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FORMULATION AND EVALUATION OF HALOPERIDOL TRANSDERMAL PATCH

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ABSTRACT
Different polymeric Patches containing Haloperidol were prepared and evaluated for physicochemical, in vitro drug release and Kinetic studies. The IR spectral analysis of Haloperidol showed that the principal peaks and for the mixture of Haloperidol with different polymers additional to the principal peaks, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The presence of all the characteristic bands due to functional groups in polymer mixtures suggests that there is no interaction between the drug and polymers used in the present study. The prepared transdermal patches were evaluated for their physiochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content, drug content were suitable. Transdermal patches with Xanthum gum showed better release than patches with Guar Gum. The release rate was increased with an increase in Xanthum gum content. The release kinetics of the optimized formulations followed Higuchi and release mechanism was Non-fickian diffusion rate controlled mechanism.

Key Words: Haloperidol, Transdermal patches, Xanthum gum

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INTRODUCTION
A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to first pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery system are also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation. Apart from these advantages the pharmaceutical companies recognize the possibility of re-patenting successful drugs by applying the concepts and techniques of controlled drug delivery system coupled with the

increased expense in bringing new drug moiety to the market. One of the methods most often utilized has been transdermal delivery i.e. transport of therapeutic substances through the skin for systemic effect. The present study was designed to develop a suitable matrix type transdermal drug delivery systems of ziprasidone using two different polymeric combinations, E RS100 and HPMC E 15; E RL 100 with HPMC E 15. E RL100 and E RS 100 are acrylic acid matrices which have been used to make drug-polymer matrix films for transdermal delivery systems which are reported as compatible with many drugs. Penetration enhancers that alter the partitioning can be useful to enhance the drug permeation. In this study various penetration enhancers D-Limonene, Oleic acid and were used in different concentrations to determine their effect on permeation of drug (1-4).Aim of the study is toprepare and evaluate Matrix type Transdermal patches of Haloperidol using natural polymers Xanthum Gum and Guar gum in different ratios.

MATERIALS AND METHODS

Preparation of Haloperidol transdermal patches

Matrix type trans dermal patches containing Haloperidol were prepared by solvent evaporation technique, using different ratios of Xanthum Gum (F2,F4,F6,F8) and Guar gum (F1,F3,F5,F7). The polymers were weighed in requisite ratios by and allowed for swelling for about 24hrs in solvent mixture(1:1ratioofdi- chloromethane, methanol). 15%v/w propylene glycol was in corporated as plasticizer. Then the drug solution was added to the polymeric solution, casted on to an umbra petriplate of surface area about 69.42sq.cm, allowed for air drying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into small patches with an area of 6.9cm^2 i.e. with a diameter of 2.9cm.About 7 patches were obtained from each sheet. All formulations carried 1ml Dimethyl Sulfoxide as penetration enhancer and Propylene glycol as plasticizer (Table-1).

Table-1 Composition of Haloperidoltransdermal patches

Formulation code	Drug (mg)	Guar Gum (%)	Xanthum gum (%)	Propylene Glycol (%)	DMSO	Water
F1	10	0.5	--	8	1ml	20ml
F2	10	--	0.5	8	1ml	20ml
F3	10	1	--	8	1ml	20ml
F4	10	--	1	8	1ml	20ml
F5	10	1.5	--	8	1ml	20ml
F6	10	--	1.5	8	1ml	20ml
F7	10	1.5	--	10	1ml	20ml
F8	10	--	1.5	10	1ml	20ml

*Invitro*ReleaseStudies

The drug release studies from Haloperidol transdermal patches were performed using Franz diffusion cell. The drug containing patches was kept between donor and receptor compartments, separated from these compartments by Cellophane membrane. The receptor compartment containing diffusion medium was stirred with magnetic bead operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the Cellophane membrane. 5ml of sample was collected from the receptor compartment at appropriate time intervals and replaced with phosphate buffer pH 6.8. Analysis was carried out using UV-Visible spectrophotometer at 247 nm against phosphate buffer pH 6.8 as reference (5-7).

Permeation Studies

Preparation of Rat Abdominal Skin

The male albinorats weighing150-200gm were sacrificed using an aesthetic ether. The hair of test animals was carefully trimmed short(<2mm) with a trimmer taking extreme precaution not to damage the skin and the full thickness skin was removed from the abdominal region. The epidermis was prepared

surgically by heat separation technique, which involved soaking the entire abdominal skininwaterat60^{o}Cfor45sec, followed by careful removal of the epidermis. The epidermis was washed with water, dried in a desiccator, wrapped in aluminium foil and stored at 4±1^{o}C. At the time of use, the epidermis was rehydrated by immersion in water for 1hr at room temperature.

***Ex vivo* Permeation Studies**

Franz diffusion cell with a surface area of 4.15cm^2 was used for *ex vivo* permeation studies. The rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDD Sunder test. A dialysis membrane was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receptorphaseis14mlof phosphate buffer saline (PBS) pH6.8 stirred at 500 rpm on a magnetic stirrer. The amount of drug permeated was determined by removing 5ml of sample at appropriate time intervals up to 24hr, the volume was replenished with an equal volume of pH6.8 buffer.The absorbance was measured at 242nm spectrophotometrically. Cumulative amounts of drug permeated in µg/cm^2 were calculated and plotted against time.

RESULTS AND DISCUSSION

The results of weight variation test for various transdermal Patches were shown in Table-2.The results of thickness variation test for various transdermal Patches were shown in Table-2.In thickness variation test, the thickness was found to be uniform. The folding endurance numbers of formulations are presented in the Table-2.patches did not show any cracks even after folding for more than 50 times. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing Xanthum gum. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.The results of drug content for various transdermal Patches were shown in Table-3. The results of content uniformity indicated that the drug was uniformly dispersed in all transdermal patches. The drug content analysis of the prepared formulations had shown that the process shown employed to prepare patches in the study was capable of giving patches with a uniform drug content and minimum batch variability.The results of moisture content were shown in Table-3. The results revealed that the moisture content was found to increase with increasing the concentration of polymer. The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

Table-2 Weight, thickness and folding endurance of Haloperidol transdermal patches

Formulation	Weight (mg)	Thickness (mm)	Folding endurance
F1	48	0.15	**251**
F2	47	0.14	**259**
F3	46	0.13	**256**
F4	44	0.17	**271**
F5	49	0.13	**279**
F6	48	0.16	**241**
F7	43	0.15	**210**
F8	48	0.16	**230**

Table-3 Drug content and % Moisture content of Haloperidol transdermal patches

Formulation	Drug content (%)	% Moisture content
F1	93.6	1.33
F2	97.8	1.46

F3	95.5	1.38
F4	95.0	1.49
F5	96.3	1.22
F6	97.1	1.53
F7	96.8	1.32
F8	95.8	1.63
F9	98.1	1.58

The cumulative amount of drug released from Transdermal patches are shown in the Fig-1. The results indicate that there was increase in the amount of drug release with an increase in Xathum gum. Formulations F8 exhibited greatest (99%) percentage of drug release values when compared with the other formulations.In the present study it was observed that as the concentrations of Xanthum Gum increased in the formulations, the drug release rate increased substantially.

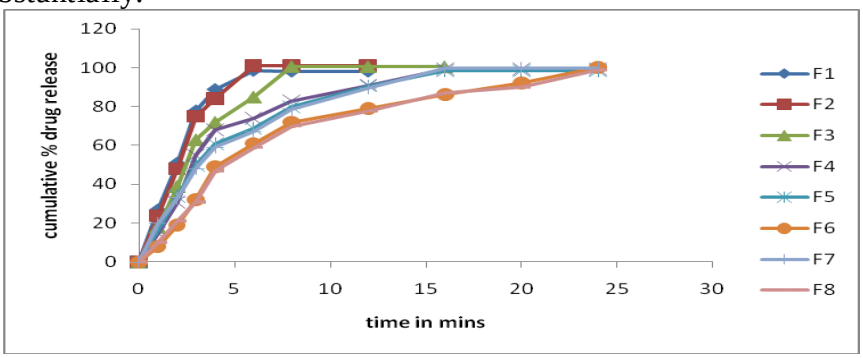

Fig-1 Cumulative percent release of Haloperidol from transdermal patches F1-F8

CONCLUSION

Transdermal patches with Xanthum gum showed better release than patches with Guar Gum. The release rate was increased with an increase in Xanthum gum content. The release kinetics of the optimized formulations followed Higuchi and release mechanism was Non-fickian diffusion rate controlled mechanism.The research work gives a rational guideline for formulating a controlled release transdermal delivery system F8 for effective therapy of Schizophrenia.

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