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Formulation And Assessment Of Transdermal Patches Containing Sustained-Release Haloperidol For The Treatment Of Antipsychotic Illness

Arpita Srivastava[1], Kapil Malviya[2], Naveen Gupta[3], Dharmendra Rajput[4], Ankita Shukla[5]
[1,2,3,4,5]Patel College of Pharmacy, Madhyanchal Professional University, Ratibad, Bhopal-462044, Madhya Pradesh, India, srivastavaarpita810@gmail.com

Abstract
Standard oral dosage formulations have a number of drawbacks, such as a tendency to cause rapid blood level spikes (both high and low) and poor bioavailability due to hepatic first pass metabolism. As a result, large and/or frequent dosage is required, which can be inconvenient and inappropriately costly. The transdermal drug delivery system (TDDS) was developed in order to enhance or improve such a character. By administering medications more precisely (i.e., site-specifically) inside the body, this approach will reduce the size and quantity of dosages while increasing therapeutic efficacy and safety. When it comes to treating conditions that require continuous care, TDDS is a great option. There are several advantages to topical delivery of medications over the more conventional oral dosage type. Due to the convenience of use and ability to improve patient compliance, the transdermal medication delivery system has become the standard remedy to this issue.
Keywords: Transdermal patches, Haloperidol, Topical administration, Enhance permeation, Anti-psychotic study.

INTRODUCTION

It is described as a self-contained, discrete dosage form that, when applied to intact skin, keeps the drug concentration within the therapeutic window for a long time and allocates the drug to the systemic circulation through the intact skin at a controlled rate [1]. It is described as a self-contained, discrete dosage form that, when applied to intact skin, keeps the drug concentration within the therapeutic window for a long time and allocates the drug to the systemic circulation through the intact skin at a controlled pace [. Such systems are known as transdermal therapeutic systems. Since only a small number of drugs have been proven to be effectively delivered via the skin, the use of transdermal patches for medicines has been limited in recent years. In order to achieve the goal of administering systemic medicine by topical application to the surface of the skin that is still intact [2]. To achieve the objective of applying topical medication to the intact skin surface in order to give systemic medication [2]. The formulation, development, and characterization of transdermal systems for haloperidol with natural permeation enhancer medicines are being carried out as part of the current study undertake. The interaction between the drug and the polymer was studied, and matrix-type transdermal patches and controlled release matrix tablets were developed. The drug's higher bioavailability and reduced dosage were demonstrated by the results [3]. The TDD patch allows the drugs to reach the bloodstream through a number of skin channels when it is applied to the skin [4]. The haloperidol medications were chosen as a promising drug option for this study in order to examine the feasibility of administering them via controlled drug delivery systems utilizing natural permeation enhancers that also have antipsychotic properties. The rationale or a reason for the selection of natural permeation enhancer (transdermal enhancer) in the TDDS system is to relieve the purpose of the topical delivery system, which is to promote the distribution of active substances at a deeper level of the skin [5]. In order to meet the goal of the topical delivery system, which is to encourage the dispersion of active ingredients at a deeper level of the skin, a natural permeation enhancer was chosen for the TDDS system [5]. Most transdermal patches are designed to release the active ingredient over a period of hours to days, with the goal of working at a zero-order rate after being applied to the skin. This is especially helpful when it comes to administering preventative therapy for chronic diseases. Evidence of percutaneous drug absorption may be seen in the patient's clinical response to the administered medication [6]. Measurable or limited blood levels of the

medication, detectable excretion or elimination of the drug and its metabolites in the urine, and the clinical experience of the patient are all ways in which this evidence can be obtained. It is the purpose of the study that is being suggested to create a polymeric transdermal patch that will allow for the programmed release of drug components for individuals suffering from mental illness. An antipsychotic medication known as haloperidol (HAL) has been linked to the adverse effects of drug-induced extrapyramidal syndrome (DIES), and it was developed as a TDDS for the purpose of maintenance treatment. By placing a medication formulation onto skin that is both healthy and undamaged, transdermal drug delivery system (TDDS) is a non invasive means of systemic drug delivery. The medication can first penetrate the stratum corneum prior to going further into the epidermis and dermis without building up in the dermal layer. The medication can be absorbed systemically through the dermal microcirculation as soon as it reaches the dermal layer.

MATERIAL AND METHODS

Preparation of the haloperidol transdermal patch

The purpose of this research or study was to develop a transdermal (percutaneous) film that contained haloperidol and was capable of releasing the medication in a relatively short amount of time. The methyl cellulose and sodium alginate solutions were prepared separately by dissolving the appropriate amounts in distilled water. However, the chitosan solution was obtained by dissolving the polymer in a 1% volume/volume acetic acid solution at forty degrees Celsius while stirring. As shown in Table 1, twenty milligrams of haloperidol, the active pharmaceutical ingredient, were dissolved in the casing solvent before the polymeric solution was added in a different phase. The drug-polymer mixture was continuously stirred on a thermostatic magnetic stirrer at 37±2 degrees Celsius. As the plasticizers were being stirring, glycerin, PVP, and PEG400 were added. Each solution was let to stand for a whole night in order to eliminate the air bubbles. After the stirring was finished, it was sonicated in an ultrasonic water bath before being placed on petri plates with a mercury base and open circular glass bangles on both sides. In order to facilitate the solvent's evaporation, aluminum foil was placed over the bangle's bottom at a temperature of 35 degrees Celsius (Olven Instruments, India). The films were produced using the solvent casting method. They were separated, cut into circular films having a surface area of 2 cm2 and a drug concentration of 4 mg, covered in aluminum foil, and put in airtight polyethylene bags to be stored in desiccators [7].

Table 1: Preparation of haloperidol containing transdermal patch

Formulation Code	Polymers (gm)				Plasticizers			
	HPMC	Methyl cellulose	Gum tragacanth	Ethyl Cellulose	Glycerin (ml)	PVP (gm)	PEG 400 (gm	Dibutyl pthalate (gm)
HTP1	2	-	-	-	2.5	2.5	-	-
HTP2	-	2	-	-	2.5	2.5	-	-
HTP3	-	-	2	-	2.5	2.5	-	-
HTP4				2	2.5	2.5	-	-
HTP5	2	-	-	-	-	-	2.5	2.5
HTP6	-	2	-	-	-	-	2.5	2.5
HTP7	-	-	2	-	-	-	2.5	2.5
HTP8				2	-	-	2.5	2.5

Evaluation of TDDS

Thickness: The thickness of each patch was measured in three different places using a micrometer, and the mean results were then calculated.

Weight variation: In order to calculate the weight variation, the randomly selected patches were individually weighed after being exposed to mass variation; such determinations were made for each and every formulation.

Drug content: Patches with a prescribed area of one square centimeter were dissolved in five milliliters of dichloromethane, and the volume was brought up to ten milliliters by adding phosphate buffer with a pH of seven and a half. A rotating vacuum evaporator fixed at 45 degrees Celsius was then used to evaporate the dichloromethane. In order to create a blank, a drug-free patch that was treated in the same manner was used. After passing the solutions through a 0.45µm membrane, they were diluted appropriately and then exposed to the HPLC technique for the purpose of determining the amount of medication present [8].

Folding endurance: A single film was folded continuously in the same area until it broke in order to evaluate folding endurance. The number of times the film could be folded at the same place without cracking or breaking was used to determine the folding endurance value.

Percentage Elongation: The percentage elongation was calculated by measuring the length immediately prior to the break point and then calculating them using the following formula:

Elongation as a Percentage = (L1-L2/L1) X 100

Tensile strength: To determine the elongation as a tensile strength, the polymeric patch was pulled using a pulley system. To increase the pulling force until the patch broke, weights were gradually added to the pan. To determine the tensile strength, this was done. Using a magnifying lens on the graph paper, the elongation the distance the pointer traveled before breaking the patch—was determined. It was found that the tensile strength was kg cm-2 [9].**n-vitro skin permeation studies:** A Franz diffusion cell with a receptor compartment capacity of 22.5 ml was utilized to perform in-vitro skin penetration studies. The skin of a Wistar albino rat's abdomen was removed and placed between the donor compartment and the receptor compartment of the diffusion cell. When applying the resulting patches to the skin, they were covered with a paraffin coating. The receptor compartment had been completed when phosphate buffer with a pH of 7.4 was added to the diffusion cell. The entire apparatus was fastened to a magnetic stirrer to maintain the temperature at 32 ± 0.5 degrees Celsius. Using magnetic beads, the fluid inside the receptor compartment was continuously agitated at a rate of 50 revolutions per minute. The samples were collected at different times, and spectrophotometric analysis was done to ascertain the quantity of drug present. To completely replace the receptor phase, the same volume of phosphate buffer with a pH of 7.4 was added at each sample removal. A figure was created that showed the cumulative percentages of medicine that was penetrated per square centimeter of patches versus the passage of time [10].**in vitro skin permeation investigation:** An in vitro drug release study was carried out in a glass Franz-diffusion cell that was assemble in the laboratory. The water used in the study was absolutely distilled. The resulting formulations were cut into 2 cm2 films, which were then uniformly spread over the cellophane membrane between the diffusion cell's donor and receptor compartments. To ensure that the films were tight, springs were used. However, the donor compartment contained no contents, while the receptor compartment had 75 milliliters of phosphate buffered saline with a pH of 7.4. At a temperature of 37±5 degrees Celsius, the magnetic stirrer was configured to operate at a speed of 100 revolutions per minute. By extracting aliquots of 5 milliliters of the medication at various time intervals up to twelve hours, the quantity of drug that was released was determined. The volume that was removed was replaced with an equivalent amount of new phosphate buffered saline that had been prewarmed at 37±5 degrees Celsius and had a pH of 7.4. The aliquates that were produced were ultrasonicated for fifteen minutes and then filtered. After being diluted with the same dissolving media, the filtrate was then put through the HPLC technique in order to determine the amount of drug present [11].

Drug Dispensation Analysis of Kinetic Data: Numerous different kinetic models have been developed to characterize the properties of drug release from a matrix. The three equations described here are frequently used as they are simple and appropriate. Plotting the cumulative percentage of drugs released vs time gives the first equation, which is the zero-order model equation. Plotting the cumulative percentage of drugs released against the square root of time reveals the second equation, which is Higuchi's square-root equation. The plotting of the logarithmic cumulative percentage of drugs released against the logarithm of time gives the third equation, also known as Korsmeyer-Peppa's equation.

RESULTS AND DISCUSSION:

The haloperidol patch that had been created was characterized by a number of factors that had been tuned. The qualities of the patches that had been created were examined by physical examination. The surface of the patches was discovered to be smooth, and they were shown to be transparent and bendable. In the study, it was discovered that the thickness of the transdermal patch fell between the range of 0.22±0.01 to 0.29±0.03. Within the range of 110.33±1.156 to 118.33±1.155, the patches exhibited a weight uniformity that was consistent. Based on the findings of the weight uniformity analysis, it was determined that the average weight of the two batches was not significantly change, which indicates that the patches were uniform throughout. Between 93 and 101 was the range of values for the folding endurance. The results of the folding endurance test showed that patches will keep their flexibility without cracking or breaking, which means that there is a lower risk of medication loss. In terms of percentage elongation, the transdermal patches that were manufactured exhibited a range of 93.74±0.15% to 119.11±0.02%. The tensile strength went from 3.66±1.18 N/mm2 to 6.69±0.23 N/mm2 during the experiment. Specifically, the formulations had a pH that fell within the range of 5.5 ± 0.14 to 5.8 ± 0.12, which corresponds to the pH of the skin, indicating that they are compatible with the skin. On average, the medication content of the transdermal patches that were manufactured ranged from 93.99±0.8% to 99.74±0.15%. According to evaluation results from an in-vitro drug release study, chitosan polymers have a hydrophilic nature and can increase the spreadability and dispersibility of water-soluble haloperidol (58.34 to 95.37 percent). The layer of hydrophilic polymer results in a film that is water-permeable and has a higher level of hydration. This kind of hydration makes it possible to lose the polymer matrix, which results in an increase in drug release of more than 95.5% within a period of six to seven hours, as required for immediate release. The polymeric films (HTP3) were selected for further investigation based on their physical characteristics, including tensile strength, percentage elongation, folding endurance, swelling ratio, moisture content, moisture absorption nature, drug content, and in-vitro drug release investigation attributes. It was concluded from the results of the release kinetic analysis that the produced patch followed the supercase II transport mechanism of diffusion kinetics, leading to a sustained release over a predetermined amount of time. It was discovered that the release exponent "n" was 1.0, indicating that Super-case II was the transport method employed. Furthermore, a variation from the Fickinan mechanism of drug release was detected.

CONCLUSION

There were a number of physicochemical properties that were examined for the transdermal patches that were created. These qualities included physical appearance, weight uniformity, thickness, folding durability, moisture content, and medication content that was acceptable. For the purpose of determining whether or not the patches that were manufactured were suitable for transdermal application, physicochemical properties were examined. The most effective medication release occurs in eight hours for formulations that include Xanthan Gum in conjunction with the plasticizer propylene glycol. The HTP3 formulation showed a drug release rate of over 90% after eight hours. As a result, HTP3 formulation is considered an optimum batch.

Table 2: Various parameters of prepared Transdermal Patch

Formulation code	Flexibility	Smoothness	Transparency	Stickness	Thickness (mm)	Average weight (mg)
HTP1	Flexible	Smooth	Transparent	Non sticky	0.29±0.03	111.32.±1.154
HTP2	Flexible	Smooth	Transparent	Non sticky	0.26±0.02	110.33±1.156
HTP3	Flexible	Smooth	Transparent	Non sticky	0.25±0.03	112.60±0.144
HTP4	Flexible	Smooth	Transparent	Son sticky	0.24±0.02	119.23±1.154
HTP5	Flexible	Smooth	Opaque	Non sticky	0.23±0.01	118.33±1.155

HTP6	Flexible	Smooth	Opaque	Non sticky	0.22±0.01	114.66±1.165
HTP7	Flexible	Smooth	Opaque	Non sticky	0.23±0.03	116.37±1.154
HTP8	Flexible	Smooth	Opaque	Non sticky	0.25±0.03	113.78±0.111

Mean ± SD; n = 3

Table 3: Various parameters of prepared Transdermal Patch

Formulation code	**Folding endurance**	**Percentage Elongation**	**Tensile Strength N/mm^2**	**Surface pH**	**Drug content (%)**
HTP1	93-97	93.74±0.15	3.66±1.18	5.5 ± 0.14	93.99±0.8
HTP2	94-98	94.81± 0.02	6.69±0.23	5.6 ± 0.14	94.95±0.9
HTP3	99-101	101.42± 0.09	5.93±0.13	5.7 ± 0.12	95.79±0.10
HTP4	92-95	116.52± 0.02	6.79±0.23	5.8± 0.12	99.59±0.11
HTP5	78-71	118.12± 0.03	5.86±1.18	5.5 ± 0.13	98.07±0.12
HTP6	82-72	119.11±0.02	6.13±0.13	5.5 ± 0.14	99.85±0.13
HTP7	86-91	95.91±0.15	5.76±1.18	5.6 ± 0.14	97.55±0.14
HTP8	75-80	104.72±0.15	5.59±0.23	5.7 ± 0.14	99.74±0.15

Mean ± SD; n = 3

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