Physical Education, Health and Social Sciences

https://journal-of-social-education.org

E-ISSN: 2958-5996

P-ISSN: 2958-5988

Design, Formulation Development and Characterization of Transdermal Patches Loaded with Pseudoephedrine and Loratadine

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DOI: https://doi.org/10.63163/jpehss.v3i2.422

Abstract

The purpose of this study was to develop the transdermal patch with a combination of pseudoephedrine HCL and Loratadine. Various formulations of these anti-anthetic drugs were prepared using Eudragit RL100 as primary polymer. Ethyl cellulose (EC), twin 80, isopropyl myristate (IPM), Propylene Glycol (PG), and Span 20 were included as those who enhance transit. The finished patch was evaluated to their visual properties, including clarity, smoothness and brittleness. Additionally, thickness, pharmaceutical content, Fourier transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD) were performed. Drug release was evaluated through in vitro disintegration studies and evaluated using a USP Dissolution apparatus. The results demonstrated that the choice of enhancers affected drug release and transit profiles. The patch made with castor oil displayed the lowest levels of drug release and transit for both pseudoephedrine HCL and Loratadine (56.37% PSE and 54.37% LT). In contrast, the formulation with isopropyl myristate showed the highest level of drug release and permit (62.42% PSE and 59.37% LT) at the end of 12 hours in vitro dissolution study. Physicochemical characterization was found stable. These findings indicate that a transdermal patch is possible to combine pseudoephedrine HCL and Loratadine drugs can be suitably developed as an alternate to conventional dosage forms. Whereas its release studies showed for both drugs can be effectively dependent by selecting proper enhancers.

Keywords: Pseudoephedrine HCl, Loratadine, Permeability Enhancers, Transdermal Patches

Introduction

The transdermal drug delivery system (TDDS) gives an alternative method to administer drugs through the skin using the patch. In this approach, the drug spreads through the skin to the bloodstream and later reaches the site of its action to increase medical effects. Compared to traditional routes, transdermal drug delivery allows releasing continuous drug over an extended period, increasing compliance with the patient and reducing dose frequency. In addition, this method bypasses hepatic first-pass metabolism, potentially reduces liver-related toxicity that is

usually associated with injected with into body (1). Pseudoephedrine (PSE) is usually used as an oral or topical decongestant. However, due to its stimulating properties, oral administration is often associated with adverse effects such as urinary retention (2)(3). Studies show that PSE may also have antitussive properties (4). Given its short half life of 4-5 hours, PSE is usually administered orally three to four times daily in a dose of 20 mg (5). Adverse effect produce by tachycardia, insomnia, hypotension, and shock. Pseudoephedrine has been indicated as an assistant in the management of nasal and sinus congestion, eustachian tube congestion, vasomotor rhinitis, and allergic rhinitis, sinusitis, otitis media and trachea bronchitis (6). The second generation of antihistamines, loratadine (LT) is widely used to treat allergies such as grass fever and urticaria. It is often combined with pseudoephedrine in oral dose forms. Common side effects include drowsiness, dry mouth and headache. Marketed since 1988, Loratadine has been included in the WHO list of essential drugs and is available as a general, over-the-counter medicine in the United States (7**).** Nonetheless, low permeability of the drugs is the major impediment for delivering the drug via skin. Permeation enhancers can be utilized to breach the barrier of skin and increase the drug permeation through skin (8). Chemical penetration enhances reversibly the structure of stratum corneum. Drug permeation may also be improved by increasing its solubility in subject's skin (9). Asthma is an inflammatory disease, and it creates a problem in breathing (10). In such a situation it necessitates multi-drug therapy (11). The aim of this study is to formulate Transdermal Patches Loaded with Pseudoephedrine and Loratadine, assess physicochemical characterization, FTIR, XRD and different chemical enhancers were used to improve its release study.

Materials:

Pseudoephedrine HCl and loratadine were generously provided as gift samples by Martindow (Quetta, Pakistan). Polyvinyl alcohol (PVA; molecular weight 72,000) and Eudragit RL 100 isopropyl myristate (IPM), Tween 20, castor oil and Span 20 were obtained from Pharmaceutics lab UOB. Propylene glycol (PG) and Methanol were sourced from Martindow.

Preparation of the Backing Membrane:

Patch backing membrane was prepared using a 4% w/v solution of polyvinyl alcohol (PVA). To formulate this solution, PVA was dissolved in distilled water under continuous stirring at 80 °C using a hot plate magnetic stirrer. After total dissolution, the solution was settled to cool to room temperature and subsequently deaerated using a sonicator for 2 minutes. A volume of 15 mL of the resulting solution was then poured into glass petri dishes (approximately 61 cm^2 surface area) and left to air-dry for 24 hours at ambient room conditions (25 °C, 75% relative humidity) (5,12). These controlled environmental parameters were maintained to promote uniform film formation, ensuring suitability for transdermal patch fabrication (13). According to Sharma and Chandy, PVA membranes formed under ambient drying conditions exhibit excellent physicochemical properties. The PVA-based membrane is water-impermeable, providing a protective barrier to shield the transdermal system from environmental exposure. Additionally, PVA creates an occlusive environment that promotes enhanced drug permeation through the skin (14). Owing to these beneficial properties, PVA is one of the most widely used polymers in the manufacture of transdermal patch backing membranes (15,16).

Formulation and Casting of the Matrix Solution:

The composition of matrix formulations per 100 mL of dispersion is outlined in Table 1. To prepare the matrix solution, 5 g of Eudragit RL 100 was dissolved in 100 mL of methanol in a 250 mL conical flask. Flask was tightly closed, and the solution was stirred at 500 rpm utilizing a

magnetic stirrer for 30 minutes. Following complete dissolution, the selected plasticizer and permeation enhancers were inserted, and the mixture was stirred for an additional 30 minutes. Subsequently, 540 mg of pseudoephedrine HCl and 180 mg of loratadine were incorporated into the solution and stirred for 30 minutes to ensure homogeneous dispersion. This amount of drug ensures each 1.5 cm^2 patch contains approximately 30 mg of pseudoephedrine and 10 mg of loratadine. The final mixture was sonicated for 5 minutes to eliminate entrapped air bubbles. Ten milliliters of the prepared matrix dispersion were carefully poured onto each petri dish containing a preformed PVA backing membrane. The dishes were then placed on a level surface and covered with inverted funnels to reduce the rate of solvent evaporation. The patches were left to dry undisturbed at room temperature for 24 hours. Once dried, the drug-loaded transdermal patches were gently peeled off, wrapped in aluminum foil, and stored at 25 °C until further evaluation (5).

Table 1. Transdermal Patches preparation.

Chemicals	F1	F2	F3	F4	F5
Eudragit R L 100 (g)	5	5	5	5	5
IPM(g)	-	5	-	-	-
Tween 20 (g)	5	-	-	-	-
Castor oil (g)	-	-	5	-	-
Span 20 (g)	-	-	-	5	-
PG (g)	1.50	1.50	1.50	1.50	1.50
Methanol (ml)	100	100	100	100	100

Cutting of Patches

The dried films were carefully cut into circular patches using a custom-designed stainless-steel cutter with a surface area of 1.5 cm^2. From each petri dish, a total of eighteen uniform patches of 1.5 cm^2 were obtained.

Physical assessment of transdermal patch

Physical Appearance and Uniformity

Transdermal patches were visually examined for physical uniformity, including the absence of surface irregularities such as texture variations, excessive lubrication, lack of clarity, and brittleness (5). Weight uniformity was assessed by selecting three patches from each formulation and weighing them individually using an analytical balance (Shimadzu AUX220, Germany) (5).

Thickness measurement

The patch thickness was measured using a digital micrometre screw gauge (Sharpfine Type-A, China). For accuracy, each patch was assessed at three diverse points, and average value was recorded (5)

Folding endures test

Folding endures were tested manually by folding each patch repeatedly in the same place until the brake or visible crack appeared. Each patch was recorded in the number of folds without breaking. The test was conducted on three patches per formulation, and the average price was reported (5,17).

Moisture content

The moisture condition was determined to evaluate patch stability and integrity under humid conditions. The exact weight 1.5 cm^2 patch samples were placed in a desiccator at room temperature for the first 24 hours. Subsequently, they were transferred to another desiccator, which was maintained on 84% relative humidity using saturated potassium chloride solution. The patch was weighed at intervals until a continuous weight was obtained. The moisture was calculated using (%) formula (18).

Tensile strength

Tensile strength was evaluated utilizing a modified diary system to determine the mechanical strength of the patch. Rectangular strips of 2 cm length and 1 cm width were held between two jaws. The weight was slowly added until the patch broke (19).

FTIR spectroscopy analysis

The Fourier Transform Infrared (FTIR) spectroscopy was employed to detect any possible chemical interactions between drugs and exercises. Both FTIR spectra were recorded for pure drug powder and selected transdermal patch formulation [5].

X-ray diffraction analysis

The X-ray diffraction (XRD) was demonstrated to examine the physical condition (unaccounted or crystalline) of the drug within the matrix. Defrectograms were obtained using a panalitical system (Netherlands) with CU-K μd on 30 kv and 15 MA. The measurements were held at ambient temperatures using a scan rate of 2 °/min, a step size of 0.02 ° and 2 ° range 2 ° to 60 ° (5).

Drug material uniformity

The drug material analysis was performed according to the methods described by Gupta et al. And Dandgi et al. The 1.5 cm drug-loaded and drug-free patch (blank) were cut into small pieces and submerged in 100 mL distilled water in separate conical flasks. The samples were continuously shaken on a magnetic sterile for 36 hours, followed by sonication for 30 minutes. The solutions were filtered, diluted appropriately, and analyzed for loratadine and pseudoedrine HCL and 283 Nm at 257 nm utilizing a double-beam UV-Visible spectrophotometer (Shimdzu-1601, Germany).

In in vitro drug release studies

The in vitro drug release was evaluated using a USP dissolution mechanism (PT-DT7, pharma test, Germany). The patches of 1.5 cm kg (30 mg PSE and 10 mg LT containing 30 mg PSE and 10 mg LT) were pasted to see glasses with stainless steel mesh and clip. Since both medicines are soluble in water, distilled water was used as a dissolution medium (500 mL). The paddle rotation was set on 50 rpm. The patch was stationed at the bottom of the basket, 5 mL samples at predetermined intervals (0, 0.5, 1, 2, 3, 4, 5, 6 and 12 hours), which were filtered through Millipore filters. Drug concentrations were determined spectrophotometrically. Each formulation was tested in triplicate, and mean values were reported.

Results and Discussion

This study aimed to formulate matrix-type transdermal patches containing a combination of anti-asthmatic drugs Pseudoephedrine and Loratadine using the solvent casting (plate casting) method, followed by comprehensive in vitro evaluation. Eudragit RL 100 was utilized as the

primary polymer matrix, whiles various permeation enhancers, including, isopropyl myristate (IPM), Tween 20, castor oil, and Span 20, were incorporated to assess their influence on drug permeation. Propylene glycol (PG) was employed as a plasticizer. The impact of each permeation enhancer on drug release was systematically investigated.

Physical Characteristics

Visual inspection revealed that patches formulated with IPM, Tween 20, castor oil, and Span 20 were smooth, transparent, furthermore not required external plasticizer (Table 2). This may be attributed to the inherent plasticizing effect of the selected permeation enhancers. Weight variation results (Table 3) demonstrated minimal standard deviations, confirming uniformity in patch mass across batches. Similarly, thickness measurements taken at three distinct points per patch confirmed consistent film thickness (Table 3). PG was mainly added as a plasticizer to reduce membrane brittleness and rigidity, thereby enhancing smoothness, flexibility, and appearance (20). However, other formulations containing IPM, Tween 20, castor oil, and Span 20 displayed satisfactory mechanical properties even without additional plasticizer, indicating these excipients possess intrinsic plasticizing potential. It was also discussed; plasticizers generally function by disrupting polymer chain interactions, leading to softer, more pliable films (21). All patches exhibited acceptable folding endurance values, further confirming flexibility and mechanical strength (Table 3).

Moisture Uptake and Tensile Strength

Moisture uptake studies, conducted at 84% relative humidity, showed low absorption across all formulations (Table 3), which is likely due to the hydrophobic nature of Eudragit RL 100. Lower moisture absorption enhances long-term stability and minimizes microbial contamination risks mentioned by (22). Tensile strength measurements confirmed that all patches possessed sufficient mechanical integrity and elasticity for potential application (Table 3).

Drug Content Uniformity:

Drug content analysis (Table 4) confirmed uniform distribution of both PSE and LT across all patches, with negligible variability between different formulations. These findings support the effectiveness of the plate casting method for producing drug-uniform films.

FTIR Spectroscopic Analysis:

FTIR analysis was conducted to detect any possible interactions between the drugs and excipients. Spectra of pure PSE, LT, and Eudragit RL 100 revealed characteristic peaks without significant shifts or disappearance in the final formulations (Fig. 1a–d). The presence of intact functional group peaks indicates no chemical interaction occurred between the drugs and polymer matrix.

X-ray Diffraction:

XRD analysis was used to assess the crystalline or amorphous nature of the drug within the patch matrix. Pure PSE and LT exhibited sharp diffraction peaks at 2θ values of 10.52°, 17.23°, and 21.18°, confirming their crystalline nature. In contrast, the drug-loaded patch formulations displayed diminished or fused peaks, indicating a transition to an amorphous state within the polymer matrix (Fig. 2a–d). This suggests molecular dispersion of the drugs in the film.

In vitro drug release:

The drug release data more than 12 hours is depicted in figures 1 and 2. Between all yogas, F2 (containing IPM as an ancestor) demonstrated the highest drug release for both PSE and LT. This

increased release can be attributed to the hydrophilic character of Eudragit RL 100, which allows water absorption, inflammation and subsequent drug proliferation also discussed (23) due to its clever ammonium groups. Additionally, the use of plasticizer and transit enhancer provided the facility to release drug by increasing polymer flexibility and permeability. The high release rate seen in F2 is likely to be due to the soluble effect of the IPM for both drugs shown in Fig 3 and Fig 4. In contrast, the formulation F5, which lacks any increase, showed the least cumulative drug release. Other enhancers -containing formulation display intermediate release profiles, which confirm the positive effects of the enhancers on drug permeability and spread.

Conclusion

This study successfully evaluated transdermal patches loaded with PSE and LT. All finished patch performed satisfactory physical chemical and mechanical properties with a similar drug spread. Between tested formulations, F2 included IPM as enhancer showed an increase in vitro drug release profiles, the most favorable in the profile. Whereas F5 showed lower release. All enhancer indicated its higher release of both drugs. The study indicated a complete data to develop and optimize transdermal patches of combine drugs by applying different enhancers.

Table 2. Visual appearance of transdermal Patches

Formulation Code	Clarity	Brittleness	Smoothness	Appearance
F1	X	+	x	Acceptable
F2	+ +	++	++	Acceptable
F3	+	x	+	Acceptable
F4	++	+	x	Acceptable
F5	X	+	++	Acceptable

Table 3. Physicochemical Properties of Transdermal Patches

Formulation	Thickness (µm)	Weight variation (mg)	Moisture content (%)	Folding endurance	Tensile strength (Kg/Cm^2)
F1	22.21	28.32	3.21	180.23	0.76
F2	31.23	30.39	2.93	176.43	0.64
F3	25.34	26.32	3.12	181.32	0.66
F4	24.32	25.43	3.12	179.43	0.76
F5	25.45	26.23	2.54	178.98	0.67

Table 4. Content uniformity of the formulation PSE and LT

Formulation	PSE	LT
F1	97.12	98.34
F2	98.11	99.45
F3	97.23	97.45
F4	98.34	98.34
F5	99.22	97.55

PSE=Pseudoephedrine,LT= Loratadine

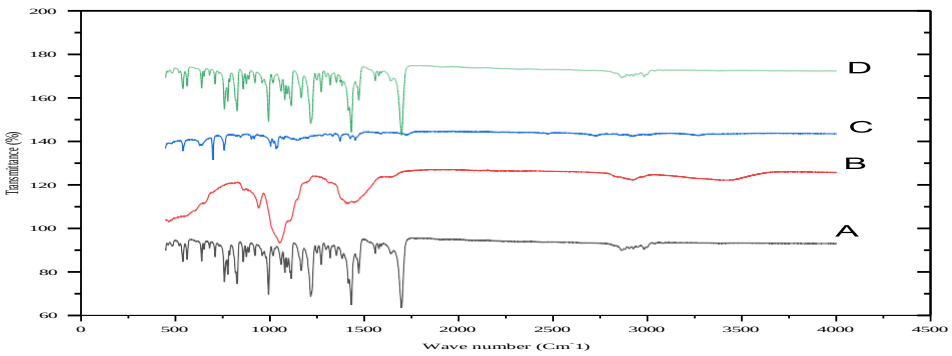

Figure.1 FTIR spectra of Pseudoephedrine drug A, Loratadine drug D, Eudragit L B, Formulation C

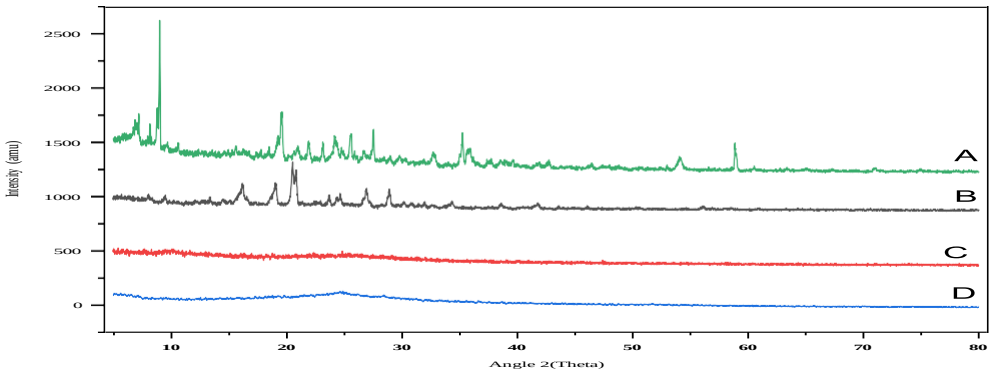

Figure 2. Xrd spectra of Pseudoephedrine drug A, Loratadine drug B, Eudragit L C, Formulation D

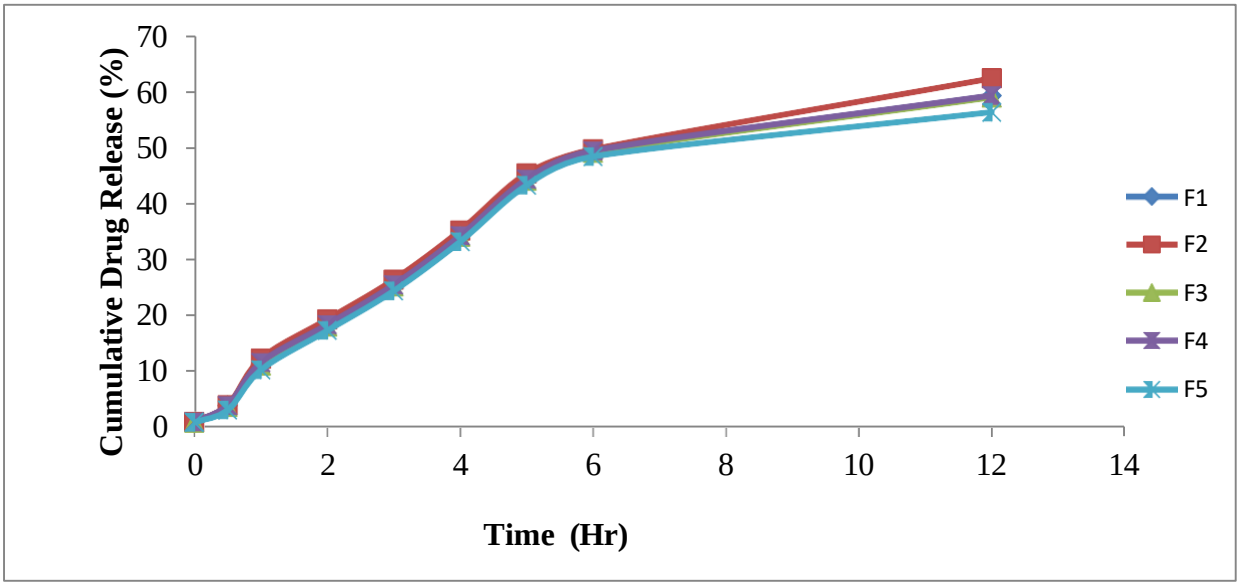

Figure.3 Release study of Pseudoephedrine from transdermal patches with various enhancers

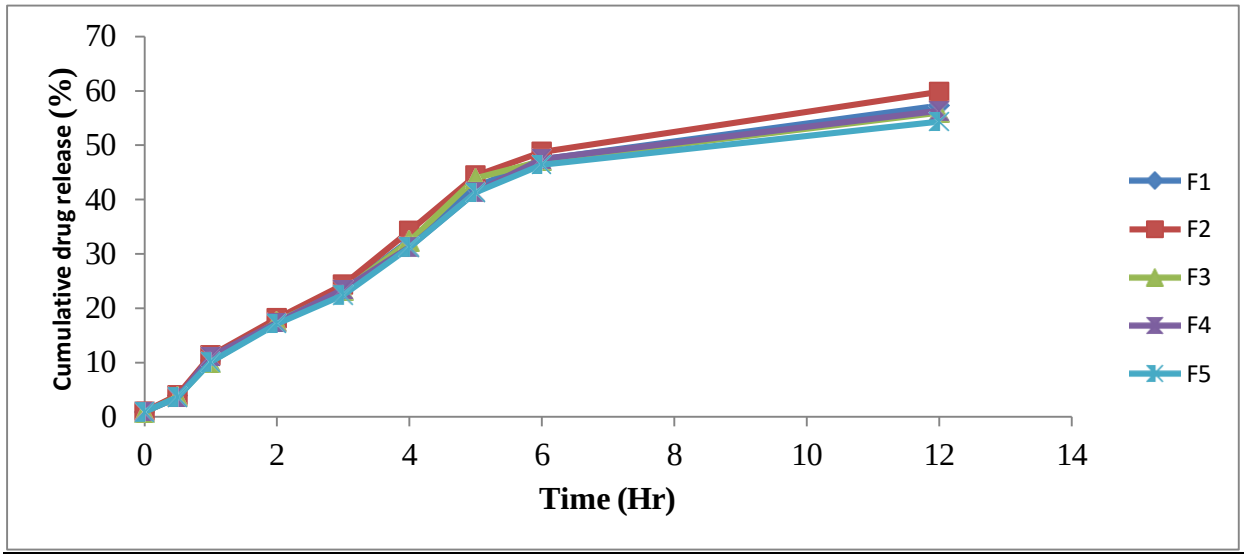

Figure.4 Release study of loratadine from transdermal patches with various enhancers

Conflict of interest

We have no conflict of interest.

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