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Research article

FORMULATION AND IN-VITRO EVALUATION OF HALOPERIDOL PATCHES FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Haloperidol is a high potency first-generation (typical) antipsychotic and one of the most frequently used antipsychotic medications used worldwide. While haloperidol has demonstrated pharmacologic activity at a number of receptors in the brain, it exerts its antipsychotic effect through its strong antagonism of the dopamine receptor (mainly D2), particularly within the mesolimbic and mesocortical systems of the brain. Haloperidol is indicated for the treatment of the manifestations of several psychotic disorders including schizophrenia, acute psychosis, Tourette syndrome, and other severe behavioural states. In present study transdermal drug delivery of Haloperidol was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Matrix type of transdermal patches was developed by using polymers various Xanthan gum, MethocelK15M and MethocelK100M as polymers Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and all the results were found to be were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F7 formulation which containMethocel K100M 100 mg had shown 97.83% cumulative drug release within 12 hours.

Key Words:-Haloperidol, Transdermal patch, Xanthan gum, MethocelK15M and MethocelK100M.

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INTRODUCTION

Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms (Sravanthi K,*et al.* 2020). These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release. The term-controlled release has a meaning that goes beyond scope of sustained release (Jaya raja kumar K,*et al.* 2012). The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other (Chakshu Bhatia,*et al*. 2012).

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Transdermal drug delivery

Transdermal therapeutic systems are defined as

self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system (Rakesh Kumar,*et al*. 2016). The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period (Rahul ShivajiraoSolunke, Praveen D. 2017).

Advantages

- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
- The activity of a drugs having s short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

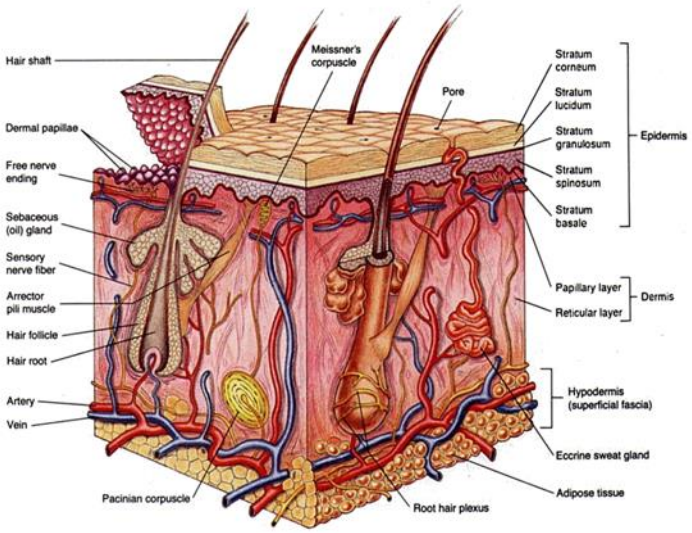
Disadvantages

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels.
- The use of transdermal delivery may be uneconomic.

Structure of skin

An average adult skin has a surface area of approximately 2 square meters and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimeters (2.97+/-0.28 mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss, and cushion internal structures (Bhumi B. Patel,*et al*. 2016).

Figure 1: Structure of skin



The Epidermis:

The outer (epidermal) layer of the skin is composed of stratified squamus epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

The Dermis:

The dermis (cornium) consists essentially of a matrix of connective tissue woven from fibrous proteins which embed in an amorphous ground substance on mucopolysaccharides providing about 20% of the mass. Blood vessels, nerves, and lymphatics cross this matrix and skin appendages (eccrine sweat glands, apocrine glands and pilosebaceous units) penetrate it. In man, the dermis divides into a superficial, thin papillary layer which forms a negative image of the rigid lower surface of the epidermis, and a thick underlying reticular layer which merges with the fat-containing subcutaneous tissue.

The Hypodermis:

This isa sheet of fat-containing areolar tissue known as superficial fascia, attaching the dermis to the underlying structure.The epidermis and dermis support several appendages: The eccrine, apocrine and sebaceous glands, the hair follicles and the nails. Of these, hair follicles and sweat ducts can act as diffusion shunts, i.e. relatively easy pathways for diffusion through the rate-limiting stratum corneum (Gorle A P,*et al*. 2017, KanabarVishvesh B,*et al.*2015, Knutson K,*et al*. 1987).

Basic components of transdermal drug delivery systems

The components of transdermal devices include:

a) Polymer matrix or matrices
b) The drug
c) Permeation enhancers
d) Other excipients

Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing (Richard H.G. 2007). It is impermeable and protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate a (aluminum foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc) etc.

Technologies for developing transdermal drug delivery systems

The technologies can be classified in four basic approaches.

A. Polymer membrane partition-controlled TDD systems:

In this type of systems, the drug reservoir is sandwiched between a drug impermeable backing laminate and a rate controlling polymeric membrane. The drug is allowed to permeate only through the rate controlling membrane. The drug solids are homogeneously dispersed in a solid polymer matrix, suspended in an unleachable, viscous liquid medium e.g. silicone fluid, to form a paste like suspension, or dissolved in a releasable solvent e.g. alkyl alcohol, to form a clear drug solution. The rate controlling membrane can be either a microporous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer, with specific drug permeability.

B. Polymer matrix diffusion-controlled TDDsystems

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and then the medicated polymer formed is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk.

C. Drug reservoir gradient-controlled TDD systems:

Polymer matrix drug dispersion-type TDD systems can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi laminate adhesive layers.

D. Microreservoir dissolution-controlled TDD systems:

A hybrid of reservoir- and matrix dispersion-type drug delivery systems, which contains dug reservoir formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer e.g. propylene glycol, then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs (Keith A.D. 1983, Goodman G. 2001).

General clinical considerations in the use of TDDS

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

1. TDDSs should be applied to clean, dry skin relatively free of hair and not oily inflamed, irritated, broken, or callused. Wet or moist skin can accelerate drug permeation beyond ondansetron time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved, nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.
2. Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.
3. Cutting should not physically alter TDDSs, since this destroys integrity of the system.
4. The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds (Sweetman S.C. 2002).

MATERIALS

Haloperidol, Methocel K15M, Methocel K100M, Xanthan gum, Dichloromethane, Ethanol, Propylene glycol, Tween-80.

Methodology

Preformulation study

Preformulation studies were primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

Selection of drug and other ingredients

- Haloperidol was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Transdermal drug delivery system.
- Xanthan gum, Methocel K15M and Methocel K100M, were selected as matrix forming polymers.
- Propylene glycol was selected as permeation enhancer and plasticizer.

Preparation of Phosphate Buffer pH 6.8: Accurately measured 250 ml of 0.2 M potassium dihydrogen phosphate in a 1000 ml of volumetric flask and added 195.5 ml of 0.2 M sodium hydroxide and then water was addedto make up the volume and adjusted pH 6.8 by using 0.2 M potassium dihydrogen phosphate/sodium hydroxide.

Construction of standard graph of Haloperidol: Standard graph of Haloperidol was plotted in PBS pH 6.8 Haloperidol was estimated spectrophotometrically at λ_{max} of 234 nm.

Preparation of standard solution: Stock solution - I was prepared by dissolving Haloperidol 100 mg in 100 ml of buffer, so as to get a solution of 1 mg/ml concentration. Then stock solution - II was prepared by taking 10 ml from the previous stock solution i.e. stock solution - I and dissolved in 100 ml of buffer, so as to get a solution of 100 µg/ml concentration (Gannu R,*et al*. 2007). Accurately measured aliquot portions of standard drug solution, from stock solution -II were taken, like 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml were transferred in to 10 ml volumetric flasks and were diluted up to the mark with buffer pH 6.8 Absorbance of each solution was measured at λ_{max} of 234 nm against buffer pH 6.8 as the blank, by using UV-spectrophotometer. A graph was plotted by taking concentration of drug vs absorbance was plotted.

Formulation

- **Development of Transdermal patches:** Transdermal drug delivery patches were prepared by solvent casting method.

Solvent casting method: Transdermal patches were prepared according to the formula shown in Table 1. Xanthan gum, Methocel K15M and Methocel K100M were weighed in requisite ratios and they were then dissolved in dimethyl formamide and ethanol as solvent using magnetic stirrer. Haloperidol (100 mg) with a magnetic stirrer. Propylene glycol was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried patches were taken out and stored in desiccator.

Table 1: Formulations of Haloperidol Transdermal Patch

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug(mg)	100	100	100	100	100	100	100	100	100
2	Xanthan gum (mg)	100	150	200	-	-	-	-	-	-
3	Methocel K15M(mg)	-	-	-	100	150	200	-	-	-
4	Methocel K100M (mg)	-	-	-	-	-	-	100	150	200
5	Dichloromethane(ml)	8	8	8	8	8	8	8	8	8
6	Ethanol(ml)	8	8	8	8	8	8	8	8	8
7	Propylene glycol(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
8	Tween-80(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

Evaluation of Transdermal patch by physical methods:

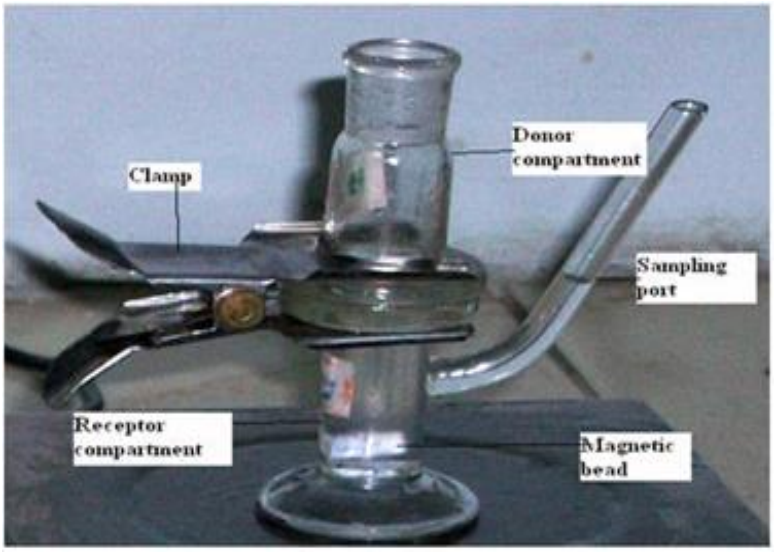
- **Physical appearance:** All the Transdermal patches were visually inspected for color, clarity, flexibility & smoothness.
- **Thickness:** This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.
- **Weight variation:** The three disks of 2x2 cm^2 was cut and weighed on electronic balance for weight variation test (Prajapati S.T,*et al*. 2011). The test was done to check the uniformity of weight and thus check the batch- to- batch variation.
- **Flatness:** Longitudinal strips were cut out from each patch, one the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness.

- **Folding endurance:** The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm) was cut evenly and repeatedly folded at the same place till it is broken.
- **Moisture uptake:** The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84 % RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found**.**
- **Moisture content:** The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40 ºC for 24 h. The patches were reweighed until a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.
- **Drug content determination:** The patch of area 3.83 cm^2 was cut and dissolved in PBS pH 6.8 Then solvent ethanol and dimethyl formamide, to make polymer soluble, were added to the mixture and the remaining volume was made up with PBS pH 6.8 to 100 ml in 100 ml volumetric flask (Paulo C & Jose M. 2001). Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 234 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Evaluation of Trandermal patch by permeation studies:

Diffusion cell: Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment.

Figure 2: Franz diffusion cell



In vitro permeation studies using dialysis membrane: In vitro permeation of Haloperidol from Transdermal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a Transdermal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 6.8 and the setup was placed over a magnetic stirrer with temperature maintained at 37^0C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Haloperidol in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 234 nm.

Kinetic modeling of drug release:

Mechanism of drug release: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release model: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$Q = K_{0\,t}$$

Where, Q= amount of drug released at time t

K_0=zero order release rate constant

The plot of % drug release versus time is linear.

First order release model: The release rate data are fitted to the following equation

$\ln (100-Q) = \ln 100 - k_1 t$

Where, Q= percent drug release at time t

K_1= first order release rate constant

The plot of log % drug release versus time is linear.

Higuchi's Release Model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation

$$Q = K_H t^{1/2}$$

Where, Q= percent drug release at time t

K_H= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

Korsmeyer-peppas release model: The release rate data were fitted to the following equation

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

Where, M_t= drug release at time t

M= total amount of drug in dosage form

F= fraction of drug release at time t

K_m=constant dependent on geometry of dosage form

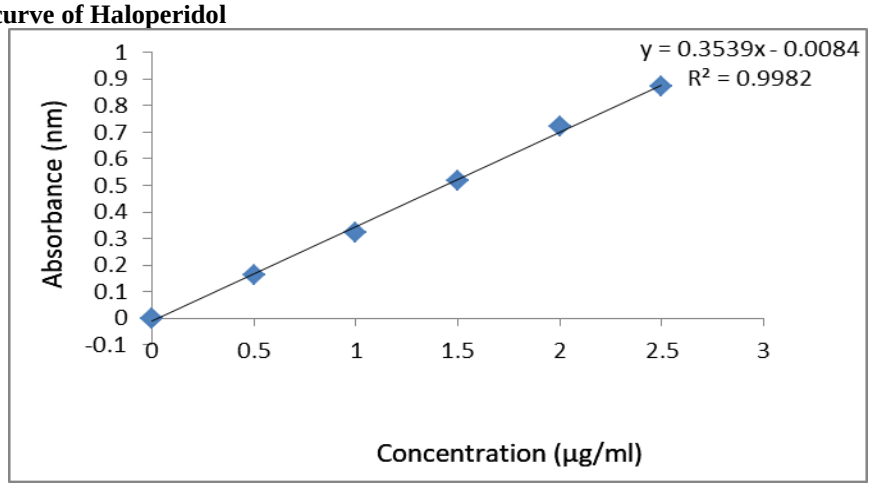
n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < n < 0.89 then the release is through anomalous diffusion or non-fickian diffusion (Swellable& Cylindrical Matrix). In this model, a plot of log (M_t/M) versus log (time) is linear.

Drug excipients interaction studies: FT-IR spectrum interpretation: IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation (F7) were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}.

RESULTS AND DISCUSSION

Figure 3: Standard curve of Haloperidol



Physical appearance: All the Transdermal patches were visually inspected for colour, clarity, flexibility.

Flatness: All the Transdermal patches were found to be flat without any foams.

Table 2: Evaluation of Haloperidol Transdermal patch by physical methods

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	202	0.110	199	98.02	1.89	2.05
F2	256	0.112	198	97.13	1.91	1.97
F3	309	0.118	191	97.77	2.05	2.04
F4	208	0.111	189	98.81	1.98	1.91
F5	255	0.119	199	97.65	2.01	2.04
F6	307	0.114	185	98.14	1.99	2.03
F7	201	0.118	189	98.16	2.02	2.01
F8	253	0.115	194	98.45	2.01	1.99
F9	305	0.115	193	97.53	1.94	2.11

The prepared Haloperidol Transdermal patches were evaluated for their physical parameters such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture

uptake, Moisture content and all the results were found to be were found to be with in the pharmacoepial limits.

Figure 4: percentage drug release of F1, F2, F3

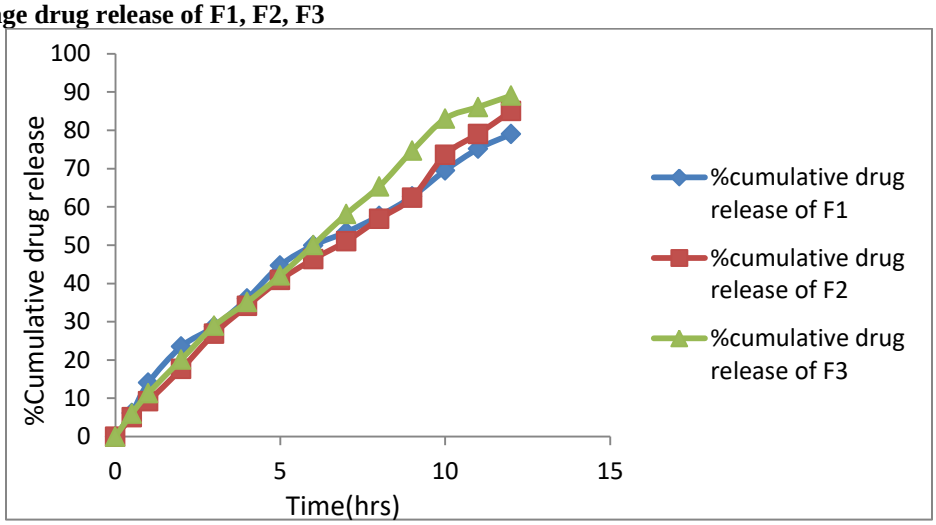


Figure 5: percentage drug release of F4, F5, F6

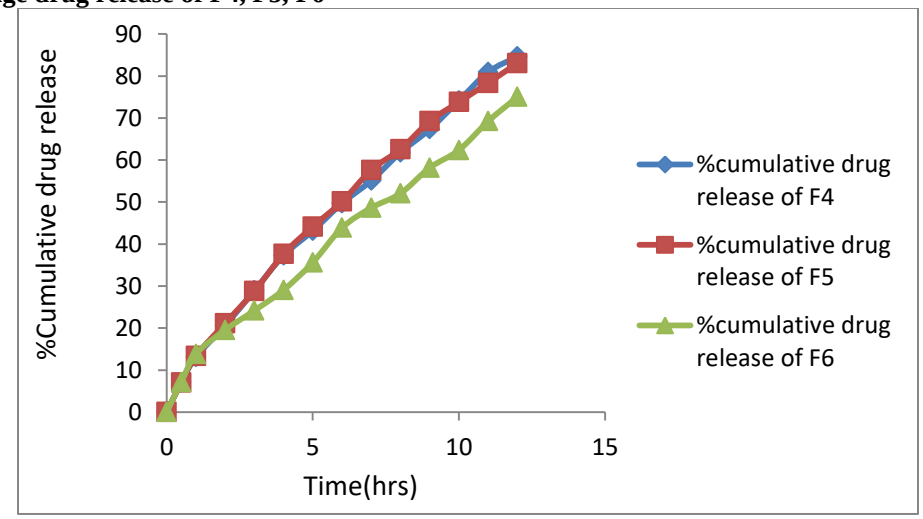
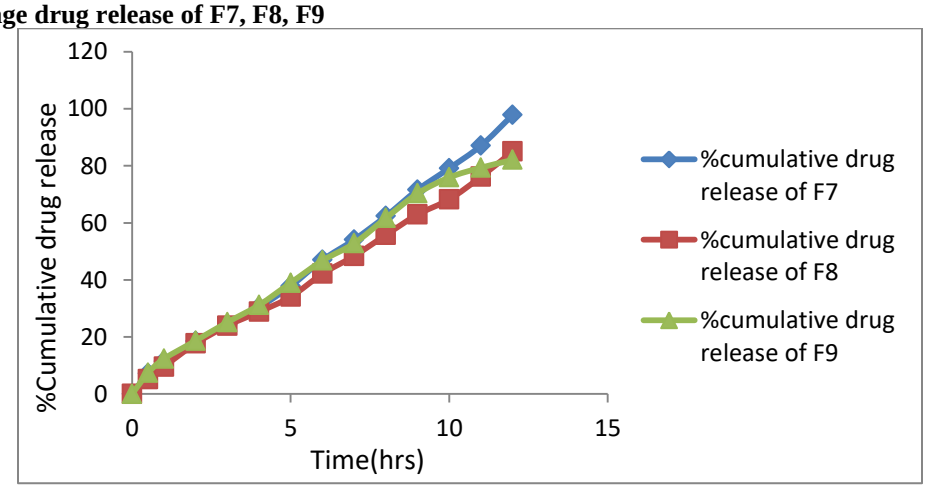


Figure 6: percentage drug release of F7, F8, F9



The prepared Haloperidol Transdermal patches were evaluated for In-vitro permeation studies using dialysis membrane, among all the 9 formulations F7 formulation was shown 98.17% cumulative drug release within 12 hours.

Kinetics of In-vitro permeation studies of optimized formulation

Figure 7: Zero order kinetics

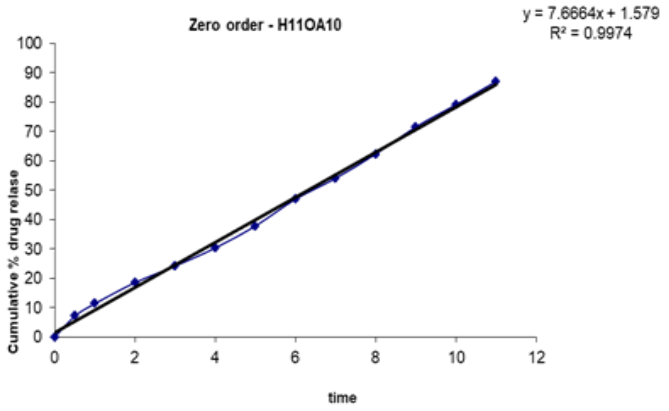


Figure 8: Higuchi plot

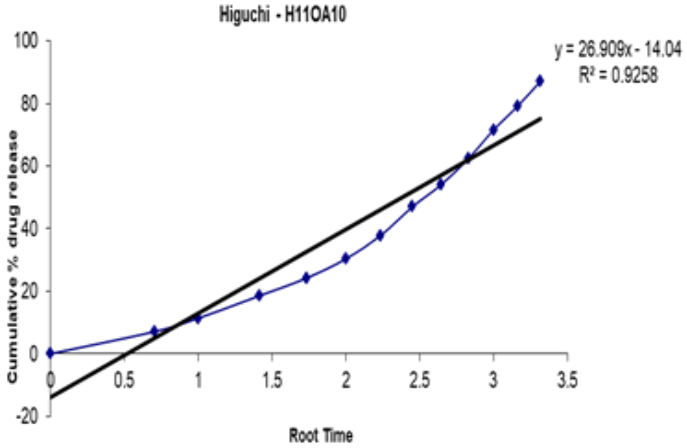


Figure 9: Peppas plot

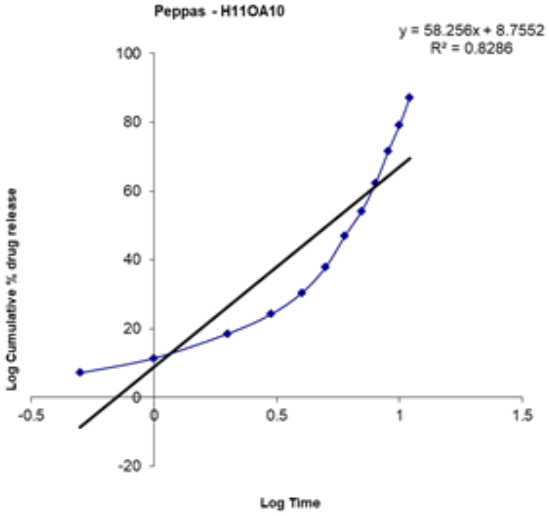
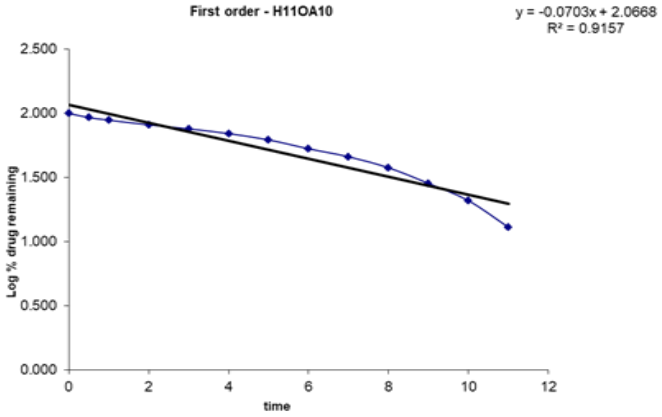


Figure 10: First order kinetics



The kinetics of In-vitro permeation studies using dialysis membrane for F7 formulation was plotted and the F3 formulation followed the zero-order mechanism of drug release.

Drug excipients interaction studies: FT-IR spectrum interpretation: IR spectral analysis was carried out using FT-IR by the KBr disc method and the results showed that there are no interactions between drug and excipients. The results were attached in the Annexure.

Figure 11: FTIR of pure drug

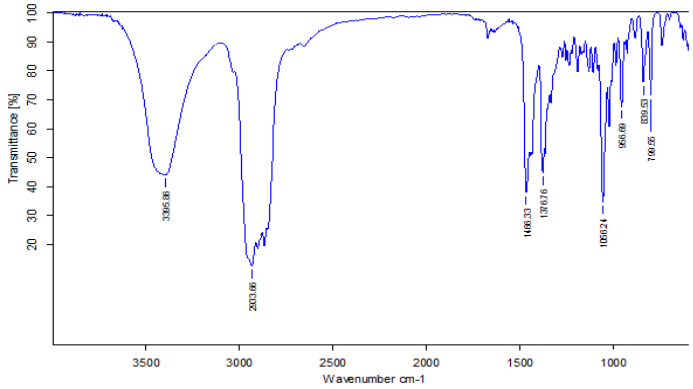
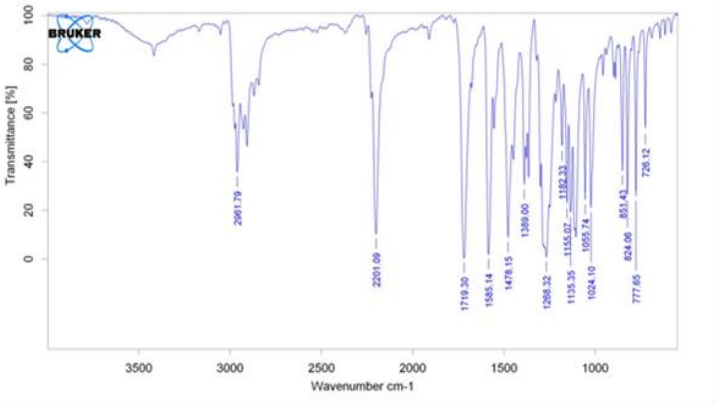


Figure 12: FTIR of optimised formulation



CONCLUSION

In present study transdermal drug delivery of Haloperidol was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) 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.

Matrix type of transdermal patches was developed by using polymers various Xanthan gum, MethocelK15M and MethocelK100M as polymers Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and all the results were found to be were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F7 formulation which containMethocel K100M 100 mg had shown 97.83% cumulative drug release within 12 hours.

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