Design and *in vitro* evaluation of haloperidol transdermal patches containing PVA-Povidone as film formers

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ABSTRACT

Matrix type TDDS of haloperidol were prepared using different ratios of Poly vinyl alcohol (PVA): Poly vinylpyrrolidone (PVP) (3:1, 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 pH, 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, 4% hyaluronidase enzyme was a good enhancer. The prepared films were subjected to SEM and FTIR spectral analysis. Higuchi and Peppas model were used for optimizing the formulation.

Key words; Haloperidol ; Transdermal Patches; PVP; PVA.

INTRODUCTION

Schizophrenia[1] has been one of the major diseases afflicting mankind in today's scenario. haloperidol , an antipyschotic drug is supposed to be effective in the treatment of the chronic schizoprenic patients. Evidence of first pass metabolism of this drug and a prolonged duration of treatment required for this particular disorder offers a major challenge in its treatment by conventional route [2]. Long-acting preparations of these drugs may be helpful because they are difficult to use by oral monotherapy for their narrow therapeutic range. Thus the haloperidol loaded TDDS improved the bioavailability and hence a better alternative during the prolonged period of psychiatric treatment.

The haloperidol is a phenothiazine group of drugs. Produces two main kinds of motor disturbances in man, namely Parkinson's 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 by psychiatrists all over the world.

The low-dose haloperidol maintenance therapy is required to control the psychotic symptoms, and long-term prophylactic treatment 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 the 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 (TDDS) of 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.

MATERIAL AND METHODS

The PVA was supplied by S.P. Pharmaceuticals USA. Polyvinylpyrrolidone (PVP K-30 was obtained from S.d.fine chemicals, Bombay. Dibutyl Phthalate was procured from Central drug house ltd, New Delhi. Water was obtained commercially from Ranbaxy fine chemicals, New Delhi. Hyaluronidase was obtained from Charles pharma ltd. Polyethylene glycol 400 and sodium chloride was purchased from S.d. fine chemicals, Bombay, India. haloperidol was received as a gift sample from Torrent pharmaceuticals, Ahmedabad.

Preparation of transdermal patches

The TDDS composed of different ratios of PVA and PVP containing haloperidol (6mg/cm^2) were prepared using anumbra petridish by solvent evaporation technique. The Dibuthy 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 petridish covered on one side with aluminum foil, at 60° for 6 h. The matrix was prepared by pouring the homogenous dispersion of drug with different blends of PVA with PVP in water on the backing membrane in petridish[4]. The above dispersion was evaporated slowly at 40° for 2 h to achieve a drug polymer matrix patch. The dry patches were kept in desiccators until use (Table. 1).

Table 1: Composition of Formulation

Formulation	Polymeric blend	Drug mg/cm^2	Ratio (w/w)	Plasticizer Dibutyl phthalate (30%)	Permeation enchancer Hyaluronida se	Solvent system
PL 1	PVA:	6	3:2	30%	4%	Water
PL 2	PVP	6	2:3	30%	4%	Water
PL 3	PVA:	6	4:1	30%	4%	Water
PL 4	PVP	6	1:2	30%	4%	Water
PL 5	PVA:	6	2:1	30%	4%	Water
PL 6	PVP	6	1:4	30%	4%	Water

Preparation of barriers: Human cadaver skin

The fresh, full thickness (75-80 µm) human cadaver skin (of thigh region) of both sex and age group 20-45 years was obtained from the postmortem department of forensic medicine, Victoria hospital. The skin was immersed in water at 60^0 for a period of 5 min. The epidermis was peeled from the dermis after the exposure. The isolated epidermis (25 ± 5µm) 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 aluminium foil.

Solubility measurement

Solubility of haloperidol was determined [6& 7] at several pH 4.0, 5.0, 6.8, 7.4, 8.0 and 9.0. Excess of haloperidol was added to 10 ml of phosphate buffer solutions. At each level the samples were stirred in a conical flask for 24 hours at 37^0. 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 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 volume 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. 25 ml of this solution was taken in 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.

$$\text{Partition coefficient} = \frac{Concentration\ of\ drug\ in\ organic\ phase}{Concentration\ of\ drug\ in\ aqueous\ phase}$$

Specatrophotometer UV/VIS analysis

            The haloperidol was determined using Shimadzu UV spPVAtrophotometer at 245 nm [11] .The standard plot indicates a slope of 0.0351 and R^2 of 0.9999.

Drug-Excipient interaction study

            FTIR spectra of haloperidol , Poly vinyl alcohol, PVP, transdermal film loaded with drug and adjuvants 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 kept in a holder and scanned between 400 to 4000 cm^{-1}. Here the patches of specified size were taken directly for the study.

Scanning electron microscopy

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

Differential scanning calorimetry

            Thermogram of haloperidol and preparation of patches were recorded using a Differential scanning calorimetry and were compared. The samples were hermetically sealed in flat-bottomed aluminum pans and heated over a temperature range of 40-240^0 at a rate of 10^0 k/min using alumina as a reference standard.

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 BAKER Digital caliper the average of five readings were calculated.
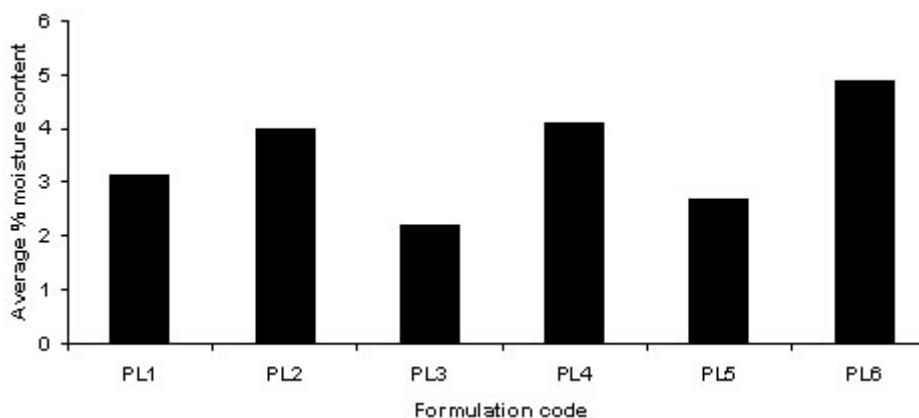

Fig. 1: Average percentage of moisture content (by weight) of different formulations.

Uniformity of weight

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

Moisture content

The film was weighed and kept in dessicator containing calcium chloride at 40° 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. (Fig. 1).

Flatness

Longitudinal strips were cut out from the prepared medicated film. The length of each strip was measured and then variation in lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

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

length of each strip and L_2 = initial length of each strip

Moisture uptake

A weighed film kept in a dessicator at 40° for 24 h was taken out and exposed to different relative humidities of 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) respectively, at room temperature. Then the weights were measured periodically to constant weights (Fig. 2).
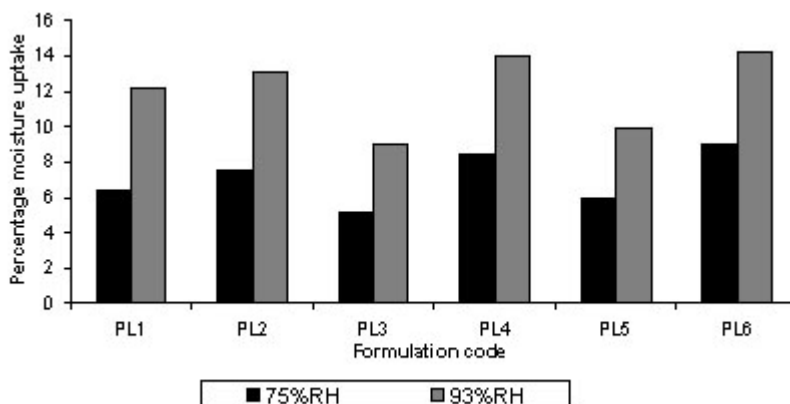

Fig. 2: Percentage moisture uptake (by weight) of the different formulations.

Determination of Tensile strength

Tensile strength was determined by using computerized precisa bottom loading balance with necessary modifications. 1 X 1 cm patch was taken and subjected to studies.

Drug content determination of film

Four pieces of 1 cm^2 each (1cm × 1cm) 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 for 6 h 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.

In vitro Diffusion Study[13-15]

Franz diffusion cell was used for the study

Table 2: Characterization of Haloperidol polymeric films

S. No.	Formulation Code	Thickness(mm)	Weight variation (mg)	Flatness	Tensile Strength (gm/cm^2)	Drug content 1cm^{2}patch
1.	PL 1	0.21	19	100%	13.88	95.66
2.	PL 2	0.20	20	100%	14.00	97.60
3.	PL 3	0.19	19	100%	14.88	98.66
4.	PL 4	0.22	19	100%	15.00	98.00
5.	PL 5	0.21	19	100%	13.58	98.66
6.	PL 6	0.20	20	100%	14.60	96.16

of in vitro release patterns from 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 was used as the barrier. The films were placed in between the donor and receptor compartment in such a way that the drug releasing surface faced towards the receptor compartment. The receptor compartment was filled with the elution medium, 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±1° by a thermostatic arrangement. An aliquot of 1ml withdrawn at predetermined intervals, being replenished by equal volumes of the elution medium 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.

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 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 system where drug release is governed by pure diffusion. However this relationship in 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. An equation proposed by Korsmeyer– Peppas for finding out the mechanism of drug release from patches of the dissolution-diffusion data obtained from the above experiments, were treated with the different release kinetic equations.

Zero order release equation;
$$Q=k_0 t \qquad \qquad ...(6)$$
Higuchi's square root of time equation;
$$Q=k_H t^{1/2} \qquad \qquad ...(7)$$
First order release equation;
$$\text{Log } Q_t = \text{Log} Q_0 + Kt/2.303 \qquad ...(8)$$
Korsmeyer– Peppas equation;
$$F=(M_t/M)=K_m t^n \qquad \qquad ...(9)$$

where Q is amount of drug release at time t, Mt is drug release at time t; M is total amount of drug in the 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, Km is 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, between 0.5 and 1.0 indicate 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 were prepared by solvent evaporation

**Table 3: Diffusion data treatments of patches of batch PL 1 to batch PL6**

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

technique using combination of hydrophilic and lipophilic polymer. PVP is added to an insoluble film former, PVA 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 co-efficient of haloperidol , in octanol / water system was found to be 1.248. Solubility and permeability studies of haloperidol was evaluated at various pH of phosphate buffer. It was seen that the solubility decreases with increasing the pH of phosphate buffer and the permeability co-efficient increases with increasing values of the pH.

The permeability studies of haloperidol in a modified Franz diffusion cell through the human cadaver skin showed that the permeability co-efficient (P) and flux of haloperidol was 15.96 m/h and 95.76µg/cm²/h respectively. The enhancement ratios of drug with different enhancers have been studied using modified Franz diffusion cell through human cadaver skin. The permeability co-efficient flux, and enhancement ratio of drug with IPM was found to be the least indicating values of 15.45 cm/hr, 92.7µg/cm²/h and 0.986 respectively and with Hyaluronidase was found to be the maximum setting values of 34.18 cm/h, 205.08 µg/cm²/h and 2.141 respectively (shown in Fig 8).

The FTIR spectral analysis showed that there were no physical and chemical interactions between the drug and polymer (shown in Fig 3 and 4).
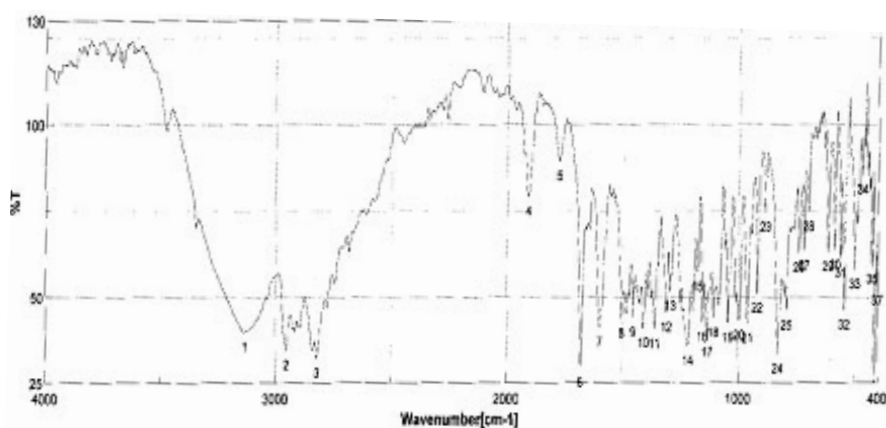
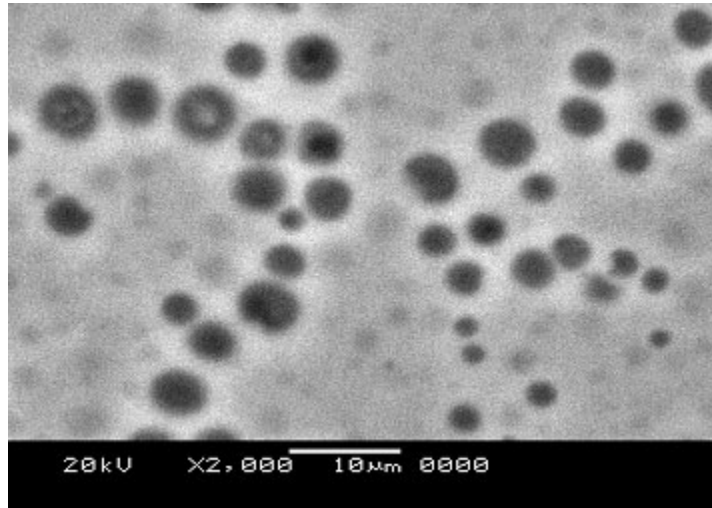**Fig. 3: IR spectra of pure drug haloperidol**

Fig. 4: SEM photographs of the haloperidol with PVA and PVP films.

The haloperidol content in the PVA-PVP transdermal drug delivery systems PL 1, PL 2, PL 3, PL 4, PL 5 and PL 6 were found to be 5.739, 5.856, 5.919, 5.88, 5.919 and 5.769 mg/ cm^2 (Table 2), respectively. This demonstrates homogenous distribution of the drug. This is further confirmed by SEM studies (Fig .5)

Table 4: Partition coefficient of drug

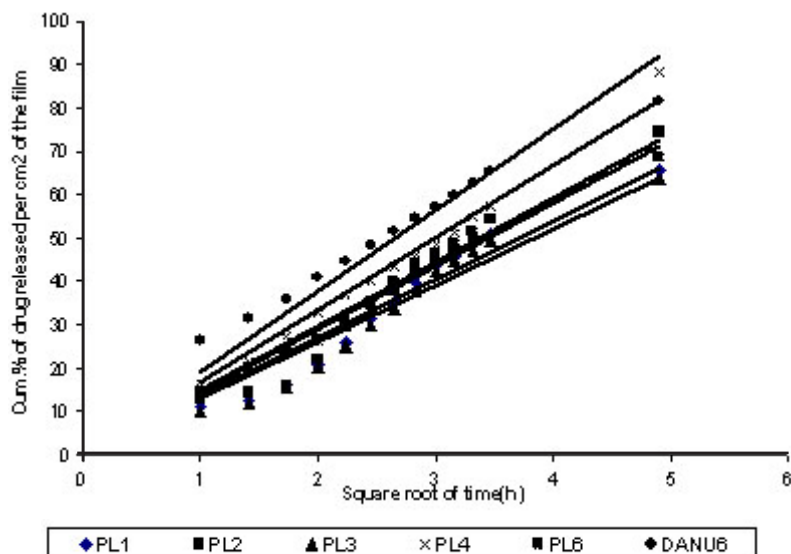| Drug	Partition coefficient (Octanol/water)
Haloperidol	1.248
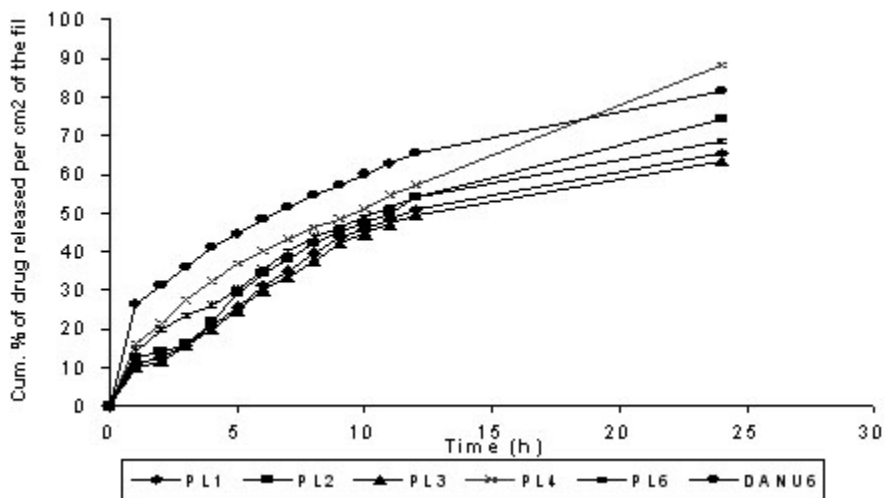
Fig. 5: *In vitro* skin permeation profile of haloperidol incorporated in transdermal patches- PL 1, PL 2, PL 3, PL 4, PL 5 and PL 6 through human cadaver skin in 20% PEG 400 in normal saline. Data shows cumulative percentage of drug per cm^2 against time: mean (n=3)

Fig. 6: *In vitro* **skin permeation profile of haloperidol incorporated in transdermal patches- PL 1, PL 2, PL 3, PL 4, PL 5 and PL 6 through human cadaver skin in 20% PEG 400 in normal saline. Data shows cumulative percentage of drug per cm² against square root of time (Higuchian plots): mean (n=3)**

A good tensile strength was found in all the films ranging from 13.50 to 15.00 gm/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 (Fig. 1and 2) were found to increase with the increase of hydrophilic polymer, PVP. It was reported that there were significant changes in properties such as reduced crushing strength, increased total porosity and increased pore diameter of the hydrophilic polymer was due to water uptake. But the moisture contents in our preparations were found to be low and it varies very little in the formulations. This little moisture content helps the formulations
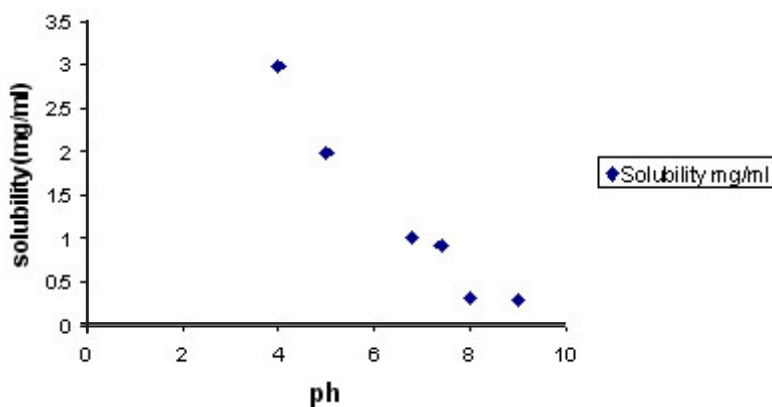

Fig. 7: Solubility profile of haloperidol at different pH of phosphate buffer
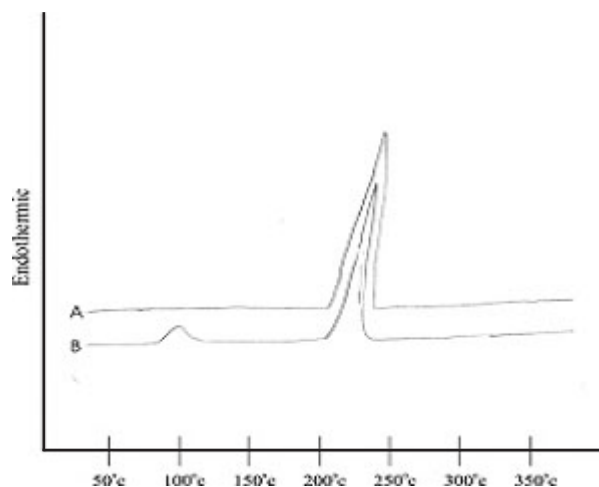
**Fig. 8: DSC spectra of drug and physical mixture. A- haloperidol.
B- Mixture A(Poly vinyl alcohol/PVP and drug film)**

stable from preventing a completely dried, brittle product. Low moisture uptake also protects the materials from microbial contamination and bulkiness of the patches.

The mean (n =3) of cumulative amounts of drug released per cm^2 of the film after 24 h from the preparations PL 1, PL 2, PL 3, PL 4, PL 5 and PL 6 were 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 formulation fitted well in to Higuchi model and the data fitment of the release profile done using Korsmeyer-peppas model showed values of diffusion co-efficient obtained in the range of 0.37-0.74. The mechanism of drug release in these cases were known to follow anomalous transport mechanism i.e. the drug was released by initial swelling and follows anomalous transport.

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

CONCLUSION

In this study, different ratio of PVA and PVP transdermal haloperidol patches were formulated using 4% Hyaluronidase as a permeation enhancer. It can be reasonably concluded that haloperidol can be formulated into transdermal polymeric patches to prolong its release characteristics. Thus the formulation PL 1 (PVA: PVP, 1:2) was found to be the best for a sustained release once a day formulation.

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