRO RELEASE AND PERMEATION KINETICS OF PENTAZOCINE FROM MATRIX-DISPERSION TYPE TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

A matrix-dispersion type Transdermal Drug Delivery System (TDS) of Pentazocine (PZ) was fabricated, using combinations of rate controlling polymers, namely Eudragits RS100 (RS), RL100 (RL), Ethylcellulose (EC) and Polyvinyl pyrrolidone (PVP), with the objective of examining the effects of formulation variables on drug-permeation profiles. In depth in-vitro drug release and skin-permeation kinetics with three different loads, and also the effects of combination of Isopropyl Myristate (IPM), as permeation enhancer, were studied using male albino mice abdominal skin. The release of PZ over a 12 hour period followed Higuchi kinetics, while in-vitro mice-skin permeation of PZ followed an apparent Zero-order kinetics over a period of 24 hours.

INTRODUCTION

Pentazocine, having both agonistic and weak opioid antagonistic activity, can be used as an analgesic for chronic severe pain (e.g., cancer, post-operative)(1). PZ, due to its short biological half-life of 2 hours (2), requires frequent dosing. Because of extensive first-pass metabolism in the liver, only about 20% of PZ enters the systemic circulation (3). Transdermal route of administration is capable of avoiding the hepatic first-pass effect (4).

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Pentazocine, with a log Potanol/water value of 4.03, can be considered as a lipophilic drug, and it may penetrate easily through the stratum corneum, which is the major hurdle to percutaneous penetration (5,6). Because of its moderately high dose, the flux through the skin may be inadequate to maintain the therapeutic PZ concentration in blood, thus needing co-administration of enhancers. Use of different enhancers have been reported (7-11) but those with Hildebrand-solubility parameters nearer to 10.5, are useful to enhance the permeation (12). Isopropyl Myristate, with a solubility parameter of 8.02, has been used to increase the permeability of PZ.

A matrix-dispersion type TDS, which earlier showed promising results with Diazepam (13), Testosterone (14) and Diclofenac Sodium (15) TDS, have been selected for PZ.

EXPERIMENTAL

Materials : Eudragits RS100 and RL100 (Röhm Pharma, Germany) Polyvinyl pyrrolidone (Loba Chemie, M.wt. appx.40,000), Polyethylene glycol 400 (Ranbaxy Laboratories), Ethylcellulose (B.D.H, England, viscosity 14 cps), Pentazocine (courtesy, Biochem Pharmaceutical Industries, Bombay, and Win-Medicare Ltd., New Delhi), Isopropyl Myristate (Aldrich, U.S.A.).

Methods :

A. Preformulation studies

Calculation of Dose : PZ needs a skin permeation rate of 77.62 mcg/hr, which has been calculated using the formula, $D=C_p x V_d x K_e$, where C_p = effective plasma concentration, V_d = Volume of distribution, K_e = the rate of elimination (16).

Fabrication of Transdermal Films :

The films were fabricated by casting method as reported earlier by Mandal et al.(13,14), using RS, RL, EC, PVP (Table I). The prepared and dried films were cut into required dimensions by a die-cutter.

Characterization of TD Films :

A. Physicochemical characterization

(i) Content uniformity : The drug content was estimated spectrophotometrically at 278 n.m. in 1(N) Hydrochloric acid. Triplicates were performed.

(ii) Film thickness : It was determined by a Comparator (Doall Company, Illinois, U.S.A.) at five separate points of a film. Triplicates were performed.

TABLE-1

Composition of TDS Films

FN.Code	Composition					
	Polymers				Enhancer	Drug
	RS100	RL100	EC	PVP	(IPM) % w/w	mg/cm²
F_1	1	1	-	-	-	8.50
F_2	-	-	1	1	-	8.49
F_3	2	1	-	-	-	8.70
F_4	-	-	4	1	-	8.50
F_5	2	1	-	-	10	9.12
F_6	-	-	4	1	10	9.01

B. Drug release study

The film sample was placed in between the donor and receptor compartment of modified Keshary-Chien diffusion cell, so as to keep the drug-releasing surface towards the receptor compartment, which was filled with a solution of 20% PEG 400 in normal saline at 32±1°C. The elution medium was stirred at 600 rpm, magnetically. Aliquots withdrawn over 12 hours were estimated spectrophotometrically at 279 n.m.

C. Skin permeation study

Abdominal skin of male albino mice was used after pre-treatment, as described elsewhere (15). The skin was fixed onto a modified Keshary-Chien diffusion cell, as described in section B. 20% PEG 400-normal saline solution was used as elution medium, at 37±1°C, being stirred magnetically at 600 rpm. Aliquots withdrawn over 24 hours were estimated at 279 n.m. spectrophotometrically. Blank was run simultaneously for each set, and calculated accordingly.

RESULTS AND DISCUSSION

Films of different compositions show minute variations in drug content, to the extent of a maximum of 5%. The maximum variations showed by the formulation F_2 is 7%, and the minimum, showed by F_6 is only 1%. Films showed uniformity in thickness, calculated in between 0.8-0.9 m.m., with a slight variation at the periphery.

Effect of Polymeric composition on release characteristics of pentazocine :

(i) In-vitro release profiles : The in-vitro release profile, depicts drug release according to matrix-diffusion kinetics model, when cumulative percent release (Q) was plotted against square root of time $\sqrt{t}$ (Fig.1). This can be explained by Higuchi's square-root kinetics equation for release from matrix-type delivery systems into sink conditions at steady state $Q=D_p (2A-C_p).C_p t^{\frac{1}{2}}$ which indicates Q and $\sqrt{t}$ follow a linear relationship. The formulations showed linearity on Q versus $\sqrt{t}$ plots, confirming square root kinetics. The release rate increased with increment of RS in RS-RL combinations. For the EC-PVP formulations, as PVP amount increasd, initial release rate increased, but gradually slowed down.

The initial augmented release with increased amounts of hydrophilic polymer, may be attributed to a greater hydration factor. Formulations F_3 and F_4 were chosen from amongst formulations F_1 to F_4, due to their maximum flux values.

(ii) In-vitro skin permeation profile : The skin permeation profiles of formulations F_3 and F_4, showed apparent zero-order kinetics, when cumulative amount permeated (Q) was plotted against time (t) (Fig.2). This can be explained by Fick's law of diffusion, under sink condition (17), as described by the equation $\dot{Q} = (DAK)/hC_d t$.

The permeation rate of PZ through the intact skin is greater for RS-RL system, than for the EC-PVP system (Table-II). This indicates, that both the delivery system as well as the skin controls the steady state permeation of PZ. The role of TDS over the control of steady state permeation of PZ is apparent from the fact that with change in release rate, there is a corresponding change in permeation rate also. Otherwise, if only the skin had controlled the steady state permeation, a proportionate increase of permeation rate along with increased release rate, would not be possible.

Effect of enhancer on in-vitro release and permeation profiles of PZ

Films with IPM as enhancer, showed greater in-vitro release rate, as compared to films without enhancer (Fig.1). The in-vitro permeation studies also showed linear profiles, and films with IPM showed greater release over 24 hours (Fig.2). The increase in release rate may be due to the formation of a two-phase continuous network within the polymer matrix. IPM has a HSP value between two extremes (δ=8.02),and may thus partition in both the lipid and polar phases of skin (12); but its lower solubility parameter makes it partition into the lipid phase to a

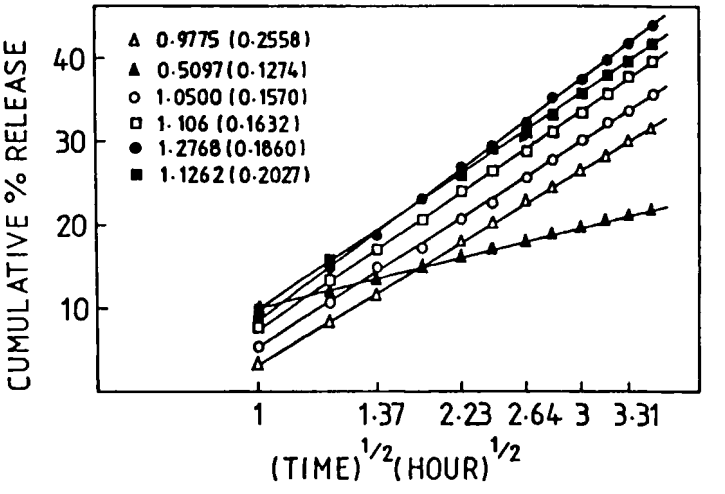

FIGURE-1

Release profiles of pentazocine from matrix type films (△—△, F_1; ▲—▲, F_2; ○—○, F_3; □—□, F_4; ●—●, F_5; ■—■, F_6). The numbers beside legend represents the steady state flux value (mg/cm²/hr$^{\frac{1}{2}}$) ± S.D. of four determinations.

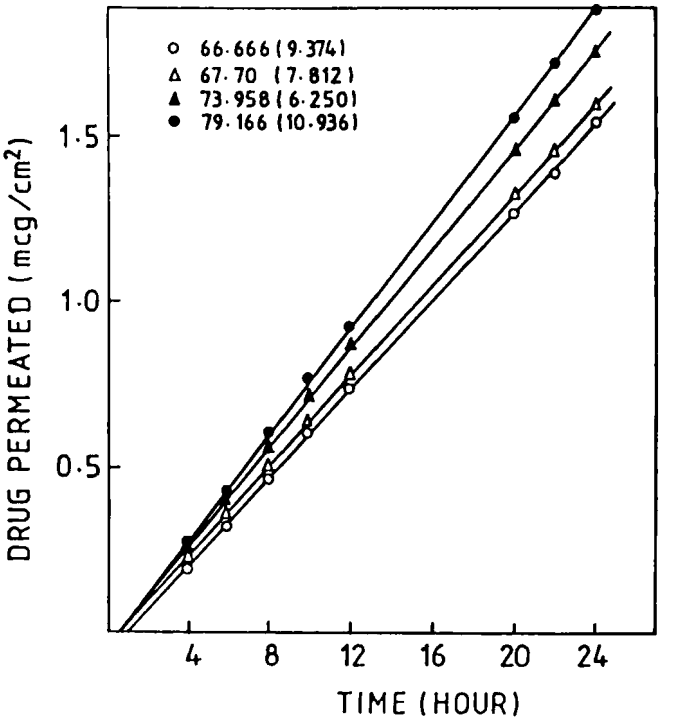

FIGURE-2

In-vitro skin permeation profiles of pentazocine. The number beside each legend represents the steady state flux value (mcg/cm²/hr.) ± S.D. of 6 determinations. ○—○, F_3; △—△, F_4; ●—●, F_5; ▲—▲, F_6

TABLE-II

Release and Permeation Flux of Films

FN.Code	Release flux ($mg/cm^2/hr^{\frac{1}{2}}$)	Permeation flux ($mcg/cm^2/hr$)
F_1	0.9775 (± 0.2558)	-
F_2	0.5097 (± 0.1274)	-
F_3	1.0500 (± 0.1570)	66.666 (± 9.374)
F_4	1.1060 (± 0.1632)	67.700 (± 7.812)
F	1.2768 (± 0.1860)	79.166 (± 10.936)
F_6^f	1.1262 (± 0.2027)	73.958 (± 6.250)

(±) standard deviation

TABLE-III

Release and permeation Flux of Films at Different Loads

FN.Code	Load mg/cm^2	Release flux $mg/cm^2/hr^{\frac{1}{2}}$	Permeation flux $mcg/cm^2/hr$
F_3	4.745	0.625 (± 0.068)	18.33 (± 5.184)
	5.653	0.700 (± 0.069)	40.00 (± 5.780)
	8.750	1.050 (± 0.157)	66.66 (± 9.371)
F_4	5.232	0.233 (± 0.0256)	21.66 (± 4.106)
	7.164	0.333 (± 0.0266)	31.66 (± 8.071)
	8.500	1.106 (± 0.1632)	67.70 (± 7.812)

(±) standard deviation

greater extent. Thus, its action on the polar phase is low, resulting in lower enhancement of skin-permeation rate.

Effect of initial drug load on release profiles

Films F_3 and F_4 were chosen for this study, incorporating three different drug loads (Table-III). Figures 3,4,5 clearly indicate an increase in both release and permeation rates, with gradual increase in drug loads, which is affirmed by the concomitant increase in flux. Thus we may postulate, that enhancement of drug release rate from the films can increase the skin permeation of PZ, and the maximum value of PZ skin permeability is yet to be attained.

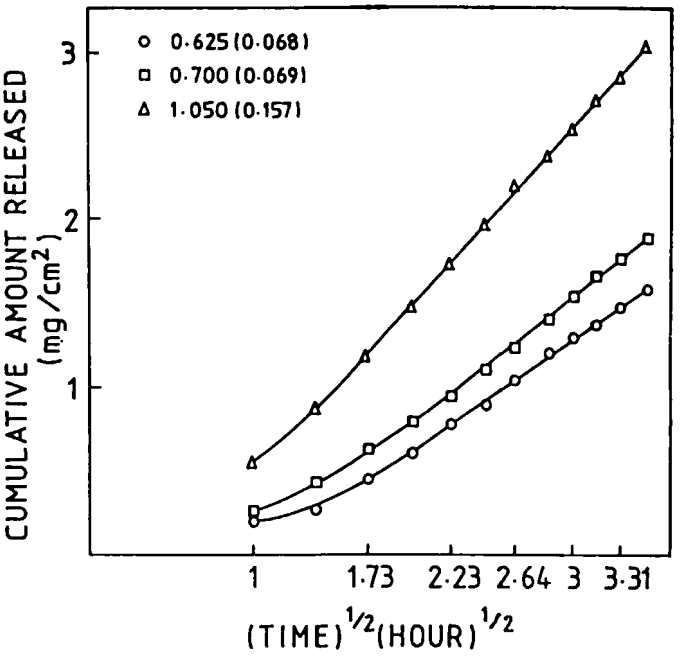

FIGURE-3

Release profiles of pentazocine from RS:RL (2:1) films at three different loads (o—o , 4.745 mg/cm², □—□, 5.6535 mg/cm²; △—△ , 8.750 mg/cm²). The number beside each legend represents the steady state flux value (mg/cm²/hr$^{\frac{1}{2}}$) ± S.D. of 4 determinations.

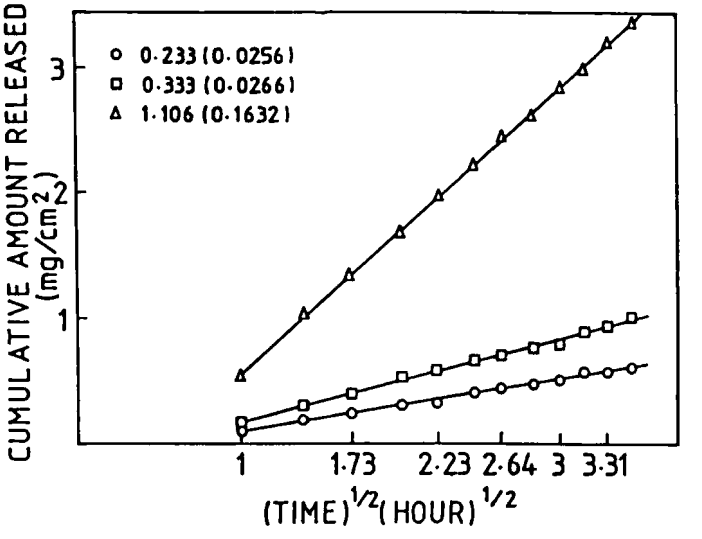

FIGURE-4

Release profiles of pentazocine from EC : PVP : (4:1) films at three loads (o—o, 5.232 mg/cm²; □—□ , 7.164 mg/cm²; △—△ , 8.500 mg/cm²). The number beside each legend represents the steady state flux value (mg/cm²/hr$^{\frac{1}{2}}$) ± S.D. of 4 determinations.

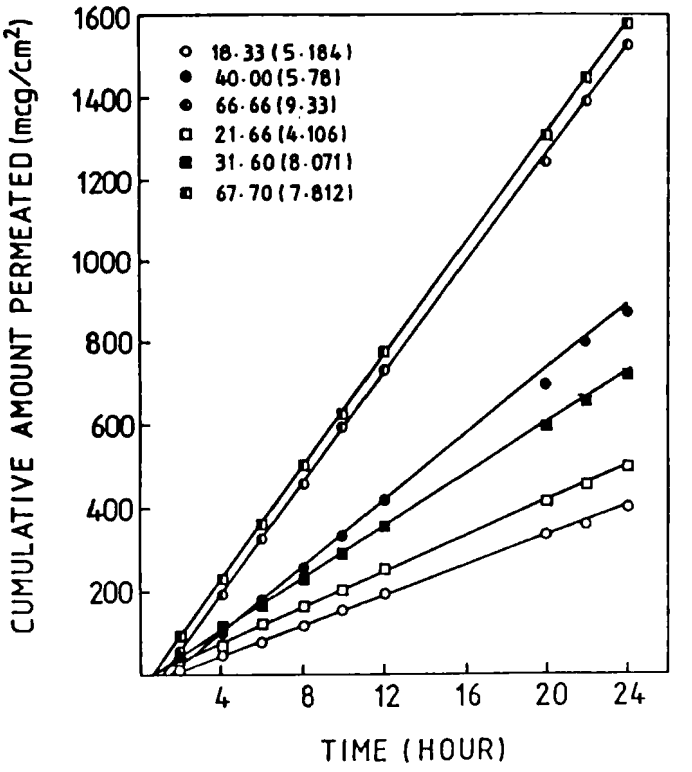

FIGURE-5

In-vitro skin permeation profiles of pentazocine from three different loads; a) From RS-RL films, o——o, 4.745 mg/cm²; ●——●, 5.6535 mg/cm²; o——o, 8.750 mg/cm²; b) From EC-PVP films, □—□ 5.232 mg/cm²; ■—■ , 7.164 mg/cm²; ▣—▣ , 8.500 mg/cm². The number beside each legend represents the steady state flux (mcg/cm²/hr) ± S.D. of 6 determinations.

The permeation rate required to maintain the therapeutic level of PZ as calculated is 77.62 mcg/hr. which is nearer to the flux value of PZ from F_5 (containing 10% IPM at a load of 9.12 mg/cm²) at 79.166 mcg/hr. Therefore, further in-vitro studies may lead to a successful formulation of TDS of pentazocine.

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