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RESEARCH PAPER

Transdermal Drug Delivery System of Haloperidol to Overcome Self-Induced Extrapyramidal Syndrome

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ABSTRACT

Haloperidol (HAL), an antipsychotic, is associated with side effects of drug-induced extrapyramidal syndrome (EPS) in conventional monotherapy. Controlled released transdermal dosage form (TDDS) of the drug was designed for maintenance therapy. Matrix-diffusion type transdermal film of HAL was designed with Eudragit NE 30D copolymer without permeation enhancer in different combinations. For the feasibility studies, all standard evaluations were performed, and their results pointed toward the suitability of TDDS. The drug release and permeation studies in Franz diffusion cell in 20% PEG-normal saline followed the Higuchi equation with optimum correlation coefficient. The neuroleptic efficacy was confirmed by maximum graded response in a rotarod apparatus. The neuroleptic-induced catatonia (EPS) in albino rats was minimum with a score of zero over a 72-hr study. The pharmacokinetic parameters in rabbit model showed a very significant prolongation of action up to 72 hr with steady-state plasma concentration (cp_{ss}) of 11.58 ng/mL. Thus, the HAL-loaded TDDS improved the therapeutic profile by preventing the neuroleptic-induced EPS and might be a better alternative during its long period of psychiatric treatment over conventional dosage form.

Key Words: Haloperidol; Transdermal; Extrapyramidal; Self-induced.

INTRODUCTION

Insanity has afflicted humanity throughout history.[11] Psychosis, in particular schizophrenia, has been called the worst disease affecting mankind; even AIDS not exempted.[1] Effective treatment, although not curative, has made an important difference in the course of the disorder, sharply reducing

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symptoms and the rate of relapse.[24] The phenothiazine group of drugs has transformed the lives of many schizophrenics by abolishing troublesome symptoms and permitting return to more normal behavior.

The evidence that continued medication is beneficial to chronic schizophrenia patients is now almost universally accepted.[14] Long-acting preparations of these drugs may be helpful because they are difficult to use by oral monotherapy for their narrow therapeutic range.[2]

Haloperidol (HAL), a phenothiazine group of drugs, produces two main kinds of motor disturbances in man, namely Parkinson's like symptoms and tardive dyskinesia.[4,15,17] Haloperidol (HAL) 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 by 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.[5,8] Long-acting modified dosage forms of haloperidol drugs are effective in patients and can help to address the problem of poor compliance.[9] The use of this drug in the lowest possible effective dosage is recommended for minimizing the risk of the major side effects.[5,21] Based on these hypotheses, we thought to develop a modified drug delivery system that specializes in phasing the drug administration so that the optimum amount of the drug is provided to control the disease conditions along with minimum side effects.

Simple drug-matrix dispersion type of transdermal drug delivery system (TDDS) of HAL is designed for prolonged period of maintenance therapy instead of conventional oral dosage forms. Moreover, the physicochemical characteristics of HAL (e.g., melting point 151°C and log *P* value 4.3) also comply with the general requirement for designing a TDDS to a good extent.

This work is expected to add to the existing knowledge in the field of proper drug regimen and maintenance therapy of schizophrenia with controlled release TDDS of haloperidol, in order to avoid the self-induced extrapyramidal Parkinson's syndrome.

MATERIALS AND METHODS

Materials

Eudragit NE 30D, a methacrylic ester copolymer, was a gift sample from M/S Rohm Pharma, West Germany. Polyvinyl alcohol (PVA, molecular weight 1,25,000), a water soluble polymer from Loba Chemicals, Mumbai, glycerol (L.R.), PIB, USP adhesive tape, and aluminum foils were used as received.

Formulation of the Transdermal Films

The transdermal films were prepared based on the approaches of matrix diffusion-controlled systems.[20] The drug reservoir was prepared by homogeneously dispersing drug particles in a polymer matrix and thereby it was molded accordingly. PVA (5 g) was dissolved in 50 mL distilled water with heating at 70°C to get a clear solution (10%).

Eudragit NE 30D is a milky-white liquid of low viscosity when poured onto a glass plate, and a clear film forms upon evaporation of the water. Here, Glass Substrate Technique was employed for the preparation of film. The required amount of glycerol was added to PVA solution and mixed properly. The drug was dispersed into it. The mixture was cooled to 30°C. The required quantity of Eudragit NE 30D was mixed with this dispersion and mixed properly in order to get the uniform distribution of the drug. After thorough mixing, the polymer casting dispersion was left to stand until all air bubbles had disappeared. Then it was poured into a clean, dry petri dish. A bowl containing mercury was arranged and the petri dish containing polymer solution was kept on the mercury surface in order to get the uniform thickness of the film. The polymer solution was left to dry at room temperature in a dust-free atmosphere. After thorough drying, the films were taken out and stored in desiccators.

Drug loaded film was circularly cut to get an effective surface area of 2.89 cm^2 since the exposed surface area of the patch to the receptor fluid in Franz diffusion cell was about 2.89 cm^2. The cut portion of the film was placed onto the central portion of a circular USP adhesive tape of approximately 5 cm^2. A circular shaped aluminum foil of 5 cm^2 area was used as the peel strip. On the other side of the adhesive tape the same circular shaped (5 cm^2 area) aluminum foil was pasted using the adhesive polyisobutylene in order to prevent the penetration of moisture into the device.

EVALUATION

All the prepared formulations of transdermal patches containing haloperidol were

subjected to different evaluations including the blank patches.

Uniformity of Weight

This was done by weighing the three different patches of the individual batch taking the uniform size at random and calculating the average weight. The individual weight should not deviate significantly from the average weight of the three. The tests were performed on films, which were dried at 60°C for 4 hr prior to the testing.

Determination of Tensile Strength

Mechanical properties of the polymer films were conveniently determined by measuring their tensile strength. Shear strength is the measurement of the cohesive strength of the polymer film. If the transdermal device has adequate cohesive strength, it will not slip after application and will leave no residue upon removal. The molecular weight, degree of cross-linking, and the composition of the polymer can influence it. The film can be deformed if cracks or voids grow and propagate under stress; if the specimen, which stretched slowly their rate of propagation, keeps up with the rate of elongation of the entire specimen. Extensive propagation of cracks or voids lowers the tensile strength of the specimen because the intact material next to these flows bears the entire load distributed over a reduced area and ruptures. Thereby, the tensile strength is determined as the stretching force applied to the sample at which point it breaks. These measurements were performed on a dumbbell shaped specimen. A specified weight was hung from the film through the specimen such that a pulling force was created. The force applied on the load cell of the apparatus was measured in g/cm^2. The size of patches taken in each case was 3 cm × 1 cm. This test was determined as per ASTM system.

Moisture Absorption Capacity

The selected films were dried (60 for 4 hr), weighed, and kept under different room conditions and the wet weight of the polymer was recorded at the end of the 24 hr. The percentage water absorbed by the film was calculated from these weights. The relative humidity and temperature were recorded with humidimeter and thermometer, respectively.[3]

Thickness Determination

The aim of the present study was to check the uniformity of thickness of the formulated films. The thickness was measured at five different points of the film, using Karl Fronk micrometer. The average of five readings was calculated.[19]

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films when subjected to frequent extreme conditions of folding. This study was carried out on a simple instrument fabricated in the laboratory, consisting of a fixed lower jaw and an upper movable jaw, which moves at a rate of 33 strokes per minute. The dried films were held in position between the two jaws in such a way that when the upper jaw was at the uppermost position, the film was straightened, and when it was at the lowermost position, the film was completely folded in the middle. Each stroke consisted of a cycle of one downward movement followed by a subsequent upward movement and the film was said to have undergone one fold. The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks on it. Each film was subjected to 1000 such strokes and if the film developed visible cracks or breaks, the specimen's endurance was recorded as $X/1000$, where X is the number of folds undergone by the film. If no visible cracks or breaking of the films were observed even after 1000 strokes, the films were declared to have good endurance.

Flatness

The prepared films were checked for their flatness with the help of vernier calipers, and the percentage flatness of different formulations was recorded.

Drug Content Determination of Films

Four pieces of 1 cm^2 each (1 cm × 1 cm) were cut from different parts of the film. Each were taken in separate stoppered conical flasks containing 25 mL of suitable dissolution medium (isopropanol–HCl mixture), stirred vigorously for 30 hr using magnetic

stirrer. The above solutions were filtered and suitable dilutions were made. Absorbance was observed using Shimadzu 160A, UV visible recording spectrophotometer at their respective wavelengths, against a blank solution which was prepared by following the same procedure containing the patch without drug. Standard curve of haloperidol in isopropanol-dilute hydrochloric acid at the wavelength of 245 nm was determined.

Microbial Study

Bacteria and fungi may proliferate under occlusive conditions due to favorable factors like increased temperature, hydration, pH, etc. The potential of TDDS for promoting growth of microorganisms can be evaluated by qualitative/quantitative bacteriological cultures. The filmstrips of different formulations were cut into small strips of $2\,cm^2$ and aseptically transferred into each conical flask containing 20 mL of media for bacterial growth and media for fungal growth. The inoculums sample was spread or made colonies uniformly on the agar plate. These plates were incubated at $37 \pm 0.5^{\circ}C$ for 2 days. After incubation, the colonies with turbidity, which were formed by microorganisms, were observed under microscope with Gram staining. After staining, red color appeared for Gram-negative bacteria but no violet to blue color for Gram-positive bacteria was found.

Compatibility Study by FTIR Spectroscopy

FTIR spectra of haloperidol, Eudragit NE30D, transdermal film loaded with drugs and adjuvant were taken using Perkin–Elmer FTIR spectrophotometer, Model 1600 (KBr disk method). 50 mg of sample and 150 mg potassium bromide were taken in a mortar and triturated. The triturated sample was placed in a pellet maker and compressed at $10\,kg/cm^2$ using a hydraulic press. The pellet was kept a sample holder and scanned from 400 to $4000\,cm^{-1}$. Here the patches of specified size were taken directly for the study.

In Vitro Diffusion Study

For the study of in vitro release patterns from the prepared TDDS formulations, a Franz diffusion cell was used. An elution medium of 20% PEG 400 in normal saline was used. The films were placed in between the donor and receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. The receptor compartment was filled with the elution medium. A small bar magnet was used to stir the elution medium at a speed of 600 rpm with the help of a magnetic stirrer. The temperature of the elution medium was maintained and controlled at $37 \pm 1^{\circ}C$ by a thermostatic arrangement. An aliquot of 2 mL was withdrawn at predetermined intervals, being replenished by equal volumes of the elution medium. This was carried out for a period of 72 hr. The drug concentration in the aliquot was determined spectrophotometrically and was calculated with the help of a standard calibration curve.

In Vitro Skin Permeation Studies

Pretreated abdominal skin of albino rat was used in the Franz diffusion cell. Hairs from the abdominal region were clipped electrically and the full thickness skin was taken out and then trimmed to remove the adherent fatty materials.[12] Next, the skin sample was examined microscopically to ensure its integrity. The transdermal film sample was fixed on 3-cm^2 sample of skin in such a way that when the skin was placed in between the donor and receptor compartments of the Franz cell, the drug releasing face was toward the receptor compartment. The medium and other conditions were kept as per the drug diffusion study. Average values were taken for determination of permeation rate.

Aging Studies of Transdermal Films

The transdermal formulations with skin permeation rate profiles meeting the legal requirements and other physicomechanical characteristics meeting in-house specifications were fabricated and submitted to a long-term (180 days) aging study program under single storage conditions (i.e., $20^{\circ}C$ and 45% RH). Throughout the course of the aging study, triplicate samples were taken at three sampling times (i.e., 0, 90th, and 180th day) and evaluated for physical texture, using drug release and skin permeation rate profiles as the indicators, and for the drug recovery assay as the indicator of chemical stability of haloperidol.

In Vivo Pharmacological Studies

Tranquilizing Efficacy by General Behavioral Response and Rotarod Method

Tranquilizers usually cause a state of sedation or indifference in mice, especially at higher doses. The presence or absence of sedation in mice given the test substance is noted. The motility is to be disturbed as a result of motor incoordination on neuroleptic drugs. This experiment was carried out by rotarod method.[22,23] Mice are placed on a scraped rod of aluminum, 2 cm in diameter, turning at the rate of 10 rotations per minute. Circular sections divide the linear space of the rod into four lengths so that four mice are tested together. The control mouse is able to remain on the rod for longer than 300 sec. The treated mice are placed on the rod at intervals and the time of the fall from the rod is noted. The test is terminated at 300 sec. From the number of mice in a group that fall off the rod before 300 sec, the ED_{50} may be calculated for any given interval after administration of the test substance. The general behaviors are observed on selected batches for a period of 24 hr and the observations noted.

Evaluation of Drug-Induced Catatonia to Find Out the Extent of EPS

The degree of drug-induced catatonia (extrapyramidal side effects of haloperidol) was studied in albino rats. Twelve-hour fasted rats (200–225 g) were divided into four groups consisting of six animals per group. Different formulations were administered either orally through oral needle or by transdermal patch, one at a time in the equivalent dose. All oral formulations were suspended in 0.5% w/v carboxy methyl cellulose (CMC) solution and immediately administered.[16] Group I—Received only 0.5% w/v CMC suspension, 1 mL/kg, which served as the solvent control. Group II—Powdered drug sample of haloperidol suspended in 0.5% w/v CMC. Group III—Powdered marketed tablets HALO of equivalent doses in 0.5% w/v CMC. Group IV—Transdermal patch with drug powder (TPH_2) of equivalent dose fixed in dorsal area.

After administering the preparations, the degree of catatonic response was observed at different intervals for a period of 72 hr.

Stage I—Rats move normally when placed on table, score = 0. Stage II—Rats move only when touched or pushed, score = 0.5. Stage III—Rats move on the table with front paws set alternatively on a 3-cm-high block, fail to correct the posture within 10 sec, score = 0.5 for each with a total score = 1.0 for this stage. Stage IV—Rats fail to remove the paws when the front paws placed alternatively on 9-cm block, score = 1.0 for each with a total score = 2.0 for the stage.

Thus, for a single rat, the maximum possible score would be 3.5, revealing total catatonia.

Primary Skin Irritation Test

A 7-day primary skin irritation testing was carried out in two groups of New Zealand white rabbits (females, nulliparous and not pregnant). Group I: One rabbit as the control, Group II: Three rabbits each received one placebo in the left pinna and one medicated patch in the right pinna. The TDDS was allowed to remain for 72 hr. Histopathological examination for appearance of red flares, wheals, or rashes at the application site was performed after removal of the patches for a 7-day observation period. The skin irritation reactions were measured on a 0 to 3 scale of none, mild, and moderate to permit the discrimination. This is to be compared in respect of the control.

A system, which results in no erythema or scaling (0 rating), is safe. Materials which induce marked irritation (+2 or +3) are likely to induce significant contact irritation during clinical use.[20]

Table 1. Preparation of haloperidol transdermal patches.

		Constituents in 25 mL dispersion			
Sl. no.	Batch code	Eudragit NE 30D (mL)	10% PVA (mL)	Glycerol (mg)	Haloperidol drugs
1	TPH_1	2	5	2	Without drug
2	TPH_2	2	5	2	10 mg pure drug

Table 2. Physical characteristics for films.

Batch code	Average weight of the three patches of size 1.0 cm^2 (mg)	Tensile strength (g/cm^2)	Film thickness (μm)	Folding endurance (X/1000)	Flatness (%)	Drug content efficiency/cm^2 (%)	Percentage of moisture absorbed at 88% RH, 17°C
TPH_1	2.79 (0.27)	13.33	25.45 (0.98)	0.987	100	0	22.5
TPH_2	3.20 (0.33)	15.00	28.88 (1.88)	1.012	100	93.8	22.2

Note: $n = 3$; ( ) ± standard deviation.

Table 3. Release flux and permeation flux of drugs from different films.

Sl. no.	Batch code	Load (mg/cm)	Release flux ($\mu g/cm^2/hr^{1/2}$)	Permeation flux ($\mu g/cm^2/hr$)
1	TPH_1	0.00	0.01 (0.00)	0.00(0.00)
2	TPH_2	0.058	6.81 (0.57)	0.70(0.03)

Note: $n = 3$; ( ) ± standard deviation.

Table 4. The ataractic activity by rotarod apparatus at different time intervals of albino mice.

Sl. no.	Dosage forms	Falling time from rotarod (sec) at			
		1st hr	6th hr	12th hr	24th hr
1	TPH_2	13	11	11	9
2	Control	300	300	300	300
3	HALO	3	4	6	13

Note: The above results showed that there was very much tranquilizing efficacy of the formulations when given to albino mice, as in all the cases, less time was taken to fall down (control—300 sec) from the rod.

In Vivo Pharmacokinetic Study in Animal Model

Eighteen healthy New Zealand white rabbits (females but not pregnant, 12; males, 6) each weighing 1.5 to 2.5 kg (average 2.0 kg) were used in this study, divided into three groups so that each group had six rabbits (males, 2 and females, 4). In the single dose study, the formulations were administered accordingly either through oral routes or application of the TDDS on rabbit's pinna following an overnight fast of 12 hr. Water was used as libitum. All the oral formulations were fed in 0.5% w/v carboxy methyl-cellulose suspension, with the help of oral needle.

For the application of the TDDS films, the pinna was first wiped out gently with a piece of cotton wool soaked in distilled water and then patted dry gently with blotting paper. An equivalent square centimeter piece of film (calculated as per body weight of rabbits) was fixed with its drug-releasing surface in contact with the pinna. Immediately after administration of the dosage forms or application of TDDS films, 2.5 mL of blood samples were withdrawn from the marginal ear vein (of the other pinna in the case of TDDS application) into heparinized (0.2 mL) glass centrifuge tube and centrifuged immediately in a cooling centrifuge at 0°C. The plasma was separated by centrifugation at 3000 rpm for 15 min and stored at −10°C. This was considered as blank. Subsequently, the same volume of blood samples was withdrawn at predetermined time intervals of 1, 4, 8, 16, 24, 48, and 72 hr and corresponding plasma was separated accordingly.

ANALYTICAL METHODOLOGY

Plasma concentrations of the drugs were measured by high-performance liquid chromatography (HPLC) method.[18,24]

A Waters® HPLC system was used for the analysis. The column used was a micron Bondapak C18 Column (10 μ, 30 cm × 3.9 mm i.d.) for haloperidol. A mixture of acetonitrile:1% ammonium acetate buffer (pH 6.85), (50:50 v/v) was used as mobile phase at a flow rate of 1.5 mL/min with an operating pressure of 3000 psig. A Rheodyne® 7125 injector with a 20-μL loop was used for the injection of samples. Detection was done at 245 nm for haloperidol, with a sensitivity of 0.005 AUFS. The mobile phase was filtered through 0.45-μ membrane filter and degassed. The separation was carried out at the room temperature of about 20°C.

Standard stock solutions of haloperidol, 500 ng/mL concentrations, were prepared separately in the mobile phase. Stock solutions of 500 ng/mL of diethyl amine for haloperidol as internal standards were prepared in the mobile phase. From the

Table 5. General behavior report in albino mice.

	HAL formulations code (hr)								
	TPH_1				TPH_2				
Observations	1	6	12	24	1	6	12	24	Remarks
Hyperactivity	+	0	0	0	+	0	0	0	In control group, all observations were normal.
Hypoactivity	0	0	0	0	0	+	+	+	
Righting reflex	0	0	0	0	+	+	+	+	
Catalepsy	—	—	—	—	—	—	—	—	
Tremor	0	0	0	0	0	0	0	0	
Ptosis	—	—	—	—	—	—	—	—	
Corneal reflex	+	0	0	0	+	0	0	0	
Sedation	0	0	0	0	0	+	+	+	

Note: +, present; —, not able to determine; 0, not present.

Table 6. Evaluation of drug-induced catatonia in albino rats.

		Catatonic picture for HAL after 72-hr study (dose—0.9 mg/kg body weight)			
Sl. no.	Formulations	Max. score (out of 3.5)	Onset (hr)	Duration of max. core (hr)	Remarks
1	Haloperidol powder drug	3.5	4.0	4.0	Max. score was observed within a short span of time.
2	Haloperidol innovator's product HALO tabs	3.5	6.0	6.0	Max. score was observed within a reasonable time.
3	TPH_2	0	Nil	Nil	No score was observed.
4	Control with blank patch	Nil	Nil	Nil	-do-

standard solutions, suitably diluted and mixed standard solutions were prepared to contain 10, 20, 30, 40, and 50 ng/mL of haloperidol containing 50 ng/mL of diethyl amine as internal standard. Each of 20 μL of standard solutions containing internal standards was injected and the chromatograms were recorded. The retention time of haloperidol and diphenyl amine (internal standard) were found to be 6.97 and 5.19 min, respectively.

A computer control data station with Baseline 810 software was used to plot the peak area vs. concentration in ng/mL. Calibration curves were obtained by using peak area ratios of standards and internal standards (response factor) vs. concentration. This was followed by injecting the sample solutions extracted from the biological fluid (plasma), and the chromatograms were recorded. From the plasma, sample solutions were made and spiked with internal standard, and response factor was used to calculate the concentration of each drug. From this concentration, amount of drug present in plasma was calculated and tabulated for haloperidol.

Extraction Procedure for Haloperidol from Plasma

Half of a milliliter of plasma was transferred into 10-mL glass stoppered centrifuge tubes and 50 ng/mL of the internal standard solution was spiked and thereafter acidified with 1.75 mL of 0.1 N hydrochloric acid. To this, 2 mL diethyl ether was added and the mixture was shaken for 5 min, and then centrifuged at 5000 rpm for 15 min. The upper ether layer was aspirated off, and then 2 mL of aqueous layer was transferred into test tube containing 0.5 mL of 1 N sodium hydroxide solution. To this, 3 mL chloroform was added. The mixture was vortexed for 10 min and then centrifuged at 5000 rpm for 15 min. The aqueous layer was aspirated off, and then the tubes were

shaken and centrifuged again to get the clear chloroform layer. Two milliliters of chloroform layer was transferred into 10-mL evaporating tubes and dried in a waterbath at 80°C. The dry residue was dissolved in 2 mL of mobile phase and then injected.

RESULTS

The matrix-diffusion type transdermal films were prepared by glass substrate technique using Eudragit NE 30D, PVA and glycerin, and the best films were prepared with 8 mL, 20 mL (10%), and 8 mg combinations, respectively. The drugs were loaded equivalent of 10 mg HAL raw drugs. The average weight of a 1-cm^2 patch lies between 2.52 and 3.53 mg. Individual weight variations were not significantly different. A good tensile strength was found in all the films ranging from 13.33 to 15 g/cm^2. Selected batches of films were tested for moisture absorption capacity at different temperature and relative humidity and a maximum percentage of moisture absorbed was found to be 22.5% at 17°C with 88% RH.

The thickness of the films was measured by Fronk micrometer, and the film thickness was found to lie between 24.47 and 30.76 μm in all the cases. A 100% flatness was observed in all the selected batches of films, and a good folding endurance was observed in all the films, indicating that the films were very much suitable for the use. The drug entrapment capacity was very good and found to be 81.2 to 93.8% for HAL.

The microbial study confirmed that no films had fungal growth, but there was some bacterial growth in some films and after isolation, it was found that the growth was due to Gram-negative bacteria.

The compatibility studies were performed in all the combinations of the formulations as such, and in some selected films, whose solvent extracts were also carried out the compatibility study by FTIR. All the observed spectral data showed that the drugs were entrapped within their respective polymers, which apparently shows that there was no drug–polymer interaction.

The in vitro drug release study was performed by Franz cell and the maximum release flux was found to be 7.38 $\mu g/cm^2/hr^{1/2}$ for HAL films. The in vitro skin permeation studies through rat skin revealed that the maximum permeation flux was 0.73 $\mu g/cm^2/hr$. The selected batches of films in the aging study were performed for a period of 180 days and no major differences of their permeation fluxes were found.

The tranquilizing efficacy of the selected batches of films was performed by rotarod method with mice, and the minimum falling time of 9 sec at 24th hr for TPH_2 was found, compared to the control of 300 sec. This indicated that the final formulations of transdermal films had sufficient therapeutic activity. This was also proved by general behavior response.

The extent of extrapyramidal syndrome of the prepared films was carried out by evaluating the HAL-induced catatonia in rats. The study revealed that TPH_2 prepared films had no catatonic score against the maximum score of 3.5.

The primary skin irritation study in rabbit's pinna revealed that mild redness was found for TPH_2 films compared to the control. In all the three rabbits (A, B, and C), right pinna showed irritation with medicated patch (TPH_2) compared to placebo, which indicates drug release might also cause the aggravation of redness of ear. The results indicated in Table 7 show mild redness in all the TPH_2 films, whereas in TPH_1 films, only one case of irritation was found, indicating that this TDDS system produced mild irritation with or without HAL drug.

The in vivo pharmacokinetic studies were performed with rabbit for formulated drug loaded

Table 7. Skin irritation study.

	Left pinna score	Right pinna score	
Group	TPH_1	TPH_2	Remarks
Control (I)	0	0	No edema, redness or flares
Test (II)			
A	+	+	Mild redness was found for TPH_2 but few for TPH_1
B	0	+	
C	0	+	

Note: +, present; 0, not present.

Table 8. Pharmacokinetic parameters of different formulations.

Sl. no.	Formulation code	C_{max}/C_{pss} (ng/mL)	t_{max} (hr)	K_{el} (hr^{-1})	AUC (0–72 hr) (ng hr/mL)	F% Rel
1	HAL drug powder	58.39(7.97)	1	0.221	281.86	100.00
2	HALO	43.32(7.66)	4	0.250	270.09	95.79
3	TPH_2	11.58(3.69)	8	0.030	487.98	173.12

Note: $n = 6$; ( ) ± S.D.; AUC (0–72 hr) was determined by trapezoidal rule. A relative bioavailability had been determined in respect of raw drug powder administered by oral route. Other data were calculated directly from graphs.

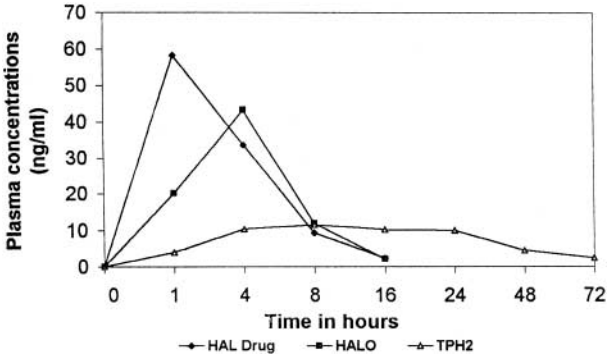

Figure 1. Formulation TPH_2 showing optimum plasma concentrations (11.58 ng/mL) compared to marketed tablet (43.32 ng/mL) and raw drug (58.39 ng/mL) nearer to toxic levels, 50 ng/mL.

films of TPH_2. After application of films, blood samples were withdrawn from rabbits and the plasma samples were analyzed by HPLC method. The different pharmacokinetic parameters were determined (see Fig. 1). C_{max} for TDDS was 11.58 (± 3.69) ng/mL against 58.39 (± 7.97) ng/mL for HAL raw drug. T_{max} for HAL films was 8 hr against 1 hr for raw drug. The K_e values for HAL films were ranged from 0.03 hr^{-1} to 0.221 hr^{-1} of raw drug. The AUC values for a 72-hr study period revealed that the HAL film was 487.98 ng hr/mL against 281.86 ng hr/mL of raw drug during a 72- hr period.

The relative bioavailability was determined with respect to raw drug powder administered by oral route. The F_{rel} for HAL film was 173.12% against 100% of pure haloperidol drug.

DISCUSSION

The review of literature has shown that low dose maintenance therapy of all conventional haloperidol is needed for prolonged psychiatric treatment with minimum occurrence of extrapyramidal side effects.[6,10] Based on this hypothesis, controlled release dosage forms of the haloperidol should be suitable for better therapeutic regimen mainly for its improved maintenance therapy. Instead of conventional oral dosage formulations, controlled release technology may be beneficial in order to improve patient compliance, with respect to reducing side effects and dosing frequency.[7,13,25]

This work embodies results of studies with HAL-TDDS. Matrix dispersion type of HAL transdermal films was prepared with Eudragit NE 30D polymer by casting over glass plate for sustaining action of the same. The prepared films were tested for their physicochemical properties. Films with acceptable qualities have been selected for further studies of in vitro release and skin permeation using albino rat skin. Finally, patches with optimum in vitro permeation rate have been taken up for in vivo pharmacological studies for extrapyramidal Parkinson's syndrome with albino rats and finally, in vivo pharmacokinetic studies in rabbits.

The marketed tablet HALO had the highest dissolution profile of 96.7% within a time period of 4 hr, whereas the release flux of the formulated transdermal patch was 7.38 $\mu g/cm^2/hr^{1/2}$ for TPH_2, and the drug release can be extended up to the required time period according to the drugs loaded and the size of the films. The permeation fluxes of the films were 0.73 $\mu g/cm^2/hr$. They also support the data for prolongation of the drug release characteristics of the formulated films.

From the results, it can be noted that TPH_2 had tranquilizing efficacy along with innovator's product HALO with respect to onset of action and duration of action for the 24-hr study on mice. But it is also to be noted that falling times were different from those of the marketed product. This is may be due to the formulation design. It is to be concluded that the prepared final transdermal films

had sufficient active drug of haloperidol, which produced the tranquilizing efficacy. This is also supported by the general behavior study of the same patches.

The basic idea of this work was fulfilled, as the catatonic picture of the formulated films had minimum to zero score against the innovator's product HALO, having maximum score of 3.5, which appeared within a short time period. These results obviously support the ideal formulation of the transdermal films of haloperidol.

The C_{max} for the marketed tablet was 43.32 ng/mL and it was very much nearer to the toxic level of 50 ng/mL. For the prepared transdermal patches, it was 11.58 ng/mL and was within the therapeutic level of 9 ng/mL. As it was far less than toxic levels, the side effects of the drug were supposed to be minimum and the same were reflected by the low catatonic score of the same formulations. The T_{max} for the marketed product was shorter than that of the formulated films, which indicates that drug-induced side effects appear very fast compared to films. The elimination rates (K_e) were comparably less than that of tablet, which indicates that the biological half-lives of the prepared films were higher than that of tablet. That means, this kind of transdermal film may be helpful for their better therapeutic profiles. The bioavailability data are also on the higher side, almost twice that of tablet formulation, which is the added advantage of these films both from bioavailability point of view and as well economical point of view due to less drug loss.

Therefore, this TDDS of haloperidol formulation may be a better alternative to conventional tablet dosage form.

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