

Design and *in vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers

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Matrix-type transdermal drug delivery systems of haloperidol lactate were prepared using different ratios of ethyl cellulose (EC):polyvinyl pyrrolidone (PVP) (3:2, 2:3, 4:1, 1:2, 2:1, and 1:4) by solvent-evaporation technique. Physicochemical parameters were characterized, and dissolution studies of the formulated films were performed. In addition, solubility studies at various values of pH were carried out, and partition coefficient in octanol/water system, flux, and enhancement ratio were also evaluated. *In vitro* permeation studies were done using modified Franz diffusion cells through human cadaver skin utilizing 20% PEG 400 in normal saline. Permeation studies illustrated that 4% hyaluronidase enzyme was a good enhancer. The prepared films were subjected to scanning electron microscopy (SEM) and fourier transform infrared spectroscopy (FT-IR) spectral analysis. Higuchi and Peppas models were used for optimizing the formulation.

Key words: Chemical enhancers, EC, haloperidol lactate, optimization, permeability study, PVP, transdermal patches

INTRODUCTION

Schizophrenia^[1] has been one of the major diseases afflicting mankind in today's scenario. Haloperidol lactate, an antipsychotic drug, is supposed to be effective in the treatment of chronic schizophrenic patients. Evidence of first-pass metabolism of this drug and prolonged duration of treatment required for this particular disorder offer a major challenge in its treatment by conventional route.^[2] Long-acting preparations of these drugs may be helpful. Thus the haloperidol lactate-loaded transdermal drug delivery system (TDDS) improved bioavailability and hence is a better alternative during the prolonged period of psychiatric treatment.

Haloperidol belongs to the phenothiazine group of drugs. It produces two main kinds of motor disturbances in humans, namely, Parkinson's disease-like symptoms and tardive dyskinesia. Haloperidol is a widely used neuroleptic, administered as intramuscular depot injection or used orally to suppress psychiatric disorders. The Parkinson's disease caused by haloperidol is of great concern for psychiatrists all over the world.

The low-dose haloperidol maintenance therapy is required to control the psychotic symptoms, and long-

term prophylactic treatment is needed to prevent relapses. Long-acting modified dosage forms of haloperidol are effective in patients and can help to address the problem of poor patient compliance. The use of this drug in the lowest possible effective dosage is recommended for minimizing the risk of major side effects. Based on these hypotheses, a modified transdermal drug delivery system was developed.

Simple drug-matrix dispersion type of transdermal drug delivery system for haloperidol was designed for prolonged period of maintenance therapy instead of convention oral dosage forms. Moreover, the physicochemical characteristics of haloperidol also comply with the general requirement for designing a TDDS to a good extent.

This search and investigation is expected to add extensively to the existing knowledge and information in the field of proper drug regimen and maintenance therapy of schizophrenia with controlled-release TDDS of haloperidol.

MATERIALS AND METHODS

Ethyl cellulose was supplied by S. P. Pharmaceuticals, USA. Polyvinyl pyrrolidone (PVP) K-30 was obtained from S. D. Fine Chemicals, Mumbai, India. Dibutyl phthalate was procured from Central Drug House Ltd., New Delhi. Chloroform was obtained commercially from Ranbaxy Fine Chemicals, New Delhi. Hyaluronidase was obtained

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from Charles Pharma Ltd. Polyethylene glycol 400 and sodium chloride were purchased from S. D. Fine Chemicals, Mumbai. Haloperidol lactate was received as a gift sample from Torrent Pharmaceuticals, Ahmedabad.

Preparation of transdermal patches

TDDSs composed of different ratios of EC- and PVP-containing haloperidol lactate (6 mg/cm²) was casted on enumbra Petri dish by solvent-evaporation technique. Dibutyl phthalate^[3] was incorporated as a plasticizer at concentration of 30% w/w of dry weight of polymer, and 4% of hyaluronidase was incorporated as a permeation enhancer. Backing membrane was cast by pouring and then evaporating 4% aqueous solution of polyvinyl alcohol in Petri dish at 60°C for 6 h. The matrix was prepared by pouring the homogenous dispersion of drug with different blends of EC with PVP in chloroform on the backing membrane in Petri dish.^[4] The above dispersion was evaporated slowly at 40°C for 2 h to achieve a drug polymer matrix patch. The dry patches were kept in desiccators until use [Table 1].

Preparation of barriers: Human cadaver skin

The fresh, full-thickness (75-80 μm) human cadaver skin (of thigh region) of both sexes and age group 20 to 45 years was obtained from the Postmortem Department of Forensic Medicine, Victoria Hospital. The skin was immersed in water at 60°C for a period of 5 min. The epidermis was peeled from the dermis after exposure. The isolated epidermis (25 ± 5 μm) was rapidly rinsed with hexane to remove surface lipids,^[5] rinsed with water, and then either used or stored frozen (for not more than 48 h) wrapped in aluminum foil.

Solubility measurement

Solubility [Figure 1] of haloperidol lactate was determined^[6,7] at several values of pH, viz., 4.0, 5.0, 6.8, 7.4, 8.0, and 9.0. Excess of haloperidol lactate was added to 10 mL of phosphate buffer solutions. At each level, the samples were stirred in a conical flask for 24 h at 37°C. The pH of the samples was checked and adjusted with 0.1-M perchloric acid whenever necessary. The suspensions were filtered using a 0.45-micron Whatman filter paper. The concentration of haloperidol lactate in the filtrate was determined spectrophotometrically by measuring at 245 nm.

Partition coefficient of drug in octanol/water system

The partition coefficient of the drug was determined by taking

equal volumes of 1-octanol and aqueous solution in a separating funnel.^[8,9] In case of water-soluble drugs, a drug solution of 25 μg/mL was prepared in distilled water; and in case of water-insoluble drugs, a drug solution of 25 μg/mL was prepared in 1-octanol. Twenty-five milliliters of this solution was taken in a separating funnel and shaken with equal volume of 1-octanol/water system for 30 min and allowed to stand for 1 h. The mixture was then centrifuged at 2000 rpm for 10 min, and concentration of drug in each phase was determined spectrophotometrically by measuring absorbance at 245 nm. The partition coefficient (Kp) was calculated from the equation.

$$\text{Partition coefficient (Kp)} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}} \quad (1)$$

Permeability coefficient (P):^[10] Permeability coefficient is the velocity of drug passage through the membrane in μg/cm²/h. The permeability coefficient was calculated from the slope of the graph of percentage of drug transported versus time as,

$$P = \text{slope} \times V_d/S \quad (2)$$

where V_d = volume of donor solution;
S = surface area of tissue.

Flux (J): Flux [Figure 2] is defined as the amount of material flowing through a unit cross-sectional barrier in unit time. It is calculated by,

$$\text{Flux (J)} = P \times CD \quad (3)$$

where CD = concentration of donor solution;
P = permeability.

Enhancement ratio: Enhancement ratio was used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules. It is calculated by,

$$\text{Enhancement ratio (\%)} = \frac{\text{Permeability coefficient of drug with enhancer}}{\text{Permeability coefficient of drug alone}} \quad (4)$$

Spectrophotometer UV/VIS analysis

Haloperidol lactate was determined using Shimadzu UV

Table 1: Composition of formulations

Formulation	Polymeric blend	Drug (mg/cm ²)	Ratio (W/W)	Plasticizer dibutyl phthalate (%)	Permeation enhancer hyaluronidase (%)	Solvent system
DANU 1	EC: PVP	6	3:2	30	4	Chloroform
DANU 2	EC: PVP	6	2:3	30	4	Chloroform
DANU 3	EC: PVP	6	4:1	30	4	Chloroform
DANU 4	EC: PVP	6	1:2	30	4	Chloroform
DANU 5	EC: PVP	6	2:1	30	4	Chloroform
DANU 6	EC: PVP	6	1:4	30	4	Chloroform

spectrophotometer at 245 nm.^[11] A correlation coefficient of 0.9999 was obtained with a slope value of 0.0351.

Drug-excipient interaction study

FT-IR spectra of haloperidol lactate, ethyl cellulose, PVP, transdermal film loaded with drug, and adjuvants were taken using Perkin-Elmer FT-IR spectrophotometer (model 1600- KBr disk method). Fifty milligrams of sample and 150 mg of KBr was taken in a mortar and triturated. The triturated sample was kept in a holder and scanned between 400 and 4000 cm^{-1} . Here the patches of specified size were taken directly for the study and shown in Figures 5 and 6.

Scanning electron microscopy

The external morphology of the transdermal patch was analyzed using a scanning electron microscope (JMS 6100 JEOL, Tokyo, Japan). The samples placed on the stubs were coated finally with gold palladium and examined under the Microscope and shown in Figure 7.

Differential scanning calorimetry

The thermograms [Figure 8] of pure and prepared patches was scanned using differential scanning calorimetry. The samples were hermetically sealed in flat-bottomed aluminum pans and heated over a temperature range of 40°C to 240°C at a rate of 10°K/min using alumina as a reference standard.

Evaluation of transdermal patches

Thickness determination

The aim of the present study was to check [Table 3] the uniformity of thickness of the formulated films. The thickness was measured at five different points of the film. Using BAKER Digital caliper, the average of five readings was calculated.

Uniformity of weight

Five different patches from individual batches were weighed individually, and the average weight was calculated; the individual weight should not deviate significantly from the average weight. The tests were performed on films which were dried at 60°C for 4 h prior to testing.

Moisture content

The film was weighed and kept in a desiccator containing calcium chloride at 40°C and dried for at least 24 h.^[12] The film was weighed until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content [Figure 3].

Flatness and elongation brake

Longitudinal strips were cut out from the prepared medicated film. The flatness was determined at various points by using vernier calipers calculated. The percentage elongation brake was determined by noting the length just before the break point and substituted in the formula no 5.

$$\text{Elongation (\%)} = \frac{L_1 - L_2 \times 100}{L^2} \quad (5)$$

where L_1 = final length of each strip; and L_2 = initial length of each strip.

Moisture uptake

A weighed film kept in a desiccator at 40°C for 24 h was taken out and exposed to relative humidities of 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) respectively, at room temperature. Then the films were measured periodically to constant weights [Figure 4].

Determination of tensile strength

Tensile strength was determined by using computerized Precisa bottom-loading balance, with necessary modifications. A 1 × 1-cm patch was taken and subjected to studies.

Drug content determination of film

Four pieces of 1 cm^2 each (1 × 1 cm) were cut from different parts of the film. Each was taken in separate stoppered conical flasks containing 100 mL of suitable dissolution medium (0.1-N HCL:methanol mixture) and stirred vigorously

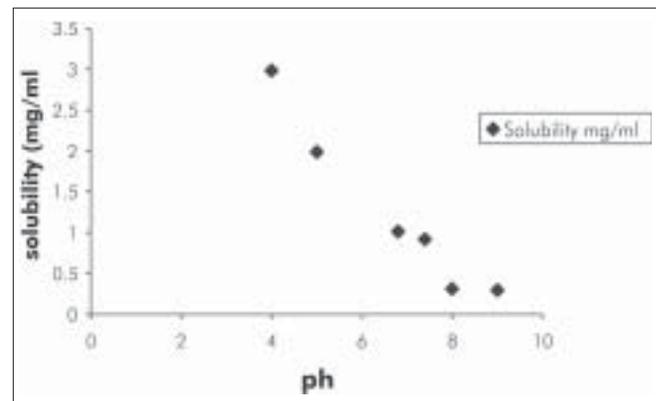


Figure 1: Solubility profile of haloperidol lactate at different values of pH of phosphate buffer

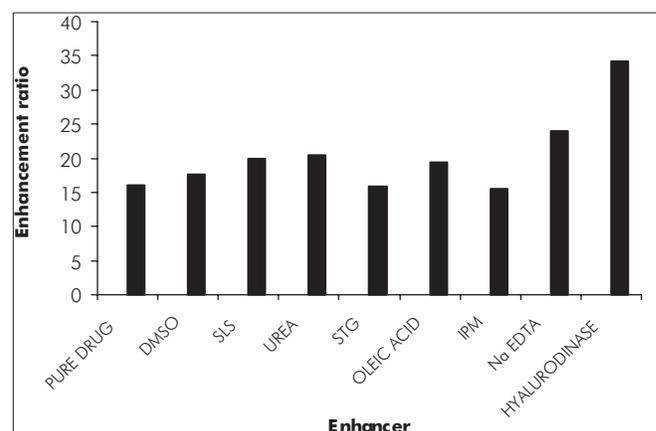


Figure 2: Bar graph showing enhancement ratio of haloperidol lactate with different enhancers

for 6 h using magnetic stirrer. The above solutions were filtered and suitable dilutions were made. Absorbances were observed using Shimadzu 160A UV-Visible recording spectrophotometer at their respective wavelengths, against a blank solution which was prepared by the same protocol but not containing drug.

In vitro diffusion study^[13-14]

Franz diffusion cell was used for the study of *in vitro* release patterns of the prepared TDDS formulations. The elution mediums of 20% PEG 400 in normal saline, and epidermis of the fresh human cadaver skin excised from the thigh portion were used as the barrier. The films were placed in between the donor and receptor compartments in such a way that the drug-releasing surface faced the receptor compartment. The receptor compartment was filled with the elution medium, and a small bar magnet was used to stir the medium at a speed of 60 rpm with the help of a magnetic stirrer. The temperature of the elution medium was maintained and controlled at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ by a thermostatic arrangement. An aliquot of 1 mL withdrawn at predetermined intervals, being replenished by equal volumes of the elution medium, withdrawal of samples was carried out for a period of 24 h. The drug concentration in the aliquot was determined spectrophotometrically and was calculated with the help of a standard calibration curve and the data was shown in Figures 9 and 10.

Data analysis

The pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) could be represented by a zero-order kinetic equation. Hixson and Crowell (1931) recognized that the particle regular area is proportional to the cubic root of its volume. Colombo *et al.* suggested that the quantity of drug from the matrix-type delivery system is often analyzed as a function of the square root of time, which is typical for a system where drug release is governed by pure diffusion. However, this relationship in a transdermal system is not justified completely as such systems can be erodible. Therefore, analysis of drug release from transdermal system must be performed with a flexible model that can identify the contribution to overall kinetics. Dissolution data was treated with different release kinetic equations.

Zero-order release equation

$$Q = k_0 t \quad (6)$$

Higuchi's square root of time equation

$$Q = k_H t^{1/2} \quad (7)$$

First-order release equation

$$\log Q_t = \log Q_0 + Kt/2.303 \quad (8)$$

Korsmeyer-Peppas equation

$$F = (M_t/M) = K_m t^n \quad (9)$$

where Q is the amount of drug release at time t ; M_t is drug release at time t ; M is the total amount of drug in dosage form; F is fraction of drug release at time t ; K_0 is zero-order release rate constant; K_H is Higuchi square root of time release rate constant; K_m is a constant dependent on geometry of dosage form; and n is diffusion exponent indicating the mechanism of drug release. If the cylinder value of n is 0.5, it indicates fickian diffusion; if between 0.5 and 1.0, anomalous transport; 1.0 indicates case-II transport; and higher than 1.0, super case-II transport [Table 3].

RESULTS AND DISCUSSION

The matrix-type transdermal films of haloperidol lactate were prepared by solvent-evaporation technique using combination of hydrophilic and lipophilic polymers. PVP is added to an insoluble film former, EC, that tends to increase its release rate. The resultant can be contributed to the leaching of soluble component, which leads to the formation of pores and then decrease in the mean diffusion path length of the drug molecules. PVP acts as a nucleating agent that retards the crystallization of the drug and enhances the solubility of the drug in the matrix by sustaining it in an amorphous form.

Partition coefficient of haloperidol lactate, in octanol/water system was found to be 1.248. Solubility and permeability of haloperidol lactate were evaluated at various values of pH of phosphate buffer. It was seen that solubility decreases with increase in the pH of phosphate buffer, and the permeability coefficient increases with increase in the value of pH.

The permeability studies of haloperidol lactate in a modified Franz diffusion cell through the human cadaver skin showed that the permeability coefficient (P) and flux of haloperidol lactate were 15.96 m/h and 95.76 $\mu\text{g}/\text{cm}^2/\text{h}$ respectively. The enhancement ratios of drug with different enhancers were evaluated using modified Franz diffusion cell through human cadaver skin. The permeability coefficient, flux, and enhancement ratio of drug with IPM were found to be 15.45 cm/h, 92.7 $\mu\text{g}/\text{cm}^2/\text{h}$, and 0.986 respectively; and with hyaluronidase, these were found to be 34.18 cm/h, 205.08 $\mu\text{g}/\text{cm}^2/\text{h}$, and 2.141 respectively [Figure 8].

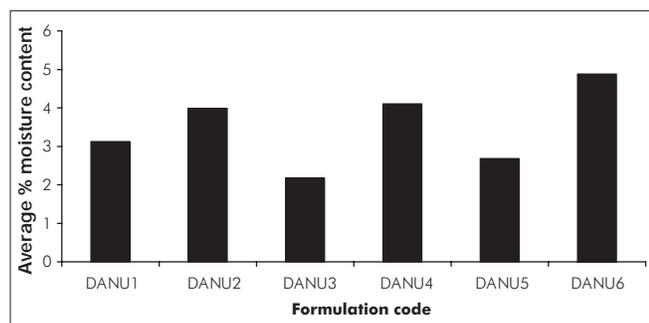
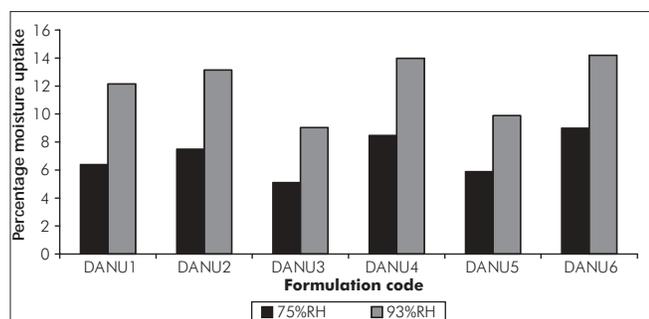
The FT-IR spectral analysis showed that there were no physical and chemical interactions between the drug and polymer [Figures 3 and 4].

Table 2: Partition coefficient of drug

Drug	Partition coefficient (Octanol/water)
Haloperidol Lactate	1.248

Table 3: Characterization of haloperidol lactate polymeric films

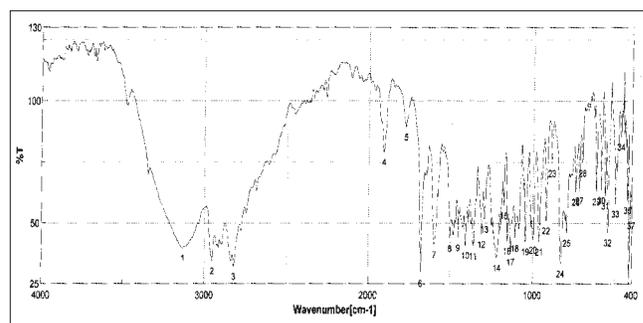
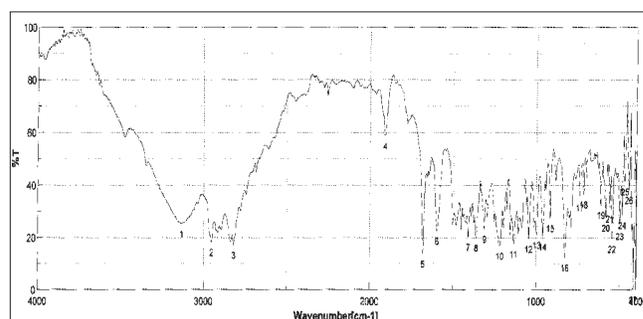
Formulation code	Thickness (mm)	Weight variation (mg)	Elongation (%)	Tensile strength (gm/cm ²)	Drug content 1 cm ² patch (%)
DANU 1	0.21	19	100	13.88	95.66
DANU 2	0.20	20	100	14.00	97.60
DANU 3	0.19	19	100	14.88	98.66
DANU 4	0.22	19	100	15.00	98.00
DANU 5	0.21	19	100	13.58	98.66
DANU 6	0.20	20	100	14.60	96.16

**Figure 3:** Average percentage of moisture content (by weight) of different formulations**Figure 4:** Percentage moisture uptake (by weight) of different formulations

The haloperidol lactate content in the EC-PVP transdermal drug delivery systems DANU 1, DANU 2, DANU 3, DANU 4, DANU 5, and DANU 6 was found to be 5.739, 5.856, 5.919, 5.88, 5.919, and 5.769 mg/cm² respectively [Table 2]. This demonstrates homogenous distribution of the drug. This is further confirmed by SEM studies [Figure 5].

A good tensile strength was found in all the films, ranging from 13.50 to 15.00 g/cm². Drug distribution was found to be uniform in the polymeric films, and its content was found to be 98.66% to 94.16% per cm² in the transdermal drug delivery system.

Moisture content and moisture uptake [Figures 1 and 2] can cause significant changes in properties such as reduced crushing strength, increased pore diameter in the patches containing hydrophilic polymer. But the moisture content in our preparations was found to be low, and it varied very little in the formulations. This little moisture content helps the

**Figure 5:** IR spectra of pure drug, haloperidol lactate**Figure 6:** IR spectra of haloperidol lactate with ethyl cellulose and polyvinyl pyrrolidone

formulations to be stable and prevents them from becoming a completely dried, brittle product. Low moisture uptake also protects the materials from microbial contamination and avoids bulkiness of the patches.

The mean ($n = 3$) of cumulative amounts of drug released per cm² of the film after 24 h from the preparations DANU 1, DANU 2, DANU 3, DANU 4, DANU 5, and DANU 6 was found to be 65.58%, 74.32%, 63.45%, 88.35%, 68.67%, and 81.59% respectively.

The dissolution and diffusion data of most of the formulations fitted well into the Higuchi model, and the data fitment of the release profile done using Korsmeyer-Peppas model showed values of diffusion coefficient obtained to be in the range of 0.37 to 0.74 [Table 4]. The mechanism of drug release in these cases was known to follow anomalous transport mechanism, i.e., the drug was released by initial swelling and followed anomalous transport.

Table 4: Diffusion-data treatments of patches of batch DANU 1 to batch DANU 6

Batch	Zero order		First order		Higuchi		Korsmeyer peppas		
	K_0	r^2	K_1	r^2	Kh	r^2	n	r^2	Km
DANU 1	2.818	0.932	0.019	0.975	13.460	0.9342	0.659	0.978	9.315
DANU 2	3.109	0.950	0.024	0.994	14.494	0.9434	0.648	0.9766	10.224
DANU 3	2.744	0.933	0.018	0.973	12.983	0.9323	0.680	0.983	8.594
DANU 4	3.199	0.959	0.034	0.978	16.719	0.9856	0.439	0.997	19.052
DANU 5	2.750	0.925	0.019	0.976	14.781	0.9770	0.532	0.992	13.757
DANU 6	2.911	0.889	0.026	0.981	18.817	0.9164	0.376	0.996	24.855

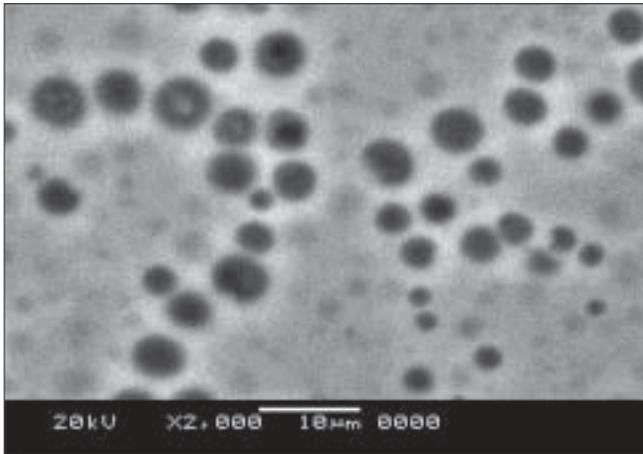


Figure 7: SEM photographs of haloperidol lactate with ethyl cellulose and polyvinyl pyrrolidone

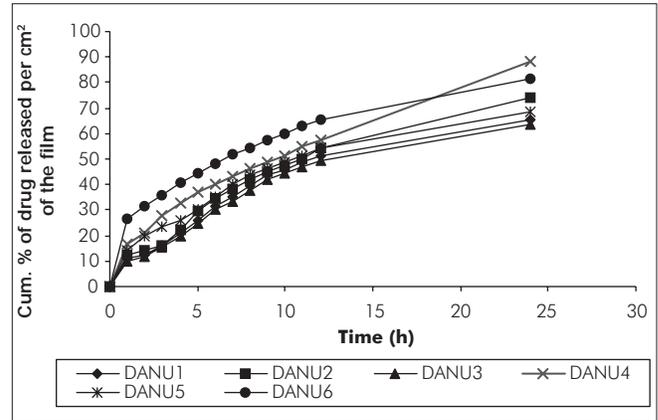


Figure 9: In vitro skin permeation profile of haloperidol lactate from the formula DANU 1, DANU 2, DANU 3, DANU 4, DANU 5, and DANU 6 through human cadaver skin in 20% PEG 400 in normal saline ($n = 3$)

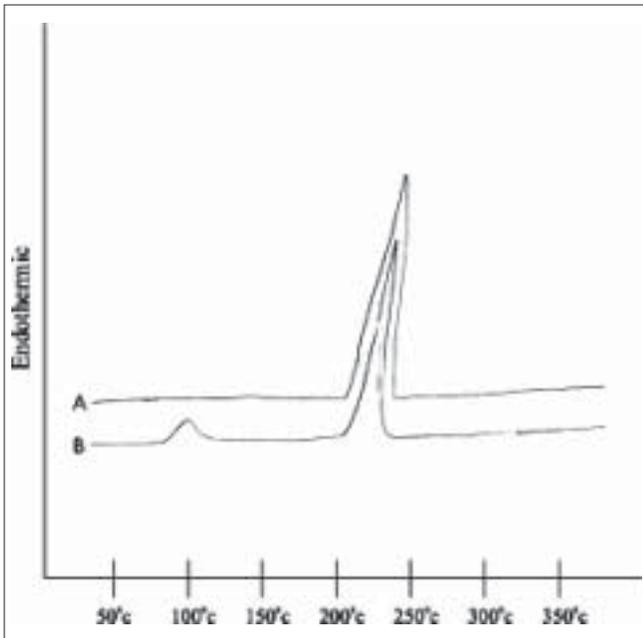


Figure 8: DSC spectra of drug and physical mixture, (A) - Haloperidol lactate, (B) - Mixture A (ethyl cellulose/PVP and drug film)

In this study, most of the formulations followed the Higuchi square root release kinetics ($k = 12.983$ to 18.817 ; and $R^2 = 0.9164$ to 0.9856). Formulations revealed linearity in the Q versus square root of time plots. Confirming square

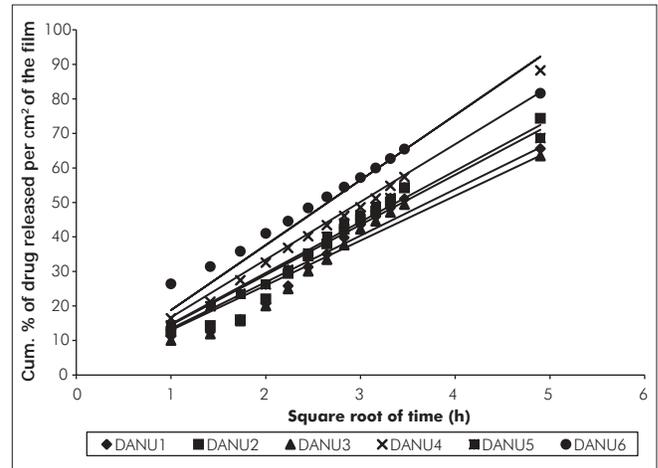


Figure 10: In vitro skin permeation profile of haloperidol lactate incorporated in transdermal patches DANU 1, DANU 2, DANU 3, DANU 4, DANU 5, and DANU 6 through human cadaver skin in 20% PEG 400 in normal saline. Data shows cumulative percentage of drug per cm^2 against square root of time (Higuchian plots): mean ($n = 3$)

root kinetics, the release rate increased with increment of PVP in EC-PVP combination.

CONCLUSION

In this study, different ratios of EC and PVP transdermal haloperidol lactate patches were formulated using 4%

hyaluronidase as a permeation enhancer. It can be reasonably concluded that haloperidol lactate can be formulated into transdermal polymeric patches to prolong its release characteristics. Thus the formulation DANU 1 (EC:PVP, 1:2) was found to be the best for a sustained-release once-a-day formulation.

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REFERENCES

1. Howells JG. *The Concept of Schizophrenia Historical Perspectives*. 1st ed. Washington: American Psychiatric Press; 1991. p. 18.
2. Hardman JG, Limbird LE. Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. New Delhi: McGraw Hill Medical Publishing Division; 2001. p. 496.
3. Lec ST, Yak SH, Kim SW, Berner B. One way membrane for transdermal drug delivery systems/system optimization. *Int J Pharm* 1991;77:231-7.
4. Krishnaiah YS, Satyanarayana V, Karthikeyan RS. Effect of the solvent system on the *In vitro* permeability of Nicardipine hydrochloride through excised rat epidermis. *Indian J Pharm Sci* 2002;5:124-30.
5. Sutariya V, Mashru R, Sunkalia MS. Transbuccal delivery of lomotrigine across porcine buccal mucosa invitro determination of roots of buccal transport. *J Pharm Sci* 2005;8:54-62.
6. Mashru R, Sutariya V, Sankalia M, Sankalia J. Transbuccal delivery of lamotrigine across porcine buccal mucosa: *In vitro* determination of routes of buccal transport. *Pharm Pharma Sci* 2005;8:54-62.
7. Shah JC, Ross JS. Reduction in skin permeation of n,n-diethyl-m-toluamide by altering the skin/vehicle partition co-efficient. *J Control Release* 2000;67:211-21.
8. Pugh WJ, Hadgraft J. Prediction of human skin permeability coefficients. *Int J Pharm* 1994;103:163-78.
9. Hsieh DS. Drug permeation enhancement. Vol.62. New York: Marcel Dekker; 1994. p. 47.
10. Deasy PB, McDaid DM. Formulation development of a transdermal drug delivery system for Amlodipine base. *Int J Pharm* 1996;133:71-83.
11. Jain NK. *Advances in controlled and novel drug delivery*. 1st ed. New Delhi: CBS Publishers; 2001. p. 108.
12. Koteswar UN. Preparation and evaluation of captopril transdermal matrices. *Indian Drugs* 1992;29:680-8.
13. Udupa N, Pandey N, Praveen SH. Formulation and evaluation of Nimesulide transdermal drug delivery systems. *Indian J Pharm Sci* 2000;62:376-9.
14. Ghosal SK, Bhattacharya M, Mandal SC. *In vitro* release and permeation kinetics of pentazocaine from matrix dispersion type transdermal drug delivery systems. *Drug Dev Ind Pharm* 1994;20:1933-41.

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