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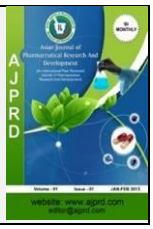

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Research Article

Design, Development and Evaluation of Transungal Adhesive Patch for Effective Treatment over Nail Fungal Infection

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ABSTRACT

Onychomycosis is one of the most common fungal nail infections and is often difficult to treat because the dense keratinized nail plate limits drug penetration. Although oral antifungal therapy is effective, prolonged treatment duration, systemic adverse effects, and drug interactions reduce patient compliance. Therefore, the development of a localized transungual drug delivery system capable of providing sustained drug release and enhanced nail permeation remains an important therapeutic objective.

The present study aimed to formulate and evaluate a Tavaborole-loaded transungual adhesive patch for the effective treatment of onychomycosis using the solvent casting technique.

Transungual adhesive patches were prepared using Hydroxypropyl Methylcellulose (HPMC E15 and HPMC K15M) and Polyvinyl Pyrrolidone K30 (PVP K30) as film-forming polymers, with Polyethylene Glycol 400 and PEG 600 as plasticizers. Multiple formulations (F1–F35) were prepared and evaluated for physicochemical characteristics, including thickness, weight variation, folding endurance, drug content, tensile strength, moisture content, and patch appearance. Drug-excipient compatibility was investigated using FTIR and DSC studies. The optimized formulation was subjected to in-vitro drug release, release kinetic modeling, and antifungal activity against Candida albicans.

Compatibility studies confirmed the absence of significant interactions between Tavaborole and the selected excipients. Among all prepared formulations, F25 exhibited optimum physicochemical characteristics with satisfactory flexibility, uniformity, and drug content. The optimized formulation demonstrated sustained drug release with high cumulative drug release, and kinetic analysis indicated that the release profile best fitted the Zero-order model. The formulation also exhibited appreciable antifungal activity against Candida albicans, confirming its potential for localized treatment of fungal nail infections.

Tavaborole-loaded transungual adhesive patches prepared by the solvent casting method demonstrated satisfactory physicochemical properties, sustained drug release, and promising antifungal activity. The optimized formulation (F25) may serve as an effective localized drug delivery system for the management of onychomycosis while minimizing systemic adverse effects.

Keyword: Tavaborole, Transungual adhesive patch, Onychomycosis, Solvent casting, HPMC, PVP K30, Franz diffusion study, Drug release kinetics.

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INTRODUCTION [1-10]

Onychomycosis is a chronic fungal infection of the fingernails or toenails caused primarily by dermatophytes, yeasts, and non-dermatophyte molds. It accounts for approximately 50% of all nail disorders and is characterized by nail discoloration, thickening, brittleness, onycholysis, and progressive destruction of the nail plate. Besides cosmetic concerns, the disease can cause pain, discomfort, impaired mobility, and a considerable reduction in patients' quality of life. Elderly individuals, diabetic patients, immunocompromised patients, and individuals with peripheral vascular disorders are particularly susceptible to developing onychomycosis.

The nail plate is composed of densely packed keratinized cells connected by extensive disulfide bonds, making it one of the most impermeable biological barriers in the human body. Compared with the stratum corneum, the nail plate is considerably thicker and exhibits low lipid content, which restricts the diffusion of most therapeutic agents. Consequently, achieving effective drug concentrations at

the site of infection through topical administration remains a major challenge in the treatment of fungal nail infections.

Conventional treatment of onychomycosis mainly involves systemic antifungal agents such as terbinafine, itraconazole, and fluconazole or topical formulations including ciclopirox, amorolfine, efinaconazole, and tavaborole. Although oral therapy generally provides higher cure rates, prolonged treatment duration, systemic toxicity, hepatotoxicity, drug interactions, and poor patient compliance limit its clinical usefulness. Conversely, topical formulations are safer but often exhibit poor therapeutic efficacy because of inadequate penetration through the highly keratinized nail plate and the need for prolonged daily application.

Transungual drug delivery has emerged as a promising approach for overcoming these limitations. Unlike conventional topical formulations, transungual delivery systems are specifically designed to enhance drug transport across the nail plate and maintain prolonged contact with the infected nail surface. Such systems improve local drug concentration while minimizing systemic exposure, thereby reducing adverse effects and improving patient compliance. Various formulation strategies, including medicated nail lacquers, hydrogels, nanoparticles, and adhesive patches, have been investigated to enhance ungual drug permeation.

Tavaborole is a novel boron-containing oxaborole antifungal agent that inhibits fungal leucyl-transfer RNA synthetase, thereby preventing fungal protein synthesis. Due to its low molecular weight and favorable physicochemical properties, Tavaborole demonstrates superior penetration through the nail plate compared with many conventional antifungal agents, making it an attractive candidate for transungual drug delivery systems.

In the present investigation, Tavaborole-loaded transungual adhesive patches were developed using the solvent casting technique with Hydroxypropyl Methylcellulose (HPMC E15 and HPMC K15M) and Polyvinyl Pyrrolidone K30 as film-forming polymers. Polyethylene Glycol 400 and Polyethylene Glycol 600 were incorporated as plasticizers to improve flexibility and facilitate drug permeation. Multiple formulations were prepared by varying polymer ratios to optimize the physicochemical and drug-release characteristics of the adhesive patches.

The formulated patches were characterized using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) to evaluate drug–excipient compatibility. The optimized formulation was further assessed for physicochemical properties, in vitro drug release using the Franz diffusion cell method, release kinetics, and antifungal activity. The objective of this work was to develop an effective transungual adhesive patch capable of providing sustained local delivery of Tavaborole for improved management of onychomycosis.

MATERIALS AND METHODS

MATERIALS

Tavaborole was received as a gift sample from Lubin Laboratories Pvt. Ltd., Mumbai, India. Hydroxypropyl methylcellulose (HPMC E15 and HPMC K15M) was procured from Colorcon Asia Pvt. Ltd., Goa, India. Polyvinyl pyrrolidone (PVP K30), polyethylene glycol 400 (PEG 400), polyethylene glycol 600 (PEG 600), methanol and acetone were purchased from S.D. Fine Chem. Ltd., Mumbai, India. All chemicals and reagents used throughout the investigation were of analytical reagent grade and were used without further purification. Double-distilled water was used throughout the study.

METHODS[11-47]

A) PREFORMULATION STUDIES

Preformulation studies were carried out to investigate the physicochemical properties of Tavaborole before formulation development. These studies provide essential information regarding the identity, purity, compatibility, and analytical characteristics of the drug, which are important for selecting suitable formulation components and ensuring the development of a stable and effective dosage form. The preformulation studies included organoleptic evaluation, melting point determination, solubility analysis, UV spectrophotometric analysis, and compatibility studies using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC).

ORGANOLEPTIC EVALUATION

Organoleptic evaluation is a preliminary qualitative assessment performed to identify the physical characteristics of a drug substance. Parameters such as colour, odour, appearance, and texture provide useful information regarding the identity and purity of the drug and help detect any visible abnormalities before formulation development.The received sample of Tavaborole was evaluated visually under normal laboratory conditions. The drug was examined for colour, odour, appearance, and physical nature by direct observation. The observed characteristics were compared with the reported standard description of Tavaborole to confirm its identity and suitability for further formulation studies.

MELTING POINT DETERMINATION

Melting point determination is one of the most important physicochemical tests performed during preformulation studies. It serves as a useful indicator of drug purity and crystalline nature. A sharp melting point within the reported range generally indicates a pure compound, whereas any significant deviation may suggest the presence of impurities or degradation products.The melting point of Tavaborole was determined by the capillary tube method. A small quantity of the pure drug was filled into a capillary tube sealed at one end. The capillary tube was attached to a thermometer and immersed in liquid paraffin contained in a Thiele's tube. The system was heated gradually over a Bunsen burner while continuously observing the drug sample. The temperature at which the drug melted completely was recorded as the melting point of Tavaborole. Care was taken to heat the sample slowly to maintain thermal equilibrium and obtain an accurate melting point.

SOLUBILITY STUDY

The solubility characteristics of a drug play a crucial role in formulation development as they influence drug dissolution, absorption, and release behaviour. Evaluation of drug solubility in different solvents assists in selecting an appropriate solvent system for formulation preparation and analytical studies. The solubility of Tavaborole was determined in methanol, ethanol, distilled water, and phosphate buffer (pH 7.4). An excess quantity of Tavaborole was added separately to each solvent and mixed thoroughly until equilibrium was achieved. The solutions were visually examined for the extent of drug dissolution, and the solubility behaviour was recorded. The observations obtained from the study were used to select a suitable solvent system for formulation development and analytical estimation.

UV SPECTROPHOTOMETRIC ANALYSIS

UV–Visible spectrophotometry is a simple, rapid, and reliable analytical technique widely used for the quantitative estimation of pharmaceutical compounds. Determination of the wavelength of maximum absorbance (λmax) and preparation of a calibration curve are essential for accurate drug estimation during formulation development, drug content analysis, and in vitro drug release studies.

DETERMINATION OF ΛMAX

A standard solution of Tavaborole was prepared by accurately weighing the required quantity of the drug and dissolving it in methanol. The prepared solution was scanned over a wavelength range of 200–400 nm using a UV–Visible spectrophotometer, with methanol serving as the blank. The wavelength corresponding to the maximum absorbance was recorded as the λmax of Tavaborole and was selected for subsequent analytical studies.

PREPARATION OF CALIBRATION CURVE

Preparation of a calibration curve is essential for establishing the linear relationship between drug concentration and absorbance. It serves as the basis for quantitative estimation of the drug in pharmaceutical formulations and ensures the reliability and accuracy of the analytical method.

A standard stock solution of Tavaborole was prepared by accurately weighing 10 mg of the drug and transferring it into a 100 mL volumetric flask. The drug was dissolved completely in methanol, and the final volume was adjusted with the same solvent to obtain a stock solution containing 100 µg/mL. The solution was sonicated for 10 minutes to ensure complete dissolution.

Working standard solutions having concentrations of 2, 4, 6, 8, and 10 µg/mL were prepared by transferring appropriate aliquots of the stock solution into separate 10 mL volumetric flasks and making up the volume with methanol. The absorbance of each solution was measured at the predetermined λmax using a UV–Visible spectrophotometer. A calibration curve was constructed by plotting concentration against absorbance, and the linear regression equation and correlation coefficient (R^2) were determined.

DRUG–EXCIPIENT COMPATIBILITY STUDY

Compatibility studies were performed to evaluate the interaction between Tavaborole and the selected excipients used in the formulation. The compatibility of the drug with polymers is an important preformulation parameter because any physicochemical interaction may affect drug stability, efficacy, and release behaviour. Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were employed to assess the compatibility of Tavaborole with HPMC and PVP.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

Fourier Transform Infrared Spectroscopy is widely employed to identify characteristic functional groups and to detect possible interactions between a drug and excipients. Comparison of the infrared spectra of the pure drug and drug–polymer mixture provides valuable information regarding the compatibility of formulation components.The FTIR spectra of pure Tavaborole and the drug–polymer mixture were recorded using an FTIR spectrophotometer (Shimadzu IR Prestige-21) operating in ATR mode. Samples were scanned over the spectral range of 4000–400 cm^{-1} with 20 scans for each sample. The obtained spectra were analyzed by comparing the characteristic absorption peaks of the pure drug with those of the drug–polymer mixture. The presence or absence of significant peak shifts, disappearance of peaks, or formation of new peaks was used to evaluate the compatibility between Tavaborole and the selected polymers.

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Differential Scanning Calorimetry is a thermal analytical technique used to evaluate the thermal behaviour, crystallinity, and compatibility of pharmaceutical compounds. DSC analysis helps identify any thermal interactions between the drug and excipients that may influence formulation stability.Differential Scanning Calorimetry was performed using a Differential Scanning Calorimeter equipped with computerized thermal analysis software. Accurately weighed samples of the pure drug and the drug–polymer mixture were sealed in aluminium pans and heated from 30°C to 300°C under a nitrogen atmosphere at a heating rate of 10°C/min. The thermograms obtained were examined for onset temperature, melting endotherm, endset temperature, and other thermal transitions. The thermal profiles of the pure drug and the drug–polymer mixture were compared to assess compatibility and identify any evidence of interaction between Tavaborole and the selected excipients.

FORMULATION DESIGN AND OPTIMIZATION

FORMULATION DESIGN

The successful development of a transungual adhesive patch depends largely on the appropriate selection of film-forming polymers, plasticizers, and solvent system. The concentration and ratio of these formulation components

significantly influence the physicochemical characteristics, mechanical strength, flexibility, and drug-release behaviour of the prepared patches. Therefore, systematic optimization of formulation variables was carried out to obtain transungual adhesive patches possessing suitable film-forming ability, adequate mechanical properties, and sustained drug release.

A total of thirty-five formulations (F1–F35) were prepared using different combinations of HPMC E15, HPMC K15M, and PVP K30 as film-forming polymers. Polyethylene glycol 400 (PEG 400) at concentrations of 25% and 30% (w/w) and polyethylene glycol 600 (PEG 600) at 30% (w/w) were employed as plasticizers to improve flexibility and prevent brittleness of the prepared patches.

The formulations were designed by varying the polymer ratios while maintaining a constant amount of Tavaborole in each formulation. The prepared formulations were classified into five formulation series based on the polymer grade and plasticizer concentration, as below:

- **Series I:** HPMC E15 : PVP K30 with PEG 400 (25% w/w)
- **Series II:** HPMC E15 : PVP K30 with PEG 400 (30% w/w)
- **Series III:** HPMC E15 : PVP K30 with PEG 600 (30% w/w)
- **Series IV:** HPMC K15M : PVP K30 with PEG 400 (25% w/w)
- **Series V:** HPMC K15M : PVP K30 with PEG 400 (30% w/w)

Table 1: Series I: HPMC E15: PVP K30 with PEG 400 (25% w/w)

Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Ratio's	(1:1)	(2:1)	(3:1)	(1:2)	(1:3)	(1:4)	(1:5)
Tavaborole (mg)	78	78	78	78	78	78	78
HPMC E-15 (mg)	200	400	600	200	200	200	200
PVP- K30 (mg)	200	200	200	400	600	800	1000
PEG - 400 (25%) (ml)	0.9	1.36	1.81	1.36	1.81	2.27	2.72
Methanol (ml)	4	4	4	4	4	4	4
Acetone (ml)	4	4	4	4	4	4	4
Water (ml)	2	2	2	2	2	2	2

Table 2: Series II: HPMC E15 : PVP K30 with PEG 400 (30% w/w)

Formulation Code	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Ratio's	(1:1)	(2:1)	(3:1)	(1:2)	(1:3)	(1:4)	(1:5)
Tavaborole (mg)	78	78	78	78	78	78	78
HPMC E-15 (mg)	200	400	600	200	200	200	200
PVP- K30 (mg)	200	200	200	400	600	800	1000
PEG - 400 (30%)(ml)	1.09	1.63	2.18	1.63	2.18	2.72	3.27
Methanol (ml)	4	4	4	4	4	4	4
Acetone (ml)	4	4	4	4	4	4	4
Water (ml)	2	2	2	2	2	2	2

Table 3: Series III: HPMC E15 : PVP K30 with PEG 600 (30% w/w)

Formulation Code	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**
Ratio's	(1:1)	(2:1)	(3:1)	(1:2)	(1:3)	(1:4)	(1:5)
Tavaborole (mg)	78	78	78	78	78	78	78
HPMC E-15 (mg)	200	400	600	200	200	200	200
PVP- K30 (mg)	200	200	200	400	600	800	1000
PEG - 600 (30%)(ml)	1.09	1.63	2.18	1.63	2.18	2.72	3.27

Methanol (ml)	4	4	4	4	4	4	4
Acetone (ml)	4	4	4	4	4	4	4
Water (ml)	2	2	2	2	2	2	2

Table 4: Series IV: HPMC K15M : PVP K30 with PEG 400 (25% w/w)

Formulation Code	**F22**	**F23**	**F24**	**F25**	**F26**	**F27**	**F28**
Ratio's	(1:1)	(2:1)	(3:1)	(1:2)	(1:3)	(1:4)	(1:5)
Tavaborole (mg)	78	78	78	78	78	78	78
HPMC K15M (mg)	200	400	600	200	200	200	200
PVP- K30 (mg)	200	200	200	400	600	800	1000
PEG - 400 (25%)(ml)	0.9	1.36	1.81	1.36	1.81	2.27	2.72
Methanol (ml)	4	4	4	4	4	4	4
Acetone (ml)	4	4	4	4	4	4	4
Water (ml)	2	2	2	2	2	2	2

Table 5: Series V: HPMC K15M : PVP K30 with PEG 400 (30% w/w)

Formulation Code	**F29**	**F30**	**F31**	**F32**	**F33**	**F34**	**F35**
Ratio's	(1:1)	(2:1)	(3:1)	(1:2)	(1:3)	(1:4)	(1:5)
Tavaborole (mg)	78	78	78	78	78	78	78
HPMC K15M (mg)	200	400	600	200	200	200	200
PVP- K30 (mg)	200	200	200	400	600	800	1000
PEG - 400 (30%)(ml)	1.09	1.63	2.18	1.63	2.18	2.72	3.27
Methanol (ml)	4	4	4	4	4	4	4
Acetone (ml)	4	4	4	4	4	4	4
Water (ml)	2	2	2	2	2	2	2

The composition of all formulations is presented in **Table 1 to Table 5**.

SELECTION OF POLYMERS, PLASTICIZERS, AND SOLVENT SYSTEM

Selection of suitable excipients is an important step in the formulation of transungual adhesive patches because the performance of the dosage form depends upon the physicochemical characteristics of the polymer matrix. Film-forming polymers provide structural integrity, while plasticizers improve flexibility and reduce brittleness. The solvent system facilitates uniform dissolution of formulation components and ensures smooth film formation during solvent evaporation.

HPMC E15 and HPMC K15M were selected as primary film-forming polymers because of their excellent film-forming ability, biocompatibility, and controlled drug-release characteristics. PVP K30 was incorporated as a hydrophilic polymer to improve drug dispersion and enhance film uniformity.

PEG 400 and PEG 600 were employed as plasticizers to improve flexibility, elasticity, and mechanical strength of the prepared patches. Methanol and acetone were selected as the solvent system because of their ability to dissolve both Tavaborole and the selected polymers efficiently, resulting in homogeneous casting solutions suitable for solvent casting.

PRELIMINARY SCREENING OF FORMULATION VARIABLES

Preliminary screening studies were carried out to identify suitable polymer ratios and plasticizer concentrations capable of producing transungual adhesive patches with desirable physicochemical and mechanical properties. Formulations exhibiting poor film formation or inadequate flexibility were excluded from further evaluation.

Different ratios of HPMC E15 or HPMC K15M and PVP K30 were prepared while maintaining a constant amount of Tavaborole. PEG 400 and PEG 600 were incorporated at predetermined concentrations according to the formulation design.

The prepared polymeric solutions were visually examined during preparation for clarity, homogeneity, viscosity, and ease of casting. After drying, the obtained patches were evaluated for film formation, transparency, smoothness, flexibility, brittleness, and overall appearance. Formulations exhibiting satisfactory film-forming characteristics were selected for further physicochemical evaluation and drug-release studies.

PREPARATION OF TAVABOROLE-LOADED TRANSUNGUAL ADHESIVE PATCHES

Solvent casting is one of the most widely employed techniques for the preparation of polymeric drug delivery systems because it produces thin, uniform, and flexible films with excellent drug distribution. The method is simple, reproducible, and suitable for preparing transungual adhesive patches with controlled drug-release characteristics.

Transungual adhesive patches containing Tavaborole were prepared by the solvent casting technique. The required quantities of HPMC E15 or HPMC K15M and PVP K30 were accurately weighed according to the formulation composition and dissolved in a solvent system consisting of 4 mL methanol, 4 mL acetone, and 2 mL distilled water

under continuous magnetic stirring until a clear and homogeneous polymeric solution was obtained.

Tavaborole (78 mg) was dissolved separately in the same solvent system and gradually incorporated into the polymeric solution under continuous stirring to ensure uniform drug distribution. PEG 400 (25 or 30% w/w) or PEG 600 (30% w/w) was then added as a plasticizer according to the formulation design, and stirring was continued until a homogeneous casting solution free from visible particulate matter was obtained.

The prepared solution was subjected to sonication to remove entrapped air bubbles and allowed to stand for a few minutes to achieve complete deaeration. The bubble-free casting solution was poured into clean glass Petri dishes of 7 cm diameter and spread uniformly to obtain films of consistent thickness. The films were allowed to dry at room temperature until complete evaporation of the solvents.

After drying, the prepared transungual adhesive films were carefully peeled from the Petri dishes and visually inspected for uniformity and defects. The films were cut into patches of 1 cm × 1 cm, wrapped individually in aluminium foil, and stored in airtight containers at room temperature until further evaluation.

DOSE CALCULATION

Dose calculation is an essential step in the development of transungual adhesive patches to ensure uniform drug loading in each individual patch. The amount of drug incorporated into the casting solution was calculated based on the total casting area of the Petri dish and the desired drug content per unit patch.

The transungual adhesive patches were prepared using a glass Petri dish having a diameter of 7 cm, corresponding to a casting area of 38.46 cm^2. Each finished patch measured 1 cm × 1 cm, providing an individual patch area of 1 cm^2.

The required dose of Tavaborole for each patch was fixed at 2 mg. Based on the total casting area, approximately 38 patches could be obtained from a single casting. Therefore, the total quantity of Tavaborole required for one casting was calculated as follows:

Casting area = πr^2 = 3.14 × $(3.5)^2$ = **38.46 cm^2**

Number of patches = 38.46 cm^2 ÷ 1 cm^2 = **38.46 patches**

Total drug required = 38.46 × 2 mg = **76.92 mg ≈ 78 mg**

Accordingly, 78 mg of Tavaborole was incorporated into each formulation to achieve a drug loading of approximately 2 mg per 1 cm^2 transungual adhesive patch.

PHYSICOCHEMICAL EVALUATION OF TRANSUNGUAL ADHESIVE PATCHES[48-53]

Physicochemical evaluation is an essential step in the development of transungual adhesive patches, as it provides information regarding the quality, uniformity, mechanical integrity, and suitability of the prepared formulations for transungual drug delivery. The prepared patches were evaluated for their physical appearance, thickness, weight variation, folding endurance, tensile strength, and drug content uniformity using standard evaluation procedures. These parameters were selected to ensure that the formulated patches possessed adequate mechanical strength, flexibility, and uniform drug distribution before biological evaluation and in vitro drug release studies.

PHYSICAL APPEARANCE

Visual examination is a simple yet important quality control test that provides preliminary information regarding the acceptability of polymeric patches. A good transungual adhesive patch should possess a smooth surface, uniform appearance, adequate flexibility, and should be free from visible defects such as air bubbles, cracks, or wrinkles.

The prepared transungual adhesive patches were visually examined under normal laboratory lighting conditions. Each formulation was inspected for colour, transparency, surface smoothness, flexibility, uniformity, and the presence of visible imperfections such as cracks, air bubbles, wrinkles, or surface irregularities. The observations were recorded, and formulations exhibiting satisfactory physical characteristics were selected for further evaluation.

THICKNESS

Thickness is an important quality attribute of polymeric patches because it directly influences drug loading, mechanical strength, and drug-release behaviour. Uniform film thickness ensures reproducible drug distribution and minimizes batch-to-batch variation.

The thickness of the prepared transungual adhesive patches was measured using a calibrated digital vernier caliper. Measurements were taken at three different positions on each patch, including the centre and two peripheral points, to evaluate thickness uniformity. The average thickness was calculated and expressed as mean ± standard deviation (SD).

WEIGHT VARIATION

Uniformity of weight is an important indicator of consistency during solvent casting. Minimal variation in patch weight reflects uniform distribution of polymers and drug throughout the casting solution and contributes to dose uniformity.

Weight variation was determined by individually weighing patches of identical dimensions using a calibrated analytical balance. Three patches from each formulation were randomly selected, and the average weight was calculated. The results were expressed as mean ± standard deviation (SD) to evaluate weight uniformity among the prepared formulations.

FOLDING ENDURANCE

Folding endurance is used to evaluate the flexibility and mechanical durability of polymeric patches. A patch with good folding endurance can withstand repeated bending during handling and application without cracking or breaking.

Folding endurance was determined by repeatedly folding each patch at the same position until visible cracks appeared or the patch broke. The total number of folds required to break the patch was recorded as the folding endurance value. The test was performed in triplicate, and the average value was calculated for each formulation.

TENSILE STRENGTH

Tensile strength is an important mechanical parameter that indicates the ability of a polymeric patch to resist breaking under applied stress. Adequate tensile strength is essential to ensure that the patch remains intact during handling, storage, and application.

The tensile strength of the prepared transungual adhesive patches was determined using a tensile strength apparatus. Each patch was fixed securely between the grips of the apparatus, and force was gradually applied until the patch ruptured. The force required to break the patch was recorded, and the tensile strength was calculated using the following equation:

Tensile Strength (kg/cm^2)= Force at Break (kg) / Thickness (cm) x Width (cm)

where,

Force at Break (kg) = Force required to rupture the patch

Thickness (cm) = Thickness of the patch

Width (cm) = Width of the patch

The results were expressed as kg/cm^2.

DRUG CONTENT UNIFORMITY

Drug content uniformity is evaluated to ensure homogeneous distribution of the active pharmaceutical ingredient throughout the polymeric matrix. Uniform drug loading is essential to achieve accurate dosing and consistent therapeutic performance.

A transungual adhesive patch of known dimensions (1 cm × 1 cm) was accurately weighed and transferred into a suitable container containing methanol. The solution was stirred until complete dissolution of the drug and polymers was achieved. The resulting solution was filtered to remove any undissolved polymeric residue and appropriately diluted with methanol.

The absorbance of the prepared solution was measured using a UV–Visible spectrophotometer at **265 nm** against methanol as the blank. The drug content was determined from the previously constructed calibration curve and expressed as the percentage of the theoretical drug content.

Drug content was calculated using the following equation:

Drug Content (%) = Actual Drug Content x Theoretical Drug Content x 100

All measurements were performed in triplicate, and the results were expressed as **mean ± standard deviation (SD)**.

IN VITRO ANTIFUNGAL ACTIVITY

The primary objective of developing the Tavaborole-loaded transungual adhesive patch was to provide effective localized therapy for fungal nail infections. Therefore, the antifungal activity of the prepared formulations was evaluated against *Candida albicans* to assess their ability to inhibit fungal growth. The agar diffusion method was selected because it is a simple, reproducible, and widely accepted technique for the preliminary evaluation of antifungal efficacy.

The antifungal activity of the prepared transungual adhesive patches was evaluated against *Candida albicans* using the agar diffusion method. Potato Dextrose Agar (PDA) medium was prepared according to standard microbiological procedures and sterilized before use. The sterile molten medium was poured into Petri dishes and allowed to solidify under aseptic conditions.

A freshly prepared suspension of *Candida albicans* was uniformly spread over the surface of the solidified agar medium using a sterile cotton swab. The prepared transungual adhesive patches were cut into suitable dimensions and carefully placed on the inoculated agar surface using sterile forceps. A standard Tavaborole preparation was used as the reference.

The inoculated plates were incubated at **37 ± 2°C for 72 h**. After incubation, the antifungal activity was assessed by measuring the diameter of the clear zone of inhibition surrounding each sample using a calibrated digital vernier caliper. The results were expressed in millimetres (mm), where a larger zone of inhibition indicated greater antifungal activity.

IN VITRO DRUG RELEASE STUDY

In vitro drug release studies are performed to evaluate the release characteristics of the active pharmaceutical ingredient from the prepared dosage form under controlled laboratory conditions. The release profile provides valuable information regarding the sustained-release behaviour of the formulation and assists in selecting the optimized formulation for further studies.

The in vitro drug release study of the prepared transungual adhesive patches was carried out using a Franz diffusion cell apparatus. A suitable diffusion membrane was carefully mounted between the donor and receptor compartments of the diffusion cell. The receptor compartment was filled with phosphate buffer (pH 7.4) containing methanol as the diffusion medium and maintained under continuous magnetic stirring to ensure uniform distribution of the released drug.

The prepared transungual adhesive patch was placed in the donor compartment with the drug-loaded surface facing the diffusion membrane. The entire assembly was maintained at controlled temperature throughout the study.

Samples were withdrawn from the receptor compartment at predetermined time intervals of 1, 2, 3, 4, 5, 6, and 7 h, and each withdrawn sample was immediately replaced with an equal volume of fresh diffusion medium to maintain sink conditions.

The collected samples were analyzed using a UV–Visible spectrophotometer at 265 nm. The cumulative percentage drug release (%CDR) was calculated for each formulation using the following equation:

% Cumulative Drug Release=Amount of Drug Released (mg) x Total Drug Content (mg) x 100

Formulations F11, F23, and F25 were selected for comparative drug-release studies based on their satisfactory physicochemical characteristics observed during formulation optimization.

DRUG RELEASE KINETIC MODELING[54-67]

Mathematical modeling of drug release is an essential part of formulation development because it provides insight into the mechanism governing drug release from the polymeric matrix. The experimental drug-release data were fitted to various kinetic models to determine whether the release followed concentration-dependent, diffusion-controlled, or constant-release behaviour.

The cumulative drug-release data obtained from the optimized formulation were fitted into different mathematical models, including Zero-order, First-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. The linear regression equation and correlation coefficient (R^2) were calculated for each model.

The kinetic model showing the highest correlation coefficient (R^2) was considered the best-fit model and was used to explain the mechanism of drug release from the prepared transungual adhesive patches.

ZERO-ORDER MODEL

The Zero-order kinetic model describes a drug-release process in which the drug is released at a constant rate over time, irrespective of its concentration within the dosage form. This model is considered ideal for controlled-release formulations because it maintains a nearly constant drug-release rate throughout the release period.

The cumulative percentage drug released was plotted against time, and linear regression analysis was performed to determine the regression coefficient (R^2). A higher R^2 value indicates better conformity of the experimental data with the Zero-order kinetic model.

The Zero-order model is represented by the following equation:

$$Q_t = Q_0 + K_0 t$$

where,

Q_t = Cumulative amount of drug released at time t

Q_0= Initial amount of drug present in the dosage form

K_0 = Zero-order release rate constant

t = Time

FIRST-ORDER MODEL

The First-order kinetic model assumes that the rate of drug release is directly proportional to the amount of drug remaining in the dosage form. As drug release proceeds, the release rate gradually decreases because less drug remains available for diffusion. This model is commonly used to describe concentration-dependent drug release from pharmaceutical formulations.

The in vitro drug release data were fitted to the First-order kinetic model by plotting the logarithm of the cumulative amount of drug remaining in the formulation against time. Linear regression analysis was performed, and the regression coefficient (R^2) was calculated to evaluate the goodness of fit. A higher R^2 value indicates better agreement between the experimental data and the First-order kinetic model.

The First-order kinetic model is represented by the following equation:

$$\log Q_t = \log Q_0 - K_1 t / 2.303$$

where,

Q_t= Amount of drug remaining in the dosage form at time t

Q_0 = Initial amount of drug in the dosage form

K_1 = First-order release rate constant

t = Time

HIGUCHI MODEL

The Higuchi kinetic model describes drug release from a homogeneous polymeric matrix as a diffusion-controlled process based on Fick's law of diffusion. According to this model, the cumulative amount of drug released is directly proportional to the square root of time. The model is widely used to evaluate diffusion-controlled drug release from matrix-based pharmaceutical formulations.

The in vitro drug release data were fitted to the Higuchi kinetic model by plotting the cumulative percentage drug released against the square root of time ($\sqrt{t}$). Linear regression analysis was performed, and the regression coefficient (R^2) was calculated to determine the goodness of fit. A higher R^2 value indicates that drug release predominantly follows a diffusion-controlled mechanism.

The Higuchi model is represented by the following equation:

$$Q = K_H \sqrt{t}$$

where,

Q = Cumulative amount (or cumulative percentage) of drug released at time t

K_H = Higuchi dissolution (diffusion) constant

t = Time

KORSMEYER–PEPPAS MODEL

The Korsmeyer–Peppas kinetic model was employed to investigate the mechanism of drug release from the polymeric matrix. This semi-empirical model is widely used to characterize drug release from polymeric systems when the release mechanism is not well understood or when more than one type of release phenomenon is involved. The model estimates the release exponent (n), which provides insight into the predominant drug-release mechanism.

The in vitro drug release data of the optimized formulation were fitted to the Korsmeyer–Peppas model by plotting the logarithm of the cumulative fraction of drug released against the logarithm of time. Linear regression analysis was performed to determine the regression coefficient (R^2), while the slope of the plot was used to obtain the release exponent (n).

The Korsmeyer–Peppas model is represented by the following equation:

$$M_t / M_\infty = K t^n$$

where,

M_t = Amount of drug released at time t

M_∞ = Total amount of drug released at infinite time

M_t / M_∞ = Fraction of drug released

K = Kinetic constant incorporating the structural and geometric characteristics of the dosage form

n = Release exponent indicating the mechanism of drug release

t = Time

The value of the release exponent (n) was used to predict the drug-release mechanism from the polymeric matrix.

HIXSON–CROWELL MODEL

The Hixson–Crowell kinetic model was employed to evaluate the effect of changes in the surface area and dimensions of the dosage form during drug release. This model assumes that drug release occurs by dissolution accompanied by a gradual reduction in the size of the dosage form while maintaining its geometric shape. It is commonly applied to formulations in which changes in surface area influence the drug-release process.

The in vitro drug release data of the optimized formulation were fitted to the Hixson–Crowell model by plotting the cube root of the percentage drug remaining against time. Linear regression analysis was performed, and the regression coefficient (R^2) was calculated to determine the goodness of fit. The model exhibiting the highest correlation coefficient was considered to best describe the release mechanism.

The Hixson–Crowell model is represented by the following equation:

$$W_0^{1/3} - W_t^{1/3} = Kt$$

where,

W_0 = Initial amount of drug in the dosage form

W_t = Amount of drug remaining in the dosage form at time t

K = Hixson–Crowell dissolution rate constant

t = Time

STABILITY STUDY

Stability studies are performed to evaluate the ability of a pharmaceutical formulation to maintain its physicochemical properties, drug content, and drug-release characteristics during storage. Accelerated stability testing provides useful information regarding the expected shelf-life and storage stability of the developed formulation.

The optimized transungual adhesive patch formulation (F25) was subjected to accelerated stability testing according to the International Council for Harmonisation (ICH) guidelines.

The prepared patches were individually wrapped in aluminium foil, packed in airtight containers, and stored at 40 ± 2°C and 75 ± 5% relative humidity for one month.

Samples were withdrawn at 0, 15, and 30 days and evaluated for the following parameters:

- Physical appearance
- Thickness
- Folding endurance
- Drug content uniformity
- In vitro drug release

Any visible changes in colour, flexibility, brittleness, or surface texture were recorded. The obtained results were compared with the initial observations to evaluate the stability of the optimized formulation during storage.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Preformulation studies were performed to characterize Tavaborole and evaluate its suitability for the development of transungual adhesive patches. The physicochemical properties of the drug, including organoleptic characteristics, melting point, solubility profile, UV spectrophotometric analysis, FTIR, and DSC, were investigated. These studies provided essential information regarding the identity, purity, compatibility, and analytical characteristics of Tavaborole and supported the selection of suitable formulation components.

ORGANOLEPTIC EVALUATION

Table 6: Organoleptic characteristics of Tavaborole

Parameter	Observation
Colour	White to off-white crystalline powder
Odour	Mild odour
Appearance	Smooth crystalline powder

The organoleptic properties of Tavaborole were evaluated as an initial step in drug characterization. The received drug sample appeared as a white to off-white crystalline powder with a mild odour and smooth crystalline

appearance (Table 6). These observations were consistent with the reported physicochemical characteristics of Tavaborole, confirming the identity and acceptable quality of the drug sample.

Evaluation of organoleptic properties provides a simple preliminary assessment of drug identity before detailed analytical characterization. The absence of discoloration, foreign particles, or abnormal odour indicated that the drug sample was free from visible impurities and suitable for formulation development.

SOLUBILITY STUDY

Table 7: Solubility profile of Tavaborole in different solvents

Solvent	Solubility
Methanol	Freely soluble
Ethanol	Soluble
Distilled water	Slightly soluble
Phosphate buffer (pH 7.4)	Sparingly soluble

The solubility profile of Tavaborole in different solvents is presented in Table 7. The drug was found to be freely soluble in methanol, soluble in ethanol, slightly soluble in distilled water, and sparingly soluble in phosphate buffer (pH 7.4).

The observed solubility behaviour indicates that Tavaborole possesses greater affinity towards organic solvents than aqueous media. Based on these findings, methanol was selected as the primary solvent for analytical studies, including UV spectrophotometric analysis and calibration curve preparation. Furthermore, the combination of methanol and acetone was selected as the solvent system for preparing transungual adhesive patches by the solvent casting technique because it ensured complete dissolution of the drug and polymers, resulting in homogeneous casting solutions.

The limited aqueous solubility of Tavaborole also supports the development of a controlled-release transungual delivery system, where gradual drug diffusion from the polymeric matrix is desirable for prolonged antifungal activity.

MELTING POINT DETERMINATION

The melting point of Tavaborole was found to be **132°C**, which lies within the reported melting range of **120–134°C**.

The observed melting point confirms the purity and crystalline nature of the received drug sample. A melting point within the reported range indicates the absence of significant impurities or degradation products that could alter the thermal behaviour of the drug. The sharp melting point further suggests that Tavaborole possesses a well-defined crystalline structure suitable for pharmaceutical formulation.

The obtained result confirmed that the received Tavaborole sample was appropriate for further formulation and analytical studies.

UV SPECTROPHOTOMETRIC ANALYSIS

DETERMINATION OF ΛMAX

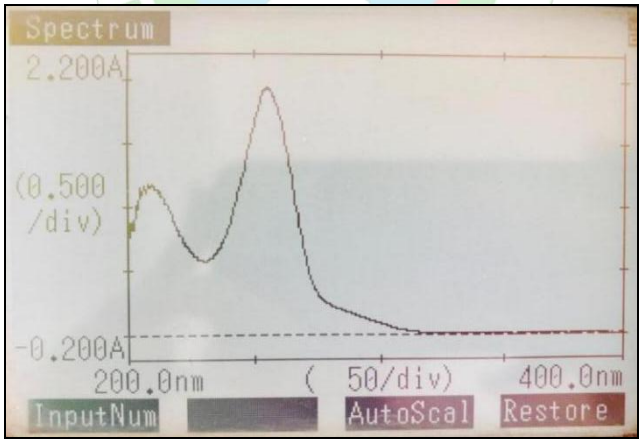


Figure 1: UV absorption spectrum of Tavaborole in methanol

The UV absorption spectrum of Tavaborole was recorded over the wavelength range of **200–400 nm** using methanol as the blank. The drug exhibited maximum absorbance (λmax) at 265 nm (Figure 1).

Selection of λmax is an important step in analytical method development because maximum absorbance provides greater analytical sensitivity and minimizes instrumental error during quantitative estimation. Therefore, 265 nm was selected for calibration curve preparation, drug content determination, and in vitro drug release studies.

The observed λmax was consistent throughout the analytical studies, indicating the suitability of the developed UV spectrophotometric method for quantitative estimation of Tavaborole.

CALIBRATION CURVE

Table 8: Calibration data of Tavaborole in methanol

Sr.No.	Concentration (ug/ml)	Absorbance
1.	2	0.027
2.	4	0.058
3.	6	0.088
4.	8	0.116
5.	10	0.153

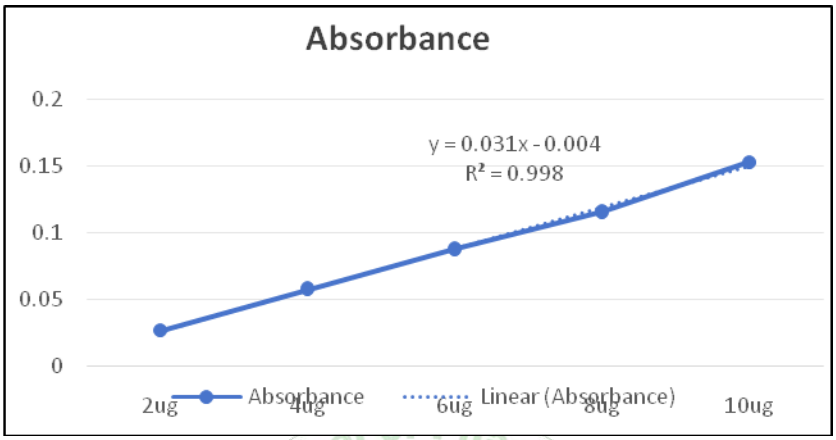


Figure 2: Calibration curve of Tavaborole

The calibration curve of Tavaborole was prepared using methanol over the concentration range of 2–10 µg/mL.

A linear increase in absorbance with increasing drug concentration was observed, demonstrating compliance with Beer–Lambert's law within the selected concentration range. The calibration plot exhibited excellent linearity, confirming the reliability of the analytical method for quantitative estimation.

The regression equation and correlation coefficient (R^2) indicated that the developed UV spectrophotometric method was accurate, reproducible, and suitable for subsequent determination of drug content and cumulative drug release from the prepared transungual adhesive patches.

DRUG–EXCIPIENT COMPATIBILITY STUDY

Compatibility studies were carried out using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) to investigate the possible interaction between Tavaborole and the selected excipients used in formulation development.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

1. Pure Drug:

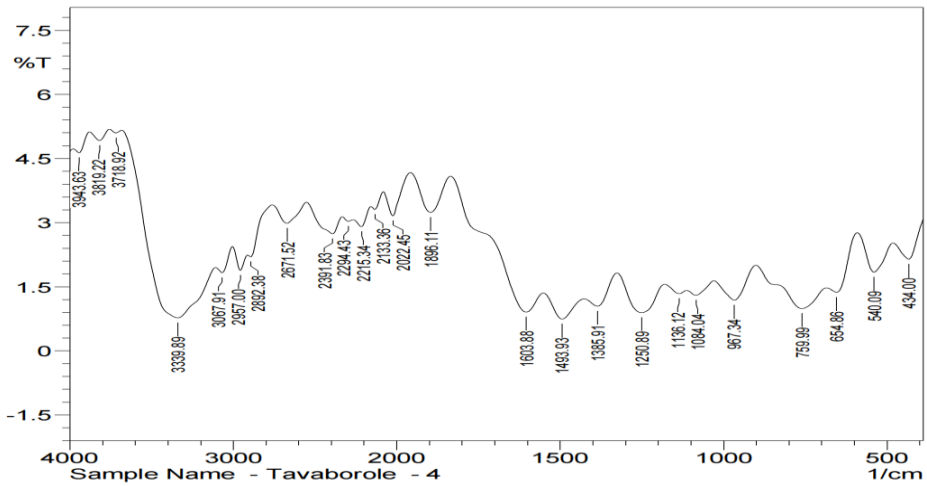


Figure 3: FTIR spectrum of pure Tavaborole

Table 9: Characteristic FTIR peaks of Tavaborole

Peak Observed (cm^{-1})	Functional Group / Assignment	Interpretation	Peak Observed (cm^{-1})
3339.89	O–H stretching	Presence of hydroxyl group	3339.89
3067.91	Aromatic C–H stretching	Aromatic ring structure	3067.91
2957.00	Aliphatic C–H stretching	Presence of alkyl group	2957.00
1603.88	C=C stretching	Aromatic ring vibration	1603.88
1493.93	C–H bending	Aromatic bending vibration	1493.93
1250.89	C–O stretching	Presence of oxygen-containing grou	1250.89
1186.12	B–O stretching	Characteristic boron-containing structure	1186.12
1084.24	C–O stretching	Confirmation of functional group	1084.24
759.99	Aromatic C–H bending	Aromatic substitution pattern	759.99
540.09	B–O vibration	Characteristic boron peak	540.09

The FTIR spectrum of pure Tavaborole exhibited characteristic absorption peaks corresponding to its functional groups. Prominent peaks observed at 3339.89 cm^{-1}, 3067.91 cm^{-1}, 2957.00 cm^{-1}, 1603.88 cm^{-1}, 1250.89 cm^{-1}, 1186.12 cm^{-1}, and 540.09 cm^{-1} confirmed the presence of hydroxyl, aromatic C–H, aliphatic C–H, C=C, C–O, and boron-containing functional groups characteristic of Tavaborole.

The observed absorption bands were consistent with the reported FTIR spectrum of Tavaborole, confirming the identity and purity of the drug. No additional peaks corresponding to impurities or degradation products were observed, indicating that the received drug sample was chemically pure.

2. Drug–Polymer Mixture:

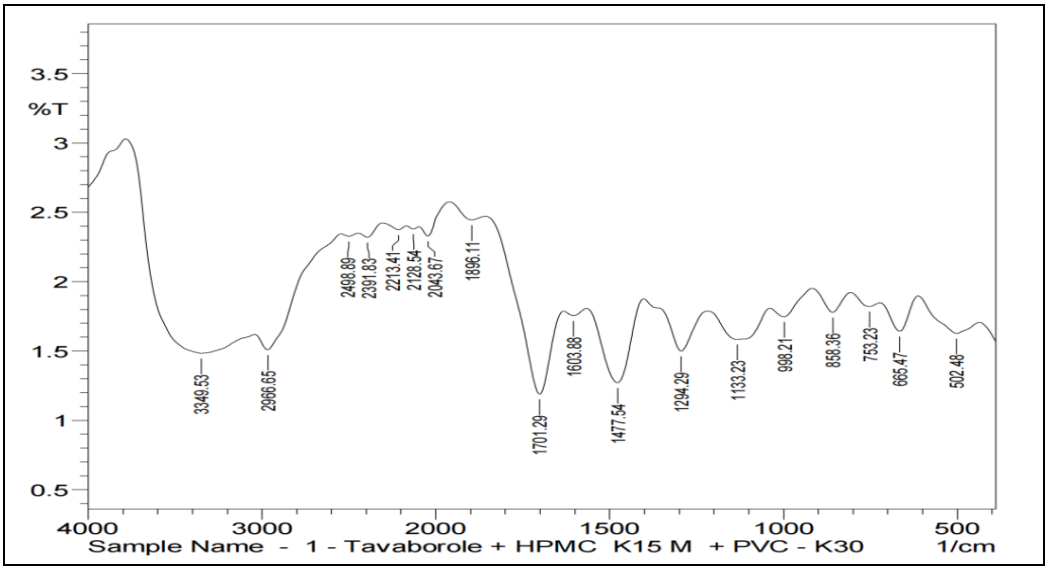


Figure 4: FTIR spectrum of Tavaborole–polymer mixture

Table 10: FTIR interpretation of drug–polymer mixture

Sr. No.	Observed Peak (cm^{-1})	Functional Group / Assignment
1	3349.53	O–H stretching
2	2969.65	C–H stretching
3	2498.89	Overtone/Combination band
4	2390.02	Overtone band
5	2231.34	Weak characteristic vibration
6	2158.54	Combination band
7	2043.67	Overtone vibration
8	1895.11	Carbonyl-associated vibration
9	1701.29	C=O stretching
10	1603.88	C=C stretching / bound water vibration
11	1477.54	CH_2 bending
12	1294.29	C–O stretching
13	1133.32	C–O–C stretching
14	992.49	Polymer backbone vibration

15	871.27	Ring vibration
16	753.32	C–H bending
17	665.47	Bending vibration
18	520.46	Fingerprint region vibration

The FTIR spectrum of the Tavaborole–polymer mixture retained all the characteristic peaks of the pure drug without any significant shift, disappearance, or appearance of new absorption bands.

The preservation of the characteristic functional group peaks indicates the absence of chemical interaction between Tavaborole and the selected polymers (HPMC K15M and PVP K30). Minor peak broadening observed in the spectrum may be attributed to hydrogen bonding and physical mixing within the polymeric matrix rather than chemical incompatibility.

These findings confirmed the compatibility of Tavaborole with the selected excipients and supported their suitability for preparing transungual adhesive patches.

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

1) Pure Drug:

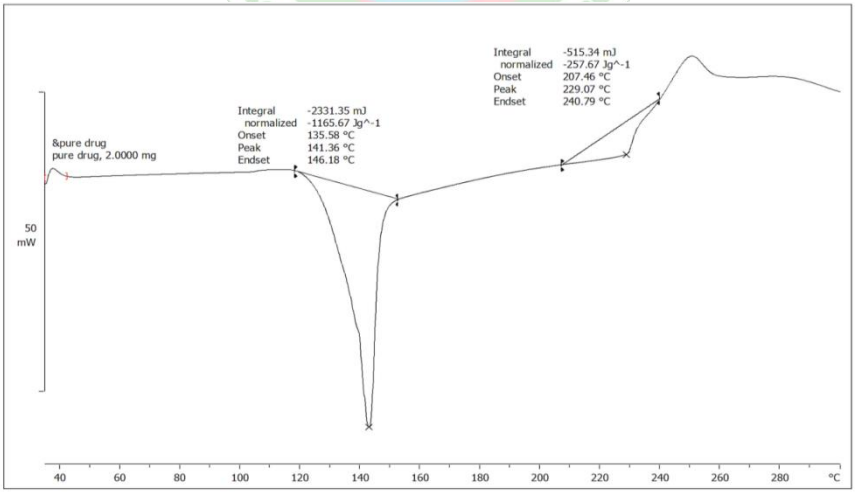


Figure 5: DSC thermogram of pure Tavaborole

The DSC thermogram of pure Tavaborole exhibited a sharp endothermic peak at **141.36°C**, corresponding to its characteristic melting point. The sharp and well-defined melting endotherm confirmed the crystalline nature and thermal stability of the drug. The absence of additional thermal transitions further indicated that the drug sample was free from detectable impurities.

2) Drug–Polymer Mixture:

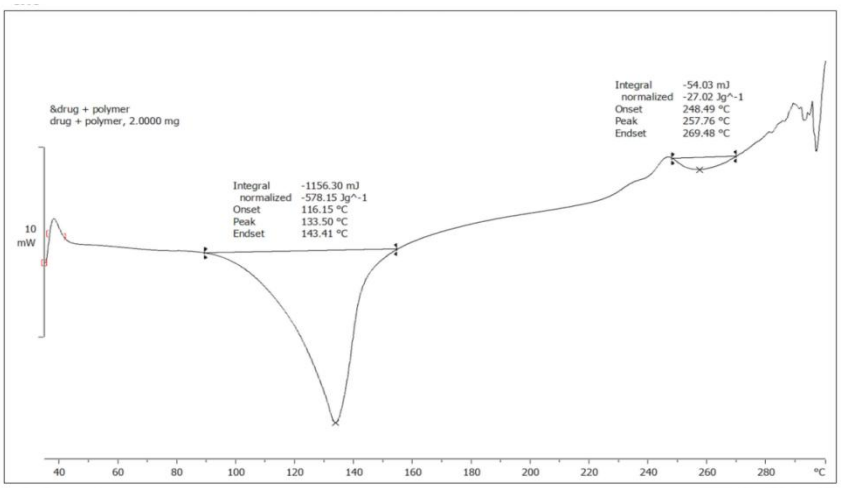


Figure 6: DSC thermogram of Tavaborole–polymer mixture

The DSC thermogram of the drug–polymer mixture showed the characteristic endothermic peak of Tavaborole at **133.50°C**, with slight peak broadening and a minor shift compared to the pure drug.

The slight reduction in melting temperature is likely due to molecular dispersion of Tavaborole within the polymeric matrix and does not indicate chemical degradation or incompatibility. Importantly, the characteristic melting endotherm of Tavaborole was retained, confirming that the drug maintained its thermal identity after incorporation into the polymer mixture.

The combined FTIR and DSC studies demonstrated that Tavaborole was compatible with HPMC K15M and PVP K30, supporting their use in the development of transungual adhesive patches.

FORMULATION DEVELOPMENT AND OPTIMIZATION

Development of transungual adhesive patches requires careful optimization of formulation variables to achieve satisfactory film-forming ability, mechanical strength, flexibility, and sustained drug release. In the present study, thirty-five formulations (F1–F35) were prepared using different combinations of HPMC E15, HPMC K15M, PVP K30, PEG 400, and PEG 600. The formulations were systematically evaluated to identify the most suitable polymer composition and plasticizer concentration for the development of Tavaborole-loaded transungual adhesive patches.

The optimization process was carried out in five formulation series by varying the polymer ratio and plasticizer concentration while maintaining a constant drug loading. Each formulation was evaluated for transparency, thickness, folding endurance, tensile strength, and patch-forming ability. Based on the obtained results, the best-performing formulations were selected for further investigation.

OPTIMIZATION OF FORMULATION SERIES I

HPMC E15: PVP K30 with PEG 400 (25% w/w)

Table 11: Evaluation of Formulation Series I (F1–F7)

F.C & Ratios		Transperency	Thickness (mm)	Folding Endurance	nsile Strength (kg/cn	Results
F1	(1:1)	-	-	-	-	No patch Formed
F2	(2:1)	Transparent	0.21 ± 0.02	126 ± 3	0.56 ± 0.03	Patch Formed
F3	(3:1)	Slightly Opaque	0.25 ± 0.02	138 ± 4	0.64 ± 0.02	Patch Formed
F4	(1:2)	Transparent	0.17 ± 0.02	104 ± 2	0.44 ± 0.01	Patch Formed
F5	(1:3)	-	-	-	-	No patch Formed
F6	(1:4)	-	-	-	-	No patch Formed
F7	(1:5)	-	-	-	-	No patch Formed

The first formulation series was prepared using HPMC E15 and PVP K30 at different polymer ratios with PEG 400 (25% w/w) as the plasticizer. Among the seven prepared formulations, F2, F3, and F4 formed satisfactory transungual adhesive patches, whereas F1, F5, F6, and F7

failed to produce acceptable films because of inadequate polymer balance.

Formulation F3 exhibited the highest thickness (0.25 ± 0.02 mm), folding endurance (138 ± 4), and tensile strength (0.64 ± 0.02 kg/cm²) within this series, indicating improved mechanical integrity. However, increasing the concentration of PVP K30 beyond the optimum level resulted in sticky films that were difficult to handle, while insufficient polymer concentration produced brittle patches.

These findings indicate that although HPMC E15 successfully formed adhesive films, the mechanical properties were highly dependent on the HPMC-to-PVP ratio, and further optimization of plasticizer concentration was required.

OPTIMIZATION OF FORMULATION SERIES II

HPMC E15 : PVP K30 with PEG 400 (30% w/w)

Table 12: Evaluation of Formulation Series II (F8–F14)

F.C & Ratios		Transperency	Thickness (mm)	Folding Endurance	Tensile Strength (kg/cm²)	Results
F8	(1:1)	-	-	-	-	No patch Formed
F9	(2:1)	Transparent	0.22 ± 0.02	132 ± 3	0.61 ± 0.03	Patch Formed
F10	(3:1)	Slightly opaque	0.26 ± 0.02	146 ± 4	0.69 ± 0.02	Patch Formed
F11	(1:2)	Transparent	0.18 ± 0.02	114 ± 2	0.47 ± 0.01	Patch Formed
F12	(1:3)	-	-	-	-	No patch Formed
F13	(1:4)	-	-	-	-	No patch Formed
F14	(1:5)	-	-	-	-	No patch Formed

The second formulation series was prepared by increasing the concentration of PEG 400 from 25% to 30% (w/w) while maintaining the same polymer ratios. The increase in plasticizer concentration noticeably improved film flexibility and transparency compared with the previous series.

Among the prepared formulations, F9, F10, and F11 formed satisfactory patches, whereas the remaining formulations failed to produce acceptable films because of excessive softness and poor film integrity.

Formulation F10 exhibited comparatively higher tensile strength (0.69 ± 0.02 kg/cm²) and folding endurance (146 ± 4), while F11 produced a transparent and flexible patch with acceptable mechanical properties. The improved flexibility observed in this series confirms the beneficial effect of increasing PEG 400 concentration; however, excessive plasticizer resulted in slight stickiness in formulations containing higher concentrations of PVP K30.

OPTIMIZATION OF FORMULATION SERIES III

HPMC E15 : PVP K30 with PEG 600 (30% w/w)

Table 13: Evaluation of Formulation Series III (F15–F21)

F.C & Ratios		Transperency	Thickness (mm)	Folding Endurance	Tensile Strength (kg/cm²)	Results
F15	(1:1)	-	-	-	-	No patch Formed
F16	(2:1)	Transparent	0.20 ± 0.02	138 ± 5	0.66 ± 0.02	Patch Formed
F17	(3:1)	Opaque	0.27 ± 0.02	147 ± 5	0.75 ± 0.02	Patch Formed
F18	(1:2)	Slightly opaque	0.19 ± 0.02	114 ± 5	0.50 ± 0.02	Patch Formed
F19	(1:3)	-	-	-	-	No patch Formed
F20	(1:4)	-	-	-	-	No patch Formed
F21	(1:5)	-	-	-	-	No patch Formed

To evaluate the influence of plasticizer type, PEG 600 was substituted for PEG 400 while maintaining the same polymer composition.

Among the prepared formulations, F16, F17, and F18 produced satisfactory adhesive patches, whereas the remaining formulations failed to form acceptable films.

Formulation F17 exhibited comparatively greater thickness (0.27 ± 0.02 mm), folding endurance (147 ± 5), and tensile strength (0.75 ± 0.02 kg/cm²). The higher molecular weight of PEG 600 contributed to improved flexibility and softness of the prepared patches. However, a slight increase in film thickness and prolonged drying time were also observed, which may limit large-scale manufacturing.

Overall, PEG 600 improved mechanical flexibility but did not provide a significant advantage over PEG 400 in terms of overall film quality.

OPTIMIZATION OF FORMULATION SERIES IV

HPMC K15M: PVP K30 with PEG 400 (25% w/w)

Table 14: Evaluation of Formulation Series IV (F22–F28)

F.C & Ratios		Transperency	Thickness (mm)	Folding Endurance	Tensile Strength (kg/cm²)	Results
F22	(1:1)	Transperent	0.22± 0.02	132 ± 5	0.64 ± 0.02	Thin/Patch Formed
F23	(2:1)	Transparent	0.26 ± 0.02	173 ± 5	0.74 ± 0.02	Patch Formed
F24	(3:1)	Opaque	0.30 ± 0.02	165 ± 5	0.82 ± 0.02	Patch Formed
F25	(1:2)	Transparent	0.21 ± 0.02	216 ± 5	0.56 ± 0.02	Flexible/Patch Formed
F26	(1:3)	-	-	-	-	No patch Formed
F27	(1:4)	-	-	-	-	No patch Formed
F28	(1:5)	-	-	-	-	No patch Formed

In the fourth formulation series, HPMC E15 was replaced with HPMC K15M, a higher-viscosity polymer, to improve matrix integrity and sustain drug release.

Among the prepared formulations, F22, F23, F24, and F25 successfully formed transungual adhesive patches with satisfactory physicochemical properties.

Formulation F25 demonstrated the highest folding endurance (216 ± 5), excellent flexibility, satisfactory thickness (0.21 ± 0.02 mm), and acceptable tensile strength (0.56 ± 0.02 kg/cm²). Formulation F23 also exhibited good transparency and mechanical strength, whereas F24 showed comparatively greater thickness and tensile strength but produced an opaque film.

The superior flexibility of F25 may be attributed to the balanced combination of HPMC K15M and PVP K30, which produced a uniform polymeric matrix capable of maintaining adequate mechanical strength while retaining flexibility. These observations suggested that HPMC K15M provided better matrix formation than HPMC E15 for the development of sustained-release transungual adhesive patches.

OPTIMIZATION OF FORMULATION SERIES V

HPMC K15M : PVP K30 with PEG 400 (30% w/w)

Table 15: Evaluation of Formulation Series V (F29–F35)

F.C & Ratios		Transperency	Thickness (mm)	Folding Endurance	Tensile Strength (kg/cm²)	Results
F29	(1:1)	Transperent	0.11± 0.02	98 ± 5	Nil	Very thin patch
F30	(2:1)	-	-	-	-	No patch Formed
F31	(3:1)	-	-	-	-	No patch Formed
F32	(1:2)	-	-	-	-	No patch Formed
F33	(1:3)	-	-	-	-	No patch Formed
F34	(1:4)	-	-	-	-	No patch Formed
F35	(1:5)	-	-	-	-	No patch Formed

The final formulation series was prepared using HPMC K15M with PEG 400 at 30% (w/w).

Among the prepared formulations, only F29 produced a very thin patch, while all remaining formulations failed to form satisfactory films.

The excessive concentration of PEG 400 reduced the structural integrity of the polymeric matrix, resulting in poor film formation and reduced mechanical strength. These findings indicate that although plasticizers improve flexibility, excessive plasticizer concentration adversely affects film integrity and should be carefully optimized.

Selection of Optimized Formulation

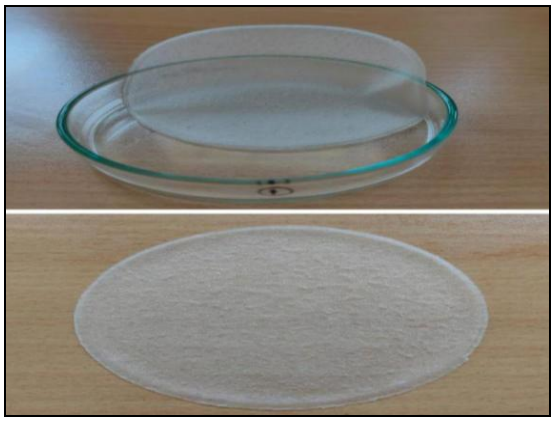


Figure 7: Optimized Tavaborole-Loaded Transungual Adhesive Patch (F25)

Based on the preliminary optimization studies, formulations F11, F23, and F25 were selected for further investigation because they exhibited satisfactory film formation, transparency, flexibility, and mechanical strength.

Among these formulations, F25 demonstrated the most desirable overall characteristics, including excellent flexibility, satisfactory thickness, the highest folding endurance, acceptable tensile strength, and uniform appearance. In addition to its superior physicochemical properties, F25 subsequently exhibited the highest cumulative drug release (95.42%) among the selected formulations and followed Zero-order release kinetics, indicating sustained and controlled drug release.

Considering its overall performance during formulation optimization, physicochemical evaluation, and in vitro drug release studies, F25 was selected as the optimized transungual adhesive patch formulation for further antifungal and stability studies.

Physicochemical Evaluation of the Optimized Transungual Adhesive Patch

Following formulation optimization, the physicochemical properties of the optimized transungual adhesive patch (F25) were further evaluated to confirm its suitability for transungual drug delivery. The formulation was assessed for its physical appearance, thickness, weight variation, folding endurance, tensile strength, and drug content uniformity. These parameters are essential to ensure uniform drug distribution, mechanical stability, flexibility, and overall quality of the developed formulation.

PHYSICAL APPEARANCE

Figure 8: Photograph of Optimized Transungual Adhesive Patch (F25)

The optimized formulation (**F25**) produced a smooth, transparent, and flexible transungual adhesive patch without visible cracks, wrinkles, air bubbles, or surface imperfections (Figure 8). The patch exhibited satisfactory film integrity and could be easily peeled from the casting surface without damage.

The uniform appearance of the patch indicates successful solvent evaporation and homogeneous distribution of the polymeric components throughout the formulation. The balanced combination of HPMC K15M and PVP K30 contributed to the formation of a continuous polymeric matrix with good flexibility and handling characteristics. Such uniformity is desirable for ensuring reproducible drug loading and consistent drug release during application.

THICKNESS

The optimized formulation exhibited a thickness of 0.21 ± 0.02 mm, indicating excellent uniformity of the solvent-

cast film. Uniform film thickness is an important quality attribute because it contributes to consistent drug loading and reproducible drug release.

The low standard deviation obtained during thickness measurement suggests that the casting solution was uniformly distributed throughout the Petri dish during solvent evaporation. The optimized polymer composition and controlled drying conditions were responsible for producing films with minimal variation in thickness.

WEIGHT VARIATION

The optimized formulation exhibited minimal variation in patch weight, indicating uniform distribution of the polymeric solution during the solvent casting process. The low variation in weight suggests that the casting procedure was reproducible and capable of producing patches with consistent composition and drug loading.

Uniform weight is directly associated with dose uniformity, which is an important quality requirement for transungual drug delivery systems.

FOLDING ENDURANCE

The optimized formulation exhibited a folding endurance value of 216 ± 5, indicating excellent flexibility and mechanical durability.

The high folding endurance may be attributed to the balanced proportion of HPMC K15M, PVP K30, and PEG 400, which produced a flexible polymeric network capable of withstanding repeated bending without cracking. Good flexibility is an essential requirement for transungual adhesive patches because it facilitates handling and application while minimizing the risk of mechanical failure during use.

TENSILE STRENGTH

The tensile strength of the optimized formulation was found to be 0.56 ± 0.02 kg/cm², indicating adequate mechanical strength to withstand handling and application without rupture.

Although formulations containing higher concentrations of HPMC K15M exhibited greater tensile strength, formulation F25 demonstrated an optimum balance between mechanical strength and flexibility. Excessive tensile strength may increase film rigidity, whereas moderate tensile strength combined with high flexibility is more desirable for transungual adhesive patches.

DRUG CONTENT UNIFORMITY

Drug content analysis demonstrated uniform distribution of Tavaborole throughout the optimized polymeric matrix. The observed drug content was found to be within acceptable pharmaceutical limits, indicating efficient incorporation of Tavaborole during the solvent casting process.

The homogeneous drug distribution may be attributed to the complete dissolution of Tavaborole in the selected solvent system and continuous stirring during formulation preparation. Uniform drug content is an essential quality parameter because it ensures accurate dosing and contributes to reproducible therapeutic performance.

BIOLOGICAL EVALUATION AND DRUG RELEASE PERFORMANCE

Following physicochemical characterization, the optimized transungual adhesive patch was evaluated for its biological activity and drug-release performance. The antifungal efficacy was assessed against *Candida albicans*, while the in vitro drug release behaviour was investigated using a Franz diffusion cell. Furthermore, the release mechanism was elucidated through kinetic modeling, and the storage stability of the optimized formulation was evaluated under accelerated conditions.

IN VITRO ANTIFUNGAL ACTIVITY

Table 16: Zone of inhibition of Tavaborole-loaded transungual adhesive patches

Sr. No.	Test Sample	Zone of Inhibition (mm)
1	F1	No significant zone observed
2	F2	No significant zone observed
3	F3	No significant zone observed
4	Reference Antibiotic (Tavaborole)	15 mm

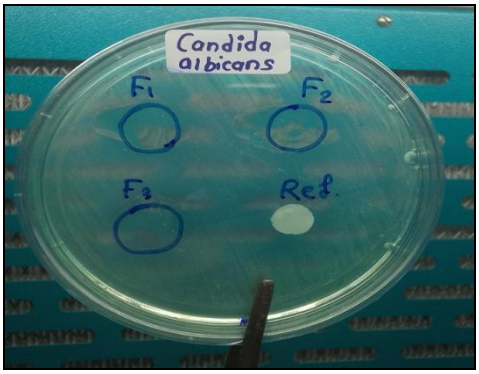


Figure 9: Antifungal activity of Tavaborole-loaded transungual adhesive patches against ***Candida albicans***

The antifungal activity of the prepared transungual adhesive patches was evaluated against *Candida albicans* using the agar diffusion method. The results are summarized in Table 16, while the representative zone of inhibition is presented in Figure 9.

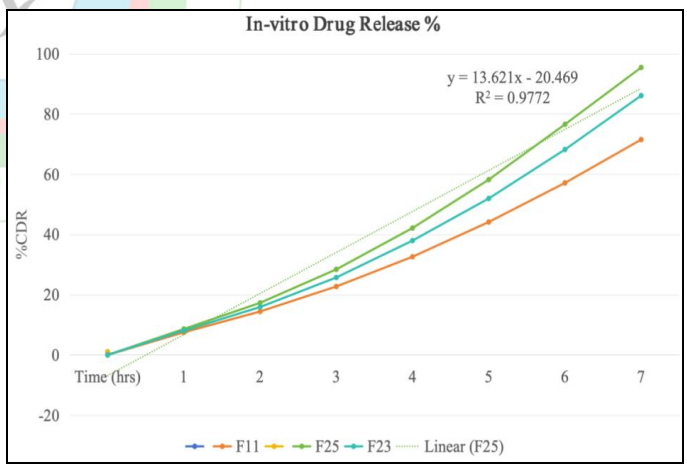
The reference Tavaborole preparation produced a distinct 15 mm zone of inhibition, confirming the antifungal susceptibility of the test organism. In contrast, formulations F1, F2, and F3 did not produce a significant visible zone of inhibition under the experimental conditions.

The absence of a prominent inhibition zone does not necessarily indicate a lack of antifungal activity. Instead, it may be attributed to the controlled-release nature of the polymeric matrix, which restricted the rapid diffusion of Tavaborole into the agar medium during the incubation period. Unlike conventional solutions or discs that release the drug immediately, polymeric transungual patches are designed to release the drug gradually, resulting in limited diffusion through the agar matrix.

These findings suggest that the developed formulation is intended to provide localized sustained drug delivery rather than an immediate burst release. Therefore, the agar diffusion method may underestimate the antifungal potential of sustained-release polymeric systems. Nevertheless, the activity observed with the reference Tavaborole confirmed the intrinsic antifungal efficacy of the drug and supported its suitability for transungual delivery in the treatment of onychomycosis.

IN VITRO DRUG RELEASE STUDY

Figure 10: Franz diffusion cell apparatus



Graph 1: Comparative cumulative drug release profile of formulations F11, F23, and F25

The in vitro drug release behaviour of the selected formulations (F11, F23, and F25) was investigated using a Franz diffusion cell over a period of 7 h. The cumulative drug release profiles are illustrated in Graph 1.

All three formulations exhibited a gradual increase in cumulative drug release throughout the study, indicating sustained release of Tavaborole from the polymeric matrix. However, significant differences in release behaviour were observed among the formulations.

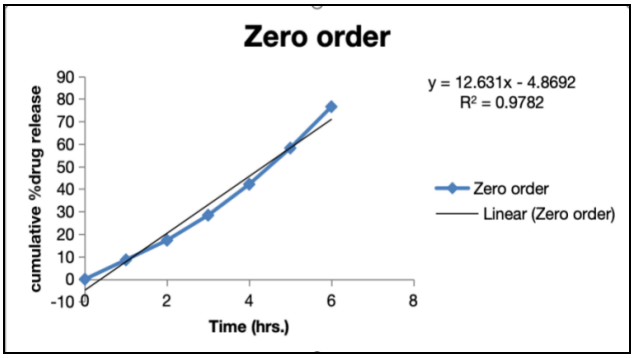
Formulation F25 demonstrated the highest cumulative drug release, reaching 95.42% at the end of 7 h, followed by F23 (86.08%) and F11 (71.48%). The superior release profile of F25 may be attributed to the optimized ratio of HPMC K15M and PVP K30, together with an appropriate concentration of PEG 400, which facilitated controlled hydration of the polymer matrix and enhanced diffusion of Tavaborole.

In comparison, formulation F23 exhibited satisfactory sustained release but at a lower extent than F25, while F11 showed the slowest release among the selected formulations,

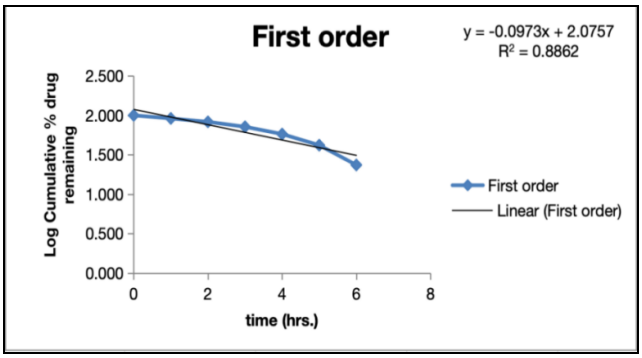
possibly due to differences in polymer composition and matrix characteristics that limited drug diffusion.

Overall, the optimized formulation (F25) demonstrated the most desirable release profile, providing sustained and controlled release of Tavaborole over the entire study period. These findings indicate that the selected polymeric composition successfully achieved prolonged drug release, which is advantageous for the effective management of fungal nail infections.

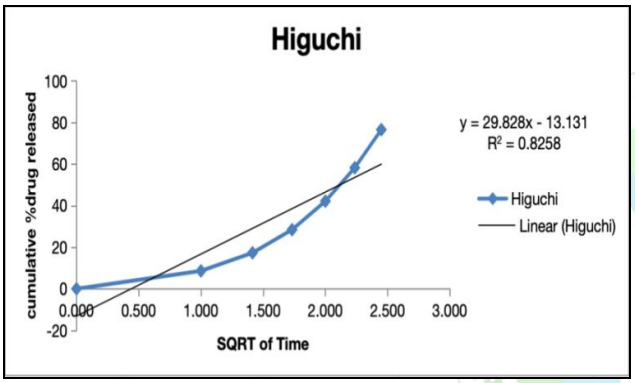
DRUG RELEASE KINETIC MODELING



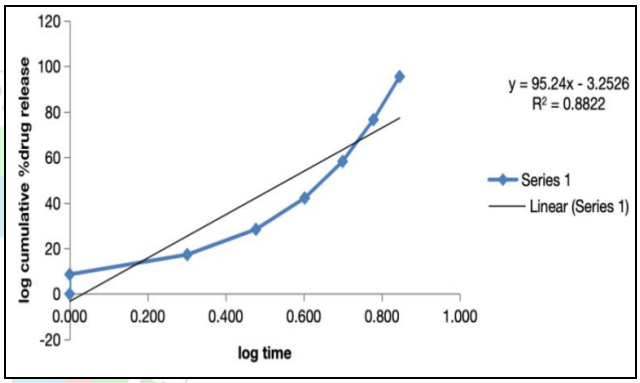
Graph 2: Zero-order release plot



Graph 3: First-order release plot



Graph 4: Higuchi release plot



Graph 5: Korsmeyer–Peppas release plot

To understand the mechanism of drug release, the cumulative release data of the optimized formulation (F25) were fitted to various mathematical models, including Zero-order, First-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models.

Among the evaluated models, theZero-order model exhibited the highest regression coefficient (R^2 = 0.9782), indicating the best fit for the experimental drug release data. The high linearity of the Zero-order plot suggests that Tavaborole was released from the polymeric matrix at an approximately constant rate throughout the study period.

The Higuchi model also demonstrated satisfactory linearity, indicating that diffusion contributed to the release process. However, the comparatively higher correlation coefficient obtained for the Zero-order model suggests that the optimized formulation provided a controlled and sustained release profile rather than a simple diffusion-controlled mechanism.

The observed release behaviour confirms the effectiveness of the optimized polymeric matrix in maintaining prolonged drug release, which is desirable for transungual drug delivery systems intended to remain in contact with the nail for extended periods.

STABILITY STUDY

The optimized formulation (F25) was subjected to accelerated stability testing at 40 ± 2°C and 75 ± 5% RH for one month in accordance with ICH recommendations. The formulation was periodically evaluated for physical appearance, mechanical properties, drug content, and in vitro drug release.

Throughout the storage period, no significant changes in colour, transparency, flexibility, or surface appearance were observed. The prepared patches remained smooth, intact, and free from cracks or brittleness, indicating good physical stability.

Similarly, only negligible variations were observed in folding endurance, drug content, and cumulative drug release when compared with the initial values. These minor changes were within acceptable pharmaceutical limits and did not significantly affect the overall performance of the formulation.

The stability results indicate that the optimized transungual adhesive patch maintained its physicochemical integrity and sustained drug-release characteristics under accelerated storage conditions. Therefore, the developed formulation may be considered sufficiently stable for further pharmaceutical development.

CONCLUSION

The present investigation was successfully carried out to design, develop, and evaluate Tavaborole-loaded transungual adhesive patches for the effective treatment of fungal nail infections. The study demonstrated that an appropriate combination of polymers and plasticizers could successfully produce flexible, uniform, and mechanically stable transungual adhesive patches capable of providing sustained drug release.

Preformulation studies confirmed the identity, purity, and suitability of Tavaborole for formulation development. The drug exhibited satisfactory physicochemical characteristics, while FTIR and DSC studies demonstrated the absence of significant interactions between Tavaborole and the selected excipients, confirming their compatibility.

A total of thirty-five formulations were prepared using different combinations of HPMC E15, HPMC K15M, PVP K30, PEG 400, and PEG 600 by the solvent casting method. Systematic optimization revealed that formulation F25, containing HPMC K15M and PVP K30 in an optimized ratio with PEG 400 as the plasticizer, exhibited the most desirable physicochemical and mechanical characteristics. The optimized formulation showed uniform thickness, excellent flexibility, satisfactory tensile strength, and good film-forming ability, indicating its suitability for transungual application.

The optimized formulation demonstrated sustained drug release, achieving 95.42% cumulative drug release over 7 h, and followed Zero-order release kinetics (R^2 = 0.9782), indicating controlled drug delivery from the polymeric matrix. The antifungal study confirmed the inherent antifungal activity of Tavaborole against *Candida albicans*. Although the polymeric patches did not produce a prominent zone of inhibition under agar diffusion conditions, this behaviour was attributed to the sustained-release nature of the formulation rather than the absence of antifungal efficacy.

Furthermore, the optimized formulation remained physically and chemically stable under accelerated stability conditions, with no significant changes in appearance, mechanical properties, or drug-release characteristics throughout the study period.

Overall, the findings of the present investigation demonstrate that the developed Tavaborole-loaded transungual adhesive patch is a promising localized drug delivery system for the management of onychomycosis. The optimized formulation has the potential to improve patient compliance by providing sustained drug release and prolonged residence time at the site of infection. However, further ex vivo nail permeation studies, in vivo pharmacodynamic investigations, and clinical studies are recommended to establish its therapeutic efficacy and clinical applicability.

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