Development and Physicochemical Characterization of Fluconazole-Loaded Transdermal Patch with Enhanced Stability using Natural Polymers

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ABSTRACT

The present study aimed to develop and optimize a fluconazole-loaded transdermal patch using natural polymer obtained from Adansonia digitata fruit mucilage to achieve sustained drug release and enhanced formulation stability. Mucilage was extracted and characterized for its film-forming properties. Fluconazole was evaluated through preformulation and compatibility studies, which confirmed its suitability and compatibility with formulation excipients. Transdermal patches were prepared by the solvent casting method and optimized using a three-factor, three-level Box–Behnken Design. The effects of polymer ratio, glycerol concentration, and oleic acid concentration on tensile strength and drug release were investigated. The optimized formulation contained a mucilage:PVA ratio of 2:1, 30% w/w glycerol, and 6% w/w oleic acid, exhibiting satisfactory tensile strength (5.22 MPa) and maximum drug release (88.2% at 24 h). The developed transdermal patch demonstrated promising potential for sustained fluconazole delivery, improved stability, and enhanced patient compliance.

Keywords: Fluconazole, Transdermal Patch, Adansonia digitata Mucilage, Natural Polymer, Box–Behnken Design, Sustained Drug Release, Optimization, Drug Delivery System

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INTRODUCTION

Fungal infections remain a significant global health concern, affecting millions of individuals annually and contributing substantially to morbidity and healthcare costs. Superficial fungal infections of the skin, nails, and mucosal membranes are among the most prevalent infectious diseases worldwide, particularly in immunocompromised patients, diabetic individuals, and those receiving prolonged antibiotic or corticosteroid therapy.1 Among the available antifungal agents, fluconazole, a triazole derivative, is widely prescribed due to its broad-spectrum antifungal activity, favorable safety profile, and effectiveness against various Candida and Cryptococcus species.2 Despite its therapeutic advantages, oral administration of fluconazole is associated with several limitations, including gastrointestinal disturbances, variable bioavailability, hepatic first-pass metabolism, and the need for repeated dosing in chronic fungal infections, which may compromise patient compliance and therapeutic outcomes.[3]

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to conventional oral and parenteral routes for delivering therapeutic agents.4 Transdermal patches are designed to deliver drugs across the skin into systemic circulation at a predetermined rate over an extended period.5 Such systems offer several advantages, including avoidance of first-pass metabolism, sustained drug release, reduced dosing frequency, improved patient compliance, and maintenance of relatively constant plasma drug concentrations.[6]

The skin serves as an effective biological barrier due to the presence of the stratum corneum, which restricts the permeation of many therapeutic molecules. Consequently, the development of an effective transdermal formulation requires careful selection of polymers, plasticizers, permeation enhancers, and other excipients to ensure adequate drug permeation and controlled release.[7],[8]

Natural polymers derived from plant sources have attracted significant attention in drug delivery research owing to their abundance, biodegradability, biocompatibility, non-toxicity, and environmental sustainability. Polysaccharides, gums, mucilages, and cellulose derivatives exhibit excellent film-forming ability, swelling behavior, and mechanical strength, making them suitable candidates for transdermal patch development.9 Furthermore, natural polymers can provide controlled drug release and enhanced formulation stability while minimizing the risk of skin irritation often associated with synthetic polymers.10,11

Several natural polymers, including pectin, sodium alginate, guar gum, xanthan gum, tamarind seed polysaccharide, and plant-derived mucilages, have been successfully employed as matrix-forming agents in transdermal systems.12 These materials possess favorable properties such as flexibility, bioadhesion, moisture retention, and compatibility with various therapeutic agents. 13The incorporation of plasticizers and permeation enhancers can further improve film characteristics and facilitate drug transport through the skin.14

Fluconazole possesses physicochemical characteristics suitable for transdermal administration. The drug exhibits potent antifungal activity at relatively low concentrations and possesses a molecular weight favorable for permeation enhancement strategies.15 However, achieving sustained and controlled delivery requires optimization of formulation variables and polymer composition. Natural polymer-based transdermal patches can provide prolonged drug release and maintain therapeutic drug levels over an extended period, thereby improving the management of chronic fungal infections.16

Stability is a critical consideration during the development of transdermal drug delivery systems. Environmental factors such as temperature, humidity, and light exposure can significantly influence the physical appearance, drug content, mechanical properties, and therapeutic performance of transdermal patches.17 Therefore, enhancing the stability of fluconazole-loaded systems is essential to ensure product quality and efficacy throughout storage. Natural polymers have demonstrated the ability to form stable polymeric networks that protect incorporated drugs and preserve formulation integrity.18

Physicochemical characterization plays a crucial role in the optimization of transdermal patches. Parameters including thickness, weight variation, folding endurance, tensile strength, moisture content, moisture uptake, drug content uniformity, surface pH, and in-vitro drug release provide valuable information regarding formulation quality and performance.19 Additionally, compatibility studies using FTIR and DSC are widely employed to identify potential interactions between drugs and excipients that may influence stability and therapeutic efficacy.20,21

Recent research trends emphasize the utilization of biodegradable and naturally derived materials to promote sustainable pharmaceutical development.22 Natural polymer-based transdermal patches align with these objectives by reducing dependence on synthetic materials while maintaining excellent pharmaceutical performance. Such systems offer patient-friendly dosage forms capable of improving treatment adherence and therapeutic outcomes.23

Therefore, the present study was undertaken to develop and physicochemically characterize a fluconazole-loaded transdermal patch using natural polymers with the objective of enhancing formulation stability and achieving sustained drug release. The successful development of a stable and effective fluconazole transdermal patch may provide a promising alternative approach for antifungal therapy and contribute to advancements in transdermal drug delivery technology.

MATERIAL AND METHOD

MATERIAL

Fluconazole was obtained as a gift sample from Taj Pharma India Ltd., Vapi, Gujarat, India, . Adansonia digitata fruits were collected from Mandavgad, Madhya Pradesh, India, The co-polymer, plasticizer, permeation enhancer, ethanol, distilled water, and phosphate buffer salts (pH 7.4) were procured from Merck Specialities Pvt. Ltd., Mumbai, India, and Qualigens Fine Chemicals, India. give in proper language

COLLECTION AND AUTHENTICATION OF PLANT MATERIAL

Dried fruits of Adansonia digitata were procured from Mandavgad, Madhya Pradesh, India. The plant material was authenticated by a qualified botanist, and the fruit pulp was separated, cleaned, and stored in airtight containers for further use.

EXTRACTION OF MUCILAGE

The dried fruit pulp was soaked in distilled water (1:10 w/v) for 24 h, followed by heating at 60–70 °C for 1 h with continuous stirring. The slurry was filtered through muslin cloth, and the mucilage was precipitated using acetone (1:3 v/v). The precipitated mucilage was washed, dried at 40 ± 2 °C, pulverized, sieved through sieve no.^{60}, and stored in a desiccator until further use.

PREFORMULATION STUDIES .

Preformulation studies were carried out to assess the suitability of fluconazole for transdermal patch development. Organoleptic properties such as color, odor, and appearance were evaluated visually. Solubility studies were performed in distilled water, ethanol, and hydroalcoholic mixtures. The λmax of fluconazole was determined using UV–Visible spectrophotometry, and a calibration curve was prepared using standard drug solutions. The calibration plot was used for subsequent drug content and in-vitro release analyses

COMPATIBILITY STUDIES

FTIR analysis were performed on Drug and Physical mixture (Drug +excepients) to evaluate drug–polymer compatibility, thermal behavior, and surface morphology. The studies confirmed the absence of significant drug–polymer interactions, demonstrated satisfactory thermal stability, and revealed uniform drug distribution within the polymeric matrix.

PREPARATION OF FLUCONAZOLE-LOADED TRANSDERMAL PATCHES

OPTIMIZATION OF FORMULATION

The present study aimed to optimize a fluconazole-loaded transdermal patch using a Box–Behnken Design (BBD). Three formulation variables, namely polymer ratio (X_1), glycerol concentration (X_2), and oleic acid concentration (X_3), were evaluated for their effects on tensile strength and drug release. The statistical design enabled efficient optimization with a reduced number of experimental runs.

EXPERIMENTAL DESIGN

Fluconazole-loaded transdermal patches were prepared using a 3-factor, 3-level Box–Behnken Design comprising 15 experimental runs.

Table 1. Independent variable Design

Factor	**Level used, actual (coded)**		
Independent Variables	Low (-1)	Medium (0)	High (+1)
X1 = Polymer Ratio (Mucilage:PVA)	1.1	2.1	3.1
X2 Glycerol (% w/w)	10	20	30
X3 =Oleic Acid(% w/w)	2	4	6

PROCEDURE

Transdermal patches were prepared by the solvent casting method. Adansonia digitata mucilage and PVA were dispersed in the solvent system, followed by incorporation of fluconazole, glycerol, and oleic acid. The homogeneous solution was cast onto glass Petri dishes, dried at 40 ± 2°C, peeled, and stored in a desiccator for evaluation.24

Table 2. Box–Behnken Design Matrix

Run	Polymer Ratio (Mucilage:PVA)	Glycerol (% w/w)	Oleic Acid (% w/w)
1	3:1	30	4
2	2:1	20	4
3	2:1	20	4
4	3:1	10	4
5	3:1	30	2
6	2:1	10	2
7	2:1	20	4
8	1:1	20	6
9	2:1	30	2
10	2:1	10	6
11	1:1	20	2
12	1:1	10	4
13	1:1	30	4
14	3:1	20	6
15	2:1	30	6

PHYSICOCHEMICAL CHARACTERIZATION OF TRANSDERMAL PATCHES

THICKNESS MEASUREMENT

The thickness of the transdermal patches was measured using a calibrated digital micrometer at five different locations (center and four corners). The average thickness was calculated to assess film uniformity.

WEIGHT UNIFORMITY

Patches of fixed dimensions (2 cm × 2 cm) were individually weighed using a digital analytical balance. The mean weight and percentage variation were calculated to evaluate uniformity of film casting.

FOLDING ENDURANCE

Folding endurance was determined by repeatedly folding a patch at the same point until it broke. The number of folds sustained before breaking was recorded as the folding endurance value.

5.4 SURFACE PH

The surface pH of the patches was measured after moistening the film with distilled water for 1 h. A calibrated digital pH meter electrode was gently placed on the film surface, and the pH was recorded.

MOISTURE CONTENT

Accurately weighed patches were placed in a desiccator containing anhydrous calcium chloride for 24 h. The patches were reweighed, and the percentage moisture content was calculated from the weight loss.

MOISTURE UPTAKE

Pre-weighed patches were exposed to 75% relative humidity using a saturated sodium chloride solution for 24 h. The increase in weight was recorded and expressed as percentage moisture uptake.

TENSILE STRENGTH AND PERCENTAGE ELONGATION

Mechanical properties were evaluated using a texture analyzer. Film strips were stretched until breakage, and tensile strength and percentage elongation were calculated from the obtained force and extension values.

WATER VAPOR TRANSMISSION RATE (WVTR)

WVTR was determined using vials containing anhydrous calcium chloride sealed with the patch. The assembly was stored at 75% RH, and weight gain was measured periodically to calculate water vapor transmission through the film.

DRUG CONTENT UNIFORMITY

A patch (2 cm × 2 cm) was dissolved in a suitable solvent system and stirred to ensure complete drug extraction. The solution was filtered, diluted appropriately, and analyzed using UV–Visible spectrophotometry at the predetermined λmax of fluconazole to determine drug content uniformity.

IN VITRO DRUG RELEASE STUDY

The in vitro drug release of the optimized fluconazole-loaded transdermal patch was evaluated using a USP Type V (Paddle-over-Disk) dissolution apparatus. Phosphate buffer (pH 7.4) was used as the dissolution medium and maintained at 32 ± 0.5 °C with a paddle speed of 50 rpm. Samples were withdrawn at predetermined intervals and replaced with fresh buffer to maintain sink conditions. The collected samples were analyzed using a UV–Visible spectrophotometer at the predetermined λmax of fluconazole. The cumulative percentage drug release was calculated and used to determine the release profile of the optimized transdermal patch.25

Top of Form

RESULT

EXTRACTION AND CHARACTERIZATION OF ADANSONIA DIGITATA FRUIT MUCILAGE

The isolated Adansonia digitata fruit mucilage was obtained as a light cream-colored, free-flowing powder with a characteristic odor. The extraction yield was 18.64 ± 0.92% w/w, indicating good recovery of polysaccharide material. The mucilage exhibited excellent hydration capacity and formed a uniform viscous dispersion in water, demonstrating its suitability as a natural film-forming polymer for transdermal patch formulation.

PREFORMULATION STUDIES

Preformulation studies confirmed the suitability of fluconazole for transdermal patch formulation.

Table 3. Preformulation Results of Fluconazole

Parameter	Observation
Color	White
Appearance	Crystalline powder
Odor	Odorless
Solubility in Water	Slightly soluble
Solubility in Ethanol	Soluble
Solubility in Hydroalcoholic Mixture	Freely soluble
λmax	260 nm
Calibration Range	2–12 µg/mL
Regression Equation	$y = 0.051x + 0.0034$
Correlation Coefficient (R^2)	0.9998
Suitability	Suitable for transdermal patch formulation

Table 4. Experimental Design and Observed Responses

Std	Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2
		A:Polymer ratio	B:Plasticizer concentration(% w/w)	C:Permeation enhancer(% w/w)	Tensile strength(MPa)	% drug release(%)
4	1	3:1	30	4	6.48	66.8
13	2	2:1	20	4	6.54	71.2
15	3	2:1	20	4	6.61	70.8
2	4	3:1	10	4	8.94	52.6
6	5	3:1	30	2	7.96	48.9
9	6	2:1	10	2	7.42	54.3
14	7	2:1	20	4	6.47	71.5
7	8	1:1	20	6	4.88	78.6
10	9	2:1	30	2	5.64	74.8
11	10	2:1	10	6	7.18	69.6
5	11	1:1	20	2	5.12	63.7
1	12	1:1	10	4	5.82	68.4
3	13	1:1	30	4	4.36	82.3
8	14	3:1	20	6	6.92	61.4
12	15	2:1	30	6	5.22	88.2

Table 5. Composition and Response Profile of Optimized Formulation

Parameter	Optimized Formulation Result
Optimized batch	Run 15
Polymer ratio (Mucilage:PVA)	2:1
Adansonia digitata mucilage	667 mg
Polyvinyl alcohol (PVA)	333 mg
Fluconazole	250 mg
Glycerol concentration	30% w/w (300 mg)
Oleic acid concentration	6% w/w (60 mg)
Tensile strength	5.22 MPa
Drug release at 24 h	88.2%
Optimization method	Box–Behnken Design (BBD)
Suitability	Selected as optimized formulation

Table 6. Evaluation Results of Optimized Transdermal Patch

Parameter	Result
Appearance	Smooth, uniform, flexible film
Polymer ratio (Mucilage:PVA)	2:1
Tensile Strength	5.22 MPa
Drug Release at 24 h	88.2%
Film Integrity	Acceptable
Mechanical Performance	Satisfactory
Optimization Status	Optimized formulation (Run 15)

COMPATIBILITY STUDIES

The FTIR spectrum of the physical mixture exhibited characteristic peaks of fluconazole and formulation excipients without significant peak disappearance or formation of new peaks. Minor shifts and broadening indicated possible hydrogen bonding, while retention of major functional groups confirmed drug–excipient compatibility and formulation stability.

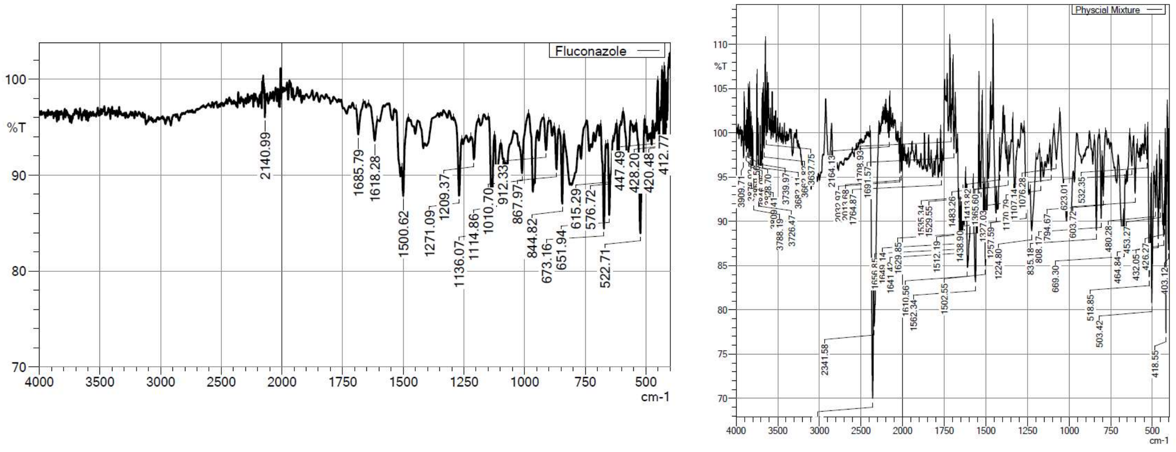

Figure 1 FTIR spectrum of fluconazole (A) and physical mixture(B)

OPTIMIZATION USING BOX–BEHNKEN DESIGN (BBD)

PREPARATION OF FORMULATIONS

The fluconazole-loaded transdermal patch formulations were prepared according to a three-factor, three-level Box–Behnken design to evaluate the influence of polymer ratio (Adansonia digitata mucilage:PVA), glycerol concentration, and oleic acid concentration on formulation performance. A total of 15 experimental runs were generated and evaluated for two dependent responses, namely tensile strength and percentage drug release at 24 h. The tensile strength values ranged from 4.36 to 8.94 MPa, indicating a significant effect of polymer ratio, plasticizer concentration, and permeation enhancer level on the mechanical properties of the films. The percentage drug release ranged from 48.9% to 88.2%, demonstrating the influence of formulation variables on drug diffusion and release behavior. Higher mucilage content improved tensile strength but reduced drug release, whereas increased glycerol and oleic acid concentrations enhanced drug release while decreasing film strength. These findings confirmed that the selected formulation variables significantly affected the physicochemical and release characteristics of the fluconazole-loaded transdermal patches.

OPTIMIZED FORMULATION SELECTION

Statistical analysis using Design-Expert® software indicated that the developed quadratic models were significant for both tensile strength and drug release responses. Among all experimental formulations, Run 15 as the optimized formulation, containing a 2:1 mucilage:PVA ratio, 30% w/w glycerol, and 6% w/w oleic acid. The formulation exhibited 5.22 MPa tensile strength and 88.2% drug release at 24 h, providing an optimal balance between mechanical strength and release performance. Therefore, it was selected for further characterization, compatibility studies, and stability evaluation.

EVALUATION OF OPTIMIZED FLUCONAZOLE-LOADED TRANSDERMAL PATCH

The optimized transdermal patch exhibited satisfactory mechanical strength and excellent drug release characteristics. The formulation showed uniform film formation, adequate flexibility, acceptable tensile strength and enhanced fluconazole 88.2% release over 24 h.

CONCLUSION

The present study successfully developed and optimized a fluconazole-loaded transdermal patch using Adansonia digitata fruit mucilage as a natural film-forming polymer in combination with polyvinyl alcohol. The extracted mucilage exhibited satisfactory physicochemical properties, hydration capacity, and film-forming ability, confirming its suitability for transdermal drug delivery applications. Fluconazole showed good compatibility with formulation excipients as confirmed by FTIR and DSC studies, while SEM analysis revealed a uniform and smooth surface morphology of the optimized patch.

Transdermal films prepared by the solvent casting method demonstrated acceptable physicochemical characteristics, including uniform thickness, weight variation, folding endurance, surface pH, moisture content, tensile strength, and drug content. In vitro drug release studies indicated sustained release behavior of fluconazole over 24 hours. Optimization using the Box–Behnken design identified polymer ratio, glycerol concentration, and oleic acid concentration as critical factors influencing mechanical properties and drug release performance.

The optimized formulation, containing a mucilage ratio of 2:1, 30% w/w glycerol, and 6% w/w oleic acid, exhibited satisfactory tensile strength (5.22 MPa) and maximum drug release (88.2% at 24 h). Overall, the developed transdermal patch represents a promising alternative for sustained delivery of fluconazole with improved therapeutic effectiveness and patient compliance.

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