RESEARCH PAPER

Optimization and Characterization of *Piper Betel Leaf* Extract Loaded Transdermal Patch for Wound Healing

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ABSTRACT:

The present study aimed to formulate, optimize, and characterize a Piper betel leaf extract-loaded transdermal patch for wound healing applications. Piper betel leaves were extracted using ethanol by Soxhlet extraction method, yielding 14.8% extract. Transdermal patches were prepared by solvent evaporation technique using HPMC, PVA, and PVP polymers with glycerol and propylene glycol as plasticizers. Six formulations (F1–F6) were evaluated for physicochemical properties, drug content, FTIR compatibility, and in-vitro drug permeation studies. All formulations showed satisfactory appearance, flexibility, and stability, while FTIR studies confirmed the absence of drug–excipient interaction. Among the formulations, F3 exhibited the best performance with optimum thickness, highest drug content (97.94%), good folding endurance, and maximum cumulative drug release (94.41% within 6 hours). The study concluded that the optimized F3 formulation can be considered a promising herbal transdermal delivery system for enhancing wound healing with improved patient compliance and sustained therapeutic effect.

Keywords: Transdermal patch, Cumulative drug release, Transdermal delivery system, Sustained therapeutic effect, Soxhlet extraction.

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Introduction:

The Transdermal Drug Delivery System (TDDS) is a novel and controlled method of administering drugs through the skin to achieve therapeutic levels in systemic circulation or to provide localized effects at the site of application. In this system, the drug is delivered through the intact skin surface in a controlled and sustained manner using specially designed formulations such as patches, gels, creams, or films. The concept of transdermal drug delivery was introduced as an alternative to conventional routes such as oral and parenteral administration. The skin, being the largest organ of the human body, provides a large surface area for drug absorption. Although the outermost layer of the skin, known as the stratum corneum, acts as a protective barrier against external substances, certain drugs with suitable physicochemical properties can penetrate this barrier and reach systemic circulation. Transdermal drug delivery systems are designed to deliver drugs at a predetermined rate for a prolonged period, thereby maintaining consistent plasma drug levels and improving therapeutic efficacy. Due to these advantages, TDDS has become an important strategy in modern drug delivery technology.

Conventional drug delivery systems, including oral and parenteral delivery, suffer from hepatic first-pass metabolism, gastrointestinal degradation, and poor controllability of drug biodistribution. Transdermal

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drug delivery (TDD) allows the medicine to penetrate the stratum corneum (SC) and reach the epidermis and dermis layers for local and systemic therapy. [1,2] These TDD platforms can be generally grouped into passive and active types.[3,4] Passive delivery refers to the spontaneous degradation of drug reservoir or diffusion-based drug release. Active delivery refers to the drug release induced by internal or external stimuli like the enzymes, pH, electrical,[5] mechanical ultrasound, [6] and optical fields. [7]

These active and passive TDDs can be grouped into patches, semi solid formulations (cream, gel, ointment) and liquid formulations (spray, lotion). Liquid and semi-solid formulations are relatively easy to apply and can cover large area without being limited by skin area and curvature. However, they're relatively messy, their ingredients can be transferred easily to other areas of the skin that might not want to be touched, and they are challenging to apply in a precise dosage. On another hand, patches can specifically act on the area in contact with the precise control of dosage applied. The first TDD patch (i.e., Transderm Scop) was approved in 1979 by the U.S. Food and Drug Administration (FDA) for delivering scopolamine against motion sickness.[8] Since then, many TDD patches have been approved for vaccination, pain relief and skin management .[9, 10]

Recently, wearability has become a new trend in the development of TDD patch. The "wearability" addresses the factors that affect the degree of comfort the wearer or patient experiences while wearing the patch, including physical, psychological, and social aspects.

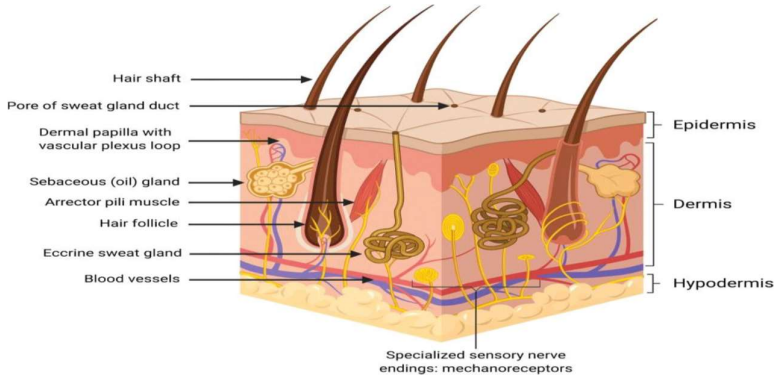

Figure 1: Anatomical structure of the skin

The skin could be roughly split into the SC and epidermis, dermis, and hypodermis layers from surface to bottom .[11] The SC layer is a dense layer on the top of the epidermis, consisting of corneocytes and a lipid matrix. The corneocytes are tightly interconnected by corneodesmosomes, forming a mechanically stable barrier that protects the inner side from pathogen invasion, ultraviolet radiation, and loss of water. The epidermis is a non-vascularized matrix which mainly composed of keratinocytes, Merkel cells and Langerha ns cells. Dermis contains a dense capillary network interconnecting with systemic circulation and is known as the first entrance for drug absorption. The hypodermis is the bottom layer of the skin, consisting of vascularized, loose, areolar connective tissue and adipose tissue.

The major benefits of transdermal delivery could include enhanced efficacy of drug absorption, decreased incidence and severity of adverse events, enhanced patient compliance, and the multitude of benefits from administering drugs through a transdermal patch has contributed immensely to patient compliance and the patches are more convenient, less invasive, and less traumatic than intravenous (IV) delivery, multi-day administration is easily achieved with one application, patches are viable for drugs with high potency or short half-lives, as well as for patients unable to tolerate or achieve their individual "best dose" effect with oral or inhalation dosage forms, patches eliminate the need for the typical resources required for IVs and enhance safety by reducing the potential for disease transmission and the fear of injections is eliminated.[12]

The ideal properties of drug for TDDS which were the drug should not be irreversibly bound in the subcutaneous tissue, should possess a favourable oil: water partition coefficient. (Log P(octanol-water) between 1 and 4), irritation of skin layers should be avoided, drugs highly acidic or alkaline in solution are not suitable for transdermal delivery, the drugs The major benefits of transdermal delivery could include enhanced efficacy of drug absorption, decreased incidence and severity of adverse events, enhanced patient compliance, and the multitude of benefits from administering drugs through a transdermal patch has contributed immensely to patient compliance and the patches are more convenient, less invasive, and less traumatic than intravenous (IV) delivery, multi-day administration is easily achieved with one application, patches are viable for drugs with high potency or short half-lives, as well as for patients unable to tolerate or achieve their individual "best dose" effect with oral or inhalation dosage forms, patches eliminate the need for the typical resources required for IVs and enhance safety by reducing the potential for disease transmission and the fear of injections is eliminated.[12]

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MATERIALS AND METHODS

The piper betel leaf extract loaded transdermal patch was carried out using chemicals like Polyvinyl alcohol, Ethanol, Hydroxy Propyl Methyl Cellulose, Glycerine. Propylene Glycol, Polyvinyl Pyrrolidine.

SOLUBILITY STUDIES

After testing solubility of leaf powder in various solvents such as acetone, chloroform, water, alcohol, and petroleum ether, it can come to know that piper betel leaf powder was more soluble in Ethanol

Figure 2: Solubility Studies of Dry Powder

Figure 3: Solubility Studies of Extract

Fabrication of Transdermal Patch

The piper betel leaf extract loaded transdermal patch was fabricated using solvent evaporation method. In this method, suitable polymers such as Hydroxypropyl Methylcellulose or Polyvinylpyrrolidone are first dissolved in a volatile organic solvent like ethanol to form a clear polymeric solution. The plant extract is then added to this solution and mixed thoroughly until it is completely dissolved. After that, a suitable plasticizer such as Propylene Glycol is incorporated to improve the flexibility and mechanical strength of the patch. The resulting homogeneous mixture is poured into a petri dish or glass mold lined with aluminium foil and allowed to dry at room temperature or in a hot air oven to evaporate the solvent. After complete solvent evaporation, a thin, uniform polymeric film containing the extract is formed. This film is carefully removed and stored in a desiccator for characterization. Compositions of Transdermal patch formulations are given in Table 1.

Characterization of Drug loaded Transdermal patch

The characterization of piper betel leaf extract loaded transdermal patch was done using the following evaluation methods.

Organoleptic Properties:

Colour, shape, clarity, texture, flexibility of the Transdermal Patch was identified.

Surface pH:

The pH of prepared transdermal patch was determined using pH meter/ pH Paper.

Moisture content:

The prepared films are weighed individually and kept in a desiccator at room temperature for 24h. The films are weighed again after a specified interval until that show a constant weight. The percent moisture content is calculated as the difference between the final and initial weight with respect to final weight.

% Moisture content = (Initial weight –Final weight) X 100/initial weight

Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value.

Thickness:

The thickness of the prepared patches was measured using screw gauge at different spots of the patch. The thickness was measured at three different spots of the patches and average was taken and SD was calculated.

Thumb Tack test:

The backing layer of the patch is removed and the adhesive side is gently pressed with the thumb for a few seconds. The tackiness is evaluated by observing how well the patch sticks when the thumb is lifted.

Elongation test:

The patch is held at both ends and slowly stretched until it breaks. The increase in length before breaking is measured to determine the elongation of the patch.

% Elongation = increase Length ÷ initial length ×100

Uniformity of weight:

Weight variation is studied by individually weighing 6 patches and calculating the average weight. The

individual weight should not deviate significantly from the average weight.

Drug Content determination:
Amount of drug entrapped in a patch was determined by completely dissolving patch of size 2×2 cm² in 100 ml phosphate buffer solution (pH 7.4). Complete dissolution was achieved by placing the solution containing patch on shaker for about 24 hours. Solution was then filtered and drug content was estimated spectrophotometrically at 411 nm after suitable dilution.

Ingredients	F1	F2	F3	F4	F5	F6
Piper betel leaf extract	0.9 gm	0.9 gm	0.9 gm	0.9 gm	0.9 gm	0.9 gm
PVA (Polyvinyl alcohol)	-	-	1 gm	1 gm	-	1 gm
PVP (Polyvinyl pyrrolidone)	1 gm	1 gm	1 gm	1 gm	1 gm	1 gm
HPMC	1.5gm	-	2 gm	-	1 gm	-
Propylene glycol	1ml	1ml	1ml	1ml	1ml	1ml
Glycerol	2ml	3ml	2ml	1ml	2ml	2ml
Ethanol	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

Table 1: Composition of *piper betel* leaf extract loaded Transdermal patch

RESULTS AND DISCUSSION

FTIR:
The FTIR spectrophotometer is switched on and allowed to stabilize. A small piece of the transdermal patch is cut, dried, and finely powdered. The powdered sample is mixed with dry potassium bromide (KBr) in a ratio of 1:100 and compressed using a hydraulic press to form a KBr pellet. The pellet is placed in the sample holder, and a background scan is recorded. Then the sample spectrum is obtained in the range of 4000–400 cm^{-1}.
The resulting spectrum is analysed to identify functional groups and drug–polymer compatibility in the transdermal patch is given Table 2.

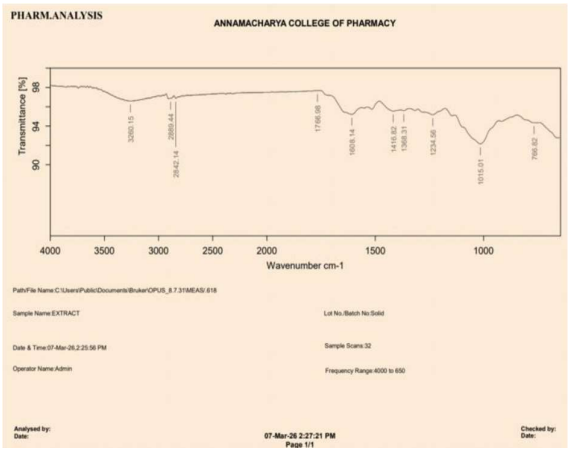


Figure 4: FTIR of Drug Extract

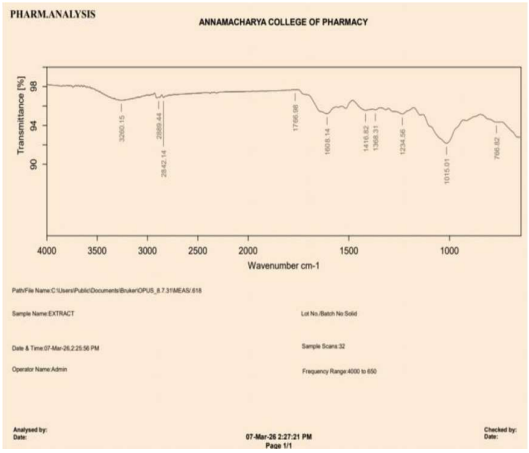


Figure 5: FTIR of F3

Interpretation	Wave NUMBER	
	Drug Extract	F3
O-H Stretch	3300.15	3141.30
C=O (Carbonyl)	1736.83	1638.03
C=C (Aromatic)	1608.41	1638.03
C-H Bending	1383.91	1336.83
C-O Stretch	1234.50	1141.74
C-O Stretch	1051.01	1044.26
C-H (Aromatic bending)	786.62	892.65

Table 2: Interpretation of Drug Extract & F3

No new peaks were observed, confirming the absence of physical & chemical incompatibility and ensuring the stability of the formulation.

Evaluation Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Colour	Pale yellow	Pale yellow	yellowish	Pale yellow	Pale yellow	Pale yellow
Clarity	Translucent	Translucent	Translucent	Translucent	Translucent	Translucent
Texture	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Thickness of patch	0.50±0.007 mm	0.40±0.047 mm	0.56±0.027 mm	0.38±0.012m m	0.48±0.034m m	0.37±0.034m m
Moisture content	0.162	0.166	0.163	0.164	0.162	0.162
Folding endurance	95±10	82±12	96±31	79±53	94±34	92±34
Weight uniformity	0.159±11	0.169±13	0.156±32	0.165±65	0.166±54	0.165±54
Drug content	84.79±32	76.98±65	97.941±11	90.63±54	92.63±13	90.63±13
pH of Patch	6.4	6.2	6.2	6.3	6.2	6.3
Thumb tack test	22	20	15	19	17	17
Elongation test	129%	125%	131%	129%	128%	126%

Table 3: Results of F1 – F6

In-vitro permeation studies:

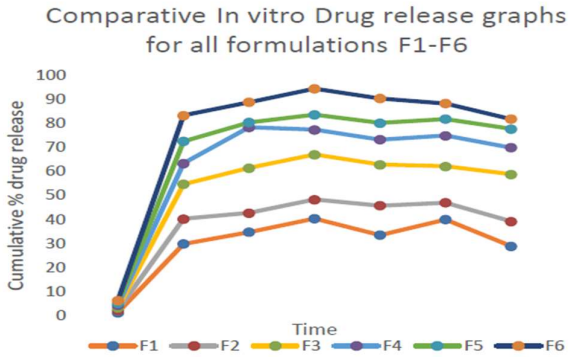
In-vitro permeation studies of the formulated Piper betel transdermal patches were carried out for 6 hours using a Diffusion cell apparatus with phosphate buffer pH 7.4 as receptor medium. Samples were withdrawn at predetermined intervals and analysed spectrophotometrically to determine cumulative drug permeation.

Time (hr)	**Cumulative % drug release**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	29.68±0.97	34.57±0.86	40.21±0.84	33.36±0.85	39.82±0.97	28.72±0.89
2	40.12±0.91	42.55±0.79	48.19±0.90	45.62±0.90	46.73±0.87	39.67±0.90
3	54.54±0.89	61.31±0.82	66.95±0.85	62.74±0.85	62.03±0.89	58.72±0.83
4	63.23±0.90	78.32±0.85	77.32±0.92	73.18±0.93	74.82±0.79	69.82±0.90
5	72.46±0.83	80.35±0.94	83.56±0.83	80.13±0.85	81.73±0.84	77.63±0.83
6	83.22±0.85	88.77±0.97	94.41±0.85	90.32±0.91	88.23±0.83	81.72±0.85

Table 4: RESULTS OF F1 – F6

Formulation code	**Regression for *In-vitro* plot (r2)**	**Regression for Higuchi's plot (r2)**	**Slope for Peppa's plot (n)**
F1	0.9789	0.9939	0.0849
F2	0.9516	0.946	0.0989
F3	0.9948	0.9943	0.0746
F4	0.9812	0.9827	0.0851
F5	0.9787	0.9582	0.0757
F6	0.9558	0.9877	0.0697

Table 5: CORRELATION COEFFICIENT(R^2)



Graph 1: Comparative In vitro Drug release graphs for all formulations F1-F6

Overall, among all the formulations, F3 exhibited optimal characteristics, including highest drug content, good folding endurance, adequate thickness, acceptable pH, and superior elongation properties etc. These results suggest that F3 is the most promising formulation for effective transdermal drug delivery and can be considered as the optimized batch.

CONCLUSION

Among all the formulations, F3 was identified as the optimized formulation due to its superior physico chem ical and mechanical properties. It showed a yellowish translucent appearance with a smooth texture, indicating uniform drug incorporation. The formulation exhibited the highest thickness (0.56±0.027 mm), which may contribute to controlled drug release. Its moisture content (0.163) was found to be optimal for maintainin g stability. F3 demonstrated the highest folding endurance (96±31), indicating excellent flexibility and durability. Weight uniformity (0.156±32) confirmed consistent distribution of formulation components. The drug content (97.94±11%) was highest, suggesting efficient drug loading with minimal drug loss. The pH value (6.2) was within the acceptable range for skin application. The thumb tack value (15) indicated balanced adhesion without causing discomfort. F3 also showed the highest elongation (131%), reflecting superior elasticity and mechanical strength. The highest Zero-order R^2 value (0.9948) indicated controlled and constant drug release behaviour. Similarly, the highest Higuchi R^2 value (0.9943) confirmed diffusion-controlled drug release. The Peppas model 'n' value of 0.0746 (<0.5) suggested that the release mechanism followed Fickian diffusion.

These findings demonstrated that F3 possessed reliable, reproducible, and prolonged diffusion - based drug rele ase characteristics.

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