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Development and Charcterization of Transdermal Patches of Antipsychotic Drugs

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KEYWORDS

Antipsychotic drug, fluphenazine, transdermal Patches, mucoadhesive polymers, aromatic oils

ABSTRACT:

Delivery of medications through the skin has been consistently a challenging yield for researchers because of obstructive barrier properties of the skin. Over the most recent twenty years, the transdermal drug delivery system has emerged as the most consistent, as well as, viable innovation that offers huge clinical advantages over other dosage forms. Transdermal drug delivery system (TDDS) involves the permeation of the drug across the skin surface on the application and arrives at the systemic circulation in adequate quantity.

Introduction

Controlled drug release can be accomplished by TDDS which can transfer the drug in a therapeutically effective amount through the skin portal over an extended time period. Additionally, it is expedient, safe, and overcomes different adverse effects, such as, first-pass metabolism and painful delivery of the drugs associated with other drug delivery systems [1]. The transfer of drugs can be dismissed at any point in TDDS by eliminating the transdermal system. The drug should have many physicochemical proper-ties, such as, low molecular weight, small half-life, high lipophilicity, low dose, and less oral bioavailability to be formulated as transdermal drug delivery [2]. The present work aimed to formulate and evaluate transdermal patches of Ketorolac Tromethamine for sustained drug release and improved patient compliance. Patches were prepared using the solvent casting method with HPMC K15 and PVP K30, incorporating plasticizers and permeation enhancers [3]. The formulations were assessed for physicochemical properties, drug content uniformity, and in-vitro drug release. The patches exhibited smooth, transparent, and non-sticky surfaces, with uniform weight, thickness, and good mechanical strength [4]. Drug content (95%–98%) and moisture content (2.22%–3.45%) were within acceptable limits. In-vitro release studies showed sustained drug release, with F6 achieving 100.02% at 10 hours. FTIR and DSC analyses confirmed drug-excipient compatibility. The results suggest that Ketorolac Tromethamine transdermal patches could be a promising alternative to conventional formulations, warranting further in-vivo studies [5]. Fluphenazine is a phenothiazine used to treat patients requiring long-term neuroleptic therapy. Fluphenazine is a trifluoro-methyl phenothiazine derivative intended for the management of schizophrenia and other psychotic disorders. Fluphenazine has not been shown effective in the management of behaviorial complications in patients with mental retardation. Fluphenazine blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis [6]. Fluphenazine hydrochloride is rapidly absorbed from the GI tract and from parenteral sites. Following oral or IM administration of fluphenazine hydrochloride, the onset of action usually occurs within 1 hour; the duration of action is 6-8 hours. Following administration of a single dose of fluphenazine hydrochloride in one limited study, peak serum fluphenazine concentrations were reached within 1.5-2-

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or 0.5-hours following IM or oral administration, respectively [7]. Creating a polymeric transdermal patch with a programmed release of medication ingredients for patients with mental illnesses is the goal of the proposed effort. One common antipsychotic in the phenothiazine family is fluphenazine (FLP). Although its exact mode of action is unknown, it is thought to be connected to its capacity to inhibit dopamine receptors. The medication's controlled-release transdermal dose form (TDDS) was created for maintenance treatment. TDDS is a painless way to apply a medication formulation to healthy, unbroken skin in order to administer the medication systemically. Without accumulating in the dermal layer, the medication first penetrates the stratum corneum before moving on to the deeper epidermis and dermis. Drugs may be absorbed systemically via the dermal microcirculation once they reach the dermal layer [8].

Material And Methods

Formulation Development of Transdermal Patches: The fluphenazine matrix-type transdermal patches were prepared by the solvent casting method with as shown sodium alginate, chitosan, guar gum, carboxy methyl cellulose, glycerin (ml), PVP (gm), SLS (gm), Tween 80 (ml), Clove oil (ml), Nutmeg oil (ml) in Table 1, were taken in a boiling tube. In this, 25 mL of a mixture of solvents, i.e. dichloromethane:methanol in the ratio 1:1 was incorporated and vortexed. Appropriate precautions were undertaken to avert the development of lumps. The boiling tube was kept separately for swelling of polymer for a period of 5 hours. After efficient swelling, weighed quantities of propylene glycol and penetration enhancers were incorporated and again vortexed. Lastly, a measured amount of fluphenazine dissolved in sufficient solvent was added to the solution of polymer and mixed well. It was then kept aside to eliminate air bubbles for a short period. Then, the gel was moved into cleaned Petri plates. These patches were dried over a horizontal surface in an oven for 24 hours, till a springy film was formed. After overnight, the dried patches were carefully [9].

Evaluation of Developed Transdermal Patches

Physical Appearance: All the developed transdermal patches of drug were assessed for color, clarity, flexibility, and smoothness.

Weight Variation: Ten patches from each batch were selected and weighed separately on a digital balance. The average weight and standard deviation were estimated. The percent deviation was calculated.

Film Thickness: The patch thickness was measured at altered points of the patch by using a screw gauge [10].

Folding Endurance: Folding endurance of the developed patches was assessed by constantly folding a patch at a similar space up until it brakes. The number of times of patch could be folded at the same spot deprived of breaking gave the estimation of the folding endurance of the patch, which was viewed as agreeable to reveal good folding patch properties [11].

Surface pH of Patches: The surface pH of the patches which employs a joined glass electrode. The transdermal patch was made in contact with 1 mL of distilled water and permitted to expand for 2 hours at room temperature. The surface pH was then determined by keeping the pH electrode on the surface of the patch and allowed to equilibrate for 1-minute [12].

Content Uniformity of the Patches: For drug content uniformity, the developed patches were assayed in each case. Three patches equivalent to 2.25 cm2 area from each formulation were assayed for the content of the drug. Patches from each formulation were cut into small pieces, dissolved in 100 mL of phosphate buffer (pH 7.4) taken into a conical flask. The solution was then filtered through 0.45 µm filter paper and diluted with phosphate buffer (pH 7.4). The drug content was estimated using a UV-visible spectrophotometer at 260 nm [13].

Moisture Absorption Studies: The moisture absorption studies give a sign about the relative dampness assimilation limits of polymers and thought of whether the developed formulation keeps up its integrity after retention of dampness. 5% w/v agar was taken in hot distilled water, moved into Petri plates [14].

***in-vivo* animal pharmacokinetic studies:** Adherence to guidelines pertaining to animal utilization was accepted by the research Ethical Committee at Madhyanchal Professional University, Bhopal, and male albino rats (wt 250 gm) were utilized in this study. Male albino rats were randomly assigned to one of two

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groups for the in vivo experiments, with a total of six rats per group. Animals in the first group were given an oral solution, while those in the second group were given an adhesive layer that included patches to apply transdermally to their skin. During the experiment, the rats wore plain Velcro jackets to keep the patches from falling off their dorsal surfaces. Hair on the backs of the subjects' necks was buzzed off at least 24 hours before the trial began. On the day of the trial, the freshly shaved area was gently washed with warm water before the patch was placed. Using medical adhesive tape and the specially constructed jackets, the patches were fastened. The drug's plasma concentrations at certain time points served as the basis for the computation of the different pharmacokinetic characteristics. The albino rats were the subjects of the experiment. After the rats were patched with the formulations, blood samples were obtained at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours later. An alcohol swab was applied topically to the shaved abdomen area to widen the rat tail vein. A 1 ml syringe with a gauge needle was used to collect the blood sample. After positioning the needle upright, it was put into the tail at an angle ranging from 25° to 30° into the vein. At specified intervals, blood samples of half a milliliter were taken. To avoid the use of anticoagulants, the blood samples were carefully transferred to sterile 2 ml centrifuge tubes. After centrifuging the tubes for 10 minutes, the serum and plasma were collected into plastic Eppendorff tubes and kept at -20°C. Then, using a micropipette, the samples were diluted with a dissolving media called "phosphate buffer saline pH 7.4". The tube was kept until the medications were calculated using a simultaneous UV technique. Using a plasma concentration time profile, we were able to determine the estimated API of fluphenazine in blood plasma, as well as its peak plasma concentration (Cmax) and the time of its occurrence (tmax). In order to determine the area under the concentration time curve (AUC0-t), the trapezoidal rule was used [14-15].

***in-vivo* animal skin irritation study:** *in-vivo* animal skin irritation test of prepared multilayered transdermal patch was carried out on healthy albino rats (average wt 250 gm). The dorsal surface (50cm^2) of the albino rats was to be cleaned by removing the hair from the dorsal surface by shaving. The rats are divided into 3 groups (n = 6). Group I acted as the normal, Group II applied with transdermal patch without drug and group III, applied with transdermal patch with drug. The application sites of patches are indexed according to a visual scoring scale. The erythema observed has scaled as follows: 0, none; 1, slight; 2, well defined; 3, moderate and 4, severe [16].

Stability Studies: The stability of the prepared transdermal patch (FTP3) patches was evaluated as per the ICH guidelines. The shelf life of API drug was identified for drug decomposition during storage at different storage conditions at different temperatures. The degradation may result in environmental changes during storage of drug amount at FTP3 due to chemical alteration or due to product instability. The prepared transdermal patch FTP3 was stored at three different temperature and relative humidity conditions in covered polythyne bags and aluminium paper. The samples were stored at 2ºC ± 0.5ºC, 25°C/60% RH and 40°C/75% RH for 180 days in stability chambers. These samples were analyzed for drug content study by using simultaneous method of estimation using UV method [17].

The shelf life of the formulations was calculated from the degradation rate constant at 25 ºC (k_{25}) by the following formula:

$$t_{10\%} = 0.104 / k_{25}$$

Results And Discussion

Several optimized parameters were used to characterize the prepared fluphenazine transdermal patch. These parameters included optical checking, color smoothness, transparency, flexibility, thickness, weight variation, content uniformity, surface pH of the patch, tensile strength, folding endurance, percent elongation, water uptake property, swelling index, and wetness of the patch. The results of the in-vitro drug release investigation showed that the hydrophilic character of the polymers chitosan improved the spreadability and dispersibility of the water-soluble Fluphenazine, with values ranging from 58.34% to 95.37%. A more hydrated patch that is water-permeable is created by the hydrophilic polymer layer. This hydration process enables the polymer matrix to be lost, leading to an improved drug release of over 95.5% within 6 to 7 hours, which is sufficient for immediate release. The qualities that were considered while choosing the polymeric transdermal patch (FLT3) were its outward

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look, percentage elongation, folding endurance, swelling ratio, moisture content, type of moisture absorption, drug content, and parameters from the in-vitro drug release research. Using diffusion kinetics with sustained release over a predetermined time period, the release kinetic investigation verified that the produced patch followed the supercase II transport mechanism. The r2 values from the regression analysis indicated that the curves were reasonably linear, and the graph allowed us to calculate the slope values. The values of the release exponent "n" ranged from 1.033 to 1.169. The observed departure from the Fickinan mechanism of drug release and the release exponent "n" being less than 1.0 indicate a Super-case II transport mechanism. When the multilayered transdermal patch FLT3 was placed to the skin of rats, it enhanced the bioavailability of the medication. The quick absorption of the drug, as shown by better Cmax and lower tmax values, led to an elevated concentration of the drug in the blood plasma of the rats. Tables 6.41–6.42 provide the pharmacokinetic parameters. Fluphenazine was released and absorbed at a rate of over 90% from 0 to 8 hours, according to the plasma drug concentration peak obtained from the manufactured transdermal patch FLT3. The area under the curve (AUC) plotting blood concentration against time is a measure of how well the model fits the data. It showed how much of the medicine makes it into the bloodstream after injection. Therefore, it is an essential metric for determining the bioavailability of a medicine in any dose form. According to Figure 6.34, the AUC0-t of the FLT3 formulation was noticeably greater ($p<0.05$). Significantly high AUC0-t values indicated that the medication concentration remained within the therapeutic effective range for an extended duration of therapy. When compared to the control patch, the main skin irritation investigation for formulation FLT3 in albino rats showed a score of less than two for erythema and edema. The results showed that the suggested formulation was skin-friendly when applied topically, suggesting that it might be suitable for commercialization down the road. It was determined that the created transdermal patches do not cause any skin irritation since formulations with scores of two or below are deemed negative. In accordance with ICH guidelines, a stability analysis of the constructed multilayered transdermal patch was conducted at various temperatures. The level or concentration of the medicinal component in the formulation did not vary or degrade much.

Summary and conclusion: A number of necessary physicochemical characteristics are included in the manufactured transdermal patches, including medication content homogeneity, weight, thickness, folding endurance, and moisture content. The researchers used enhanced in vitro diffusion assays. The most promising formulation was FLT3, which maintained the target therapeutic concentration in plasma for 12 hours while nearly matching the anticipated results. Results from FLT3's optimization efforts were shown in short-term stability experiments. According to the results of the current research, fluphenazine transdermal patches may show regulated release and stability. The formulations' stability studies showed that neither the drug concentration nor the physical properties of the patches changed significantly. The current study's aims, including enhanced bioavailability and decreased frequency of administration, were met by the formulation (FLT3). Additional pharmacodynamic and pharmacokinetic evaluation is possible, and studies have shown encouraging results. To evaluate the appropriateness, safety, and effectiveness of chosen formulations, it is necessary to conduct toxicity studies using various experimental animals.

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Table 1: Preparation of fluphenazine containing transdermal patch

F. Code	Polymers (gm)				Plasticizers		Penetration enhancer			
	Sodium alginate	Chitosan	Guar gum	Carboxy methyl cellulose	Glycerin (ml)	PVP (gm)	SLS (gm)	Tween 80 (ml)	Clove oil (ml)	Nutmeg oil (ml)

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FLT1	2	-	-	-	5	-	-	-	1	1
FLT2	-	2	-	-	5	-	-	-	1	1
FLT3	-	-	2	-	5	-	-	-	1	1
FLT4	-	-	-	2	5	-	-	-	1	1
FLT5	2	-	-	-	-	1	-	-	1	1
FLT6	-	2	-	-	-	1	-	-	1	1
FLT7	-	-	2	-	-	1	-	-	1	1
FLT8	-	-	-	2		1	-	-	1	1

Table 2: *in-vivo* animal study group division

S. No	Group	Formulation
1	I	oral solution
2	II	Transdermal patch (FLT3)

Table 3: *in-vivo* animal study group division

S. No	Group	Formulation
1	I	Normal
2	II	Blank
3	III	Transdermal patch (FLT3)

Table 4: Physical appearance of patch of Fluphenazine containing transdermal patch

Formulation code	Flexibility	Smoothness	Transparency	Stickness	Thickness (mm)	Average weight (mg)
FLT1	Flexible	Smooth	Opaque	Non sticky	0.27±0.02	114.43±1.152
FLT2	Flexible	Smooth	Opaque	Non sticky	0.34±0.031	141.31±1.112
FLT3	Flexible	Smooth	Opaque	Non sticky	0.32±0.022	114.23±1.121
FLT4	Flexible	Smooth	Opaque	Non sticky	0.33±0.011	135.50±0.124
FLT5	Flexible	Smooth	Opaque	Non sticky	0.34±0.014	127.13±1.104
FLT6	Flexible	Smooth - Rough	Opaque	Non sticky	0.31±0.015	115.23±1.105
FLT7	Flexible	Smooth - Rough	Opaque	Sticky	0.29±0.012	116.41±1.121
FLT8	Flexible	Smooth - Rough	Opaque	Sticky	0.32±0.021	118.17±1.124

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Table 4: Physical appearance of patch of Fluphenazine containing transdermal patch

Formulation code	Folding endurance	Percentage Elongation	Tensile Strength N/mm^2	Swelling ratio (%)	Surface pH	Drug content of patch (%)
FLT1	82-80	105.72±0.15	5.63 ±0.13	25.48 ± 0.45	5.6 ± 0.12	97.99±0.16
FLT2	61-60	84.22±0.25	5.61±1.02	24.01± 0.23	5.1 ± 0.04	94.91±0.15
FLT3	63-61	87.14± 0.11	6.29±0.14	38.02 ± 0.19	5.2 ± 0.04	96.05±0.85
FLT4	69-71	99.92± 0.21	7.08±0.14	49.01 ± 0.18	5.5 ± 0.02	97.19±0.24
FLT5	72-72	101.01± 0.27	7.19±0.15	43.01 ± 0.51	5.6± 0.02	98.19±0.19
FLT6	69-77	99.19± 0.16	7.01±1.11	32.01 ± 0.27	5.6 ± 0.03	99.03±0.18
FLT7	60-64	82.18±0.21	6.11±0.11	31.03 ± 0.34	5.2 ± 0.02	94.01±0.17
FLT8	72-73	93.01±0.18	6.01±1.01	41.03 ± 0.15	5.4 ± 0.04	99.48±0.19

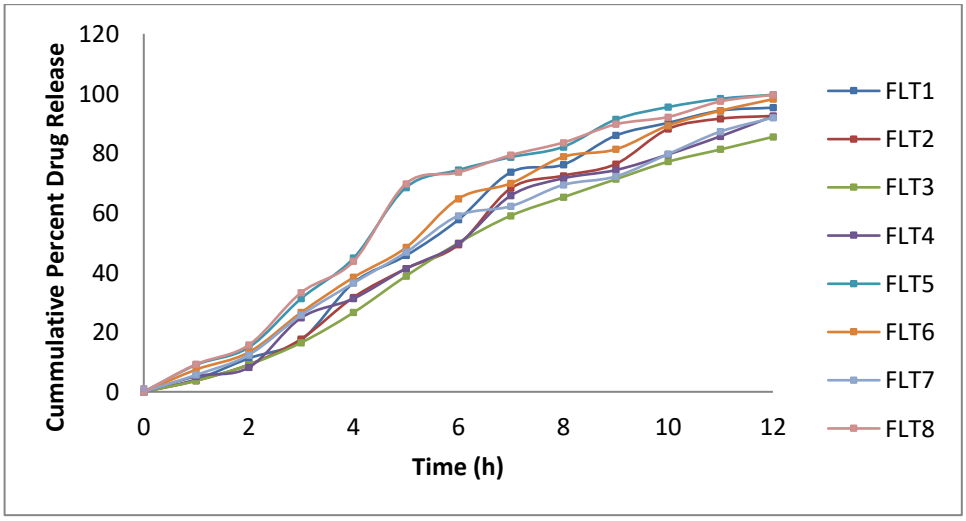

Figure 4: In vitro drug release profile (Zero-order) of Fluphenazine containing transdermal patch (FLT1-FLT8)

Table 5: Pharmacokinetic Studies of transdermal patch (FLT3)

S. No	Parameters	FTP3
1	C_{max} (µg/ml)	89.89±2.012
2	AUC $_{0-t}$ (µg h/ml)	186.707±3.144
3	T_{max} (h)	15.34± 0.12
4	t $_{1/2}$ (h)	3.31 ± 0.014
Mean ± SD, n = 3		

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Table 6: Results of skin irritation studies transdermal patch (FTP3)

S. No	Formulation	Visual observation	
		Erythmea	Edema
1	Normal	0.0±0.00	0.0±0.00
2	Blank	2.11±0.04	2.05 ± 0.04
3	Transdermal patch (FTP3)	2.71± 0.03	2.81 ± 0.11