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Herbal transdermal patch for wound healing: Formulation and *in-vitro* evaluation

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Abstract
Background: The biological process of wound healing is complex that includes tissue regeneration, inflammation and repair and treating it with ointments and dressings, often present challenges related to drug absorption, frequent application and patient discomfort. Transdermal patches have become an innovative drug delivery system to overcome these limitations, in matrix dispersion transdermal patch incorporates the drug into a polymer-solvent mixture, which, after solvent evaporation, forms a uniform drug-polymer matrix.
Materials and Methods: The goal of the project was to develop matrix dispersion system transdermal patch containing blend of natural wound healing agents such as aloe vera and turmeric using a combination of biocompatible polymers. Herbal transdermal patch was formulated using HPMC E15 as polymers with polyvinyl alcohol as plasticizer and polyethylene glycol as permeation enhancer.
Results: The transdermal patch underwent *in-vitro* evaluation that includes measurements of its thickness, folding endurance, weight uniformity, percentage of moisture content, pH and estimated curcumin content. Among these nine patches, formulation 6 demonstrated the best properties of the transdermal patch.
Conclusion: The results obtained from the study, demonstrated that a transdermal patch containing a combination of turmeric and aloe vera can be effectively made with HPMC E15, polyvinyl alcohol and polyethylene glycol.

Keywords: Transdermal patch, aloe vera, turmeric, wound healing, HPMC E15, *in vitro* evaluation

Introduction
A wound occurs when biological tissues are harmed [1, 2] and healing involves the complex process of natural physiological actions by regenerating or reconstructing the damaged tissue [3][4]. Open wounds can lead to serious bacterial infections like tetanus or gas gangrene, potentially causing chronic wounds, bone infections, or even death [5]. On the basis of duration of healing wounds are classified in two classes namely, acute or chronic wounds [6].
The process of repairing injured tissue is a multi-phase and highly specialized system [7]. There are different kinds of therapies for repair of skin wounds by the treatment regimens based on pharmacological agent [8], topical formulations, transdermal patch, wound dressing, skin substitutes, hydrogel-based skin grafts are some examples of conventional non-surgical wound healing remedies. These therapies remove dead tissue, restore moisture and lessen inflammation and infection. For healing wounds topical formulations which is the most popular way to administer drugs to the skin by using gels, emulsions, pastes, creams, foams, lotions and sprays, etc. [9]. These formulations have been tested over the years because of their effectiveness. However, use of it has limited drug availability as a result of their quick clearance from the wound site and staining of bed and clothes which is inconvenient that lacks patient compliance [10]. For centuries, natural substances have been utilized to treat wounds and these natural compounds have been categorized in a number of published reviews according to their properties, bioactivities and modes of action in wound healing applications. Targeting phases of natural products are classified and studied using their four main bioactivities that are collagen promotion, antioxidant, antibacterial and anti-inflammatory [11]. Herbal medicines have been utilized for centuries to treat various illnesses, and many medicinal plants used in these remedies, such as Curcuma longa, Aloe barbadensis, Azadirachta indica, and Carica papaya, have demonstrated effective wound-healing properties, making them beneficial in the treatment of wounds [12].

Aloe vera is a well-known medicinal plant with a lengthy history, intricate chemical constituents, and a wide range of pharmacological effects. The pulp of the aloe leaf is proven to be involved in a variety of pharmacological and therapeutic activities by numerous studies [13] and have shown its importance in accelerating the healing of wounds through the synergistic interactions of its many biochemical constituents. It has hemostatic, antioxidant, antibacterial, anti-inflammatory, anti-diabetic, anti-ulcer, antibacterial, anti-inflammatory, and anti-carcinogenic qualities [14]. Validating its traditional uses, investigating the underlying mechanisms of action and identifying the compounds responsible for its therapeutic effects have been the main research goals for this medicinal plant [15]. According to available data, aloe vera can effectively speed up wound healing and increase the overall success rate of healing when used in different dosage forms [16].

Numerous studies have demonstrated that curcumin, a conventional natural herbal remedy with anti-inflammatory and free-radical scavenging qualities, is a successful treatment for faster wound healing [17]. Considerable anti-inflammatory, antioxidant, anti-cancer, anti-mutagenic, anticoagulant, and anti-infective properties have been shown for curcumin [18]. Wound restoration was speed up by curcumin because it increased the synthesis of growth factors that are involved in wound healing [19] and the topical application of curcumin is more accessible to the wound site than systemic administration, it is generally preferred for cutaneous wound healing [17]. Curcumin has also been shown in recent studies to improve wound contraction, collagen deposition, granulation tissue formation, and tissue remodeling [18]. Studying curcumin's effects on wound healing could be aided by incorporating it into composite films to make a skin-dressing product [20].

Among formulations transdermal patch is the most extensively utilized for wound healing applications with gradual improvement in the design and application over the decades. The advantages of the polymer film are high vapor transmission rate, impermeability to bacteria. Furthermore, advantages of the drug administered through a transdermal patch includes uniform rate of drug release for extended period of time [21] and the drug escapes first past metabolism in liver or GIT therefore increase in bioavailability [22]. Transdermal patch is mostly composed of polymers that are obtained from variety of natural and synthetic source.

Understanding the importance of natural herbs and advantages of transdermal patch for local effect in healing the wound, in the present study we planned to design, formulate and evaluate transdermal patch loaded with mixture of curcumin and aloe vera.

Methods

Aqueous extraction of aloe vera

The scaly Aloe vera leaves were thoroughly washed with water to remove the yellow latex. The outer layer was peeled out and the gel matrix was collected and blended. To the weighed gel matrix 30%v/w of water was added and stirred using magnetic stirrer for 3 hours to form a homogenous solution. The solution was then filtered using filter paper, collected and stored in the refrigerator [23, 24].

Ethanolic extraction of turmeric

Dried turmeric rhizomes were grounded into powder and this powder was added to ethanol and then extract was filtered using Whatman filter paper and stored in an airtight container, in a cool place [25, 26].

Fig 1: Preparation of aloe vera extract

Fig 2: Ethanolic turmeric extract

Preparation transdermal patch by solvent casting method

The transdermal patch was prepared by solvent casting technique using different polymers that includes polyvinyl alcohol, HPMC E15, propylene glycol (PG). Initially, polyvinyl alcohol (PVA) was dissolved in a beaker containing distilled water on a water bath. Turmeric and aloe vera extract were added to another beaker and stirred with a magnetic stirrer to form a solution. To this solution, HPMC E15 was added with constant stirring followed by polyvinyl glycol. The prepared PVA solution was then transferred to the second beaker and continuously stirred for 30 minutes to form a homogeneous solution and this solution was casted into a petri plate coated with glycerin and left to dry in an incubator at a constant temperature of 37°C for 48 hours. The patch was then removed with a sharp blade, wrapped in aluminum foil and stored in a labelled zip lock bag [27-29].

Fig 3: Casting of solution into petri plate

Fig 4: Petri plate containing the solution

Total nine transdermal patches were formulated with two variable factors that are HPMC E15 and PVA at three levels. Complete components description of each transdermal patch is shown in Table 1.

Table 1: Composition of transdermal patch

Formulation code	HPMC E15 (mg)	PVA (mg)	PG (mg)	Water (ml)	Ethanol (ml)	Aloe vera extract (ml)	Turmeric extract (ml)
F1	150	0	1	5	5	1	10
F2	150	20	1	5	5	1	10
F3	150	30	1	5	5	1	10
F4	250	0	1	5	5	1	10
F5	250	20	1	5	5	1	10
F6	250	30	1	5	5	1	10
F7	350	0	1	5	5	1	10
F8	350	20	1	5	5	1	10
F9	350	30	1	5	5	1	10

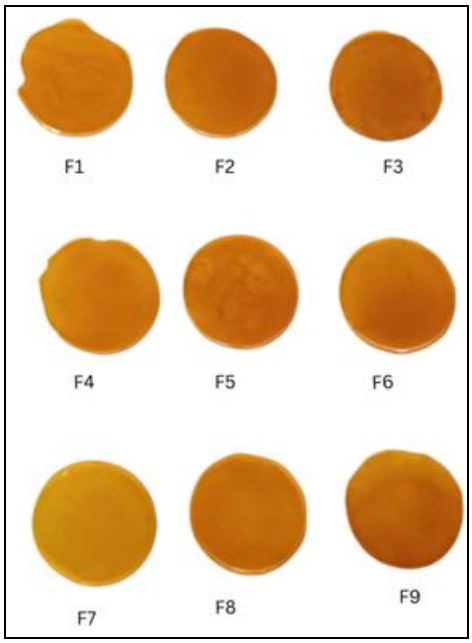

Fig 5: Nine formulated transdermal patches

Physiochemical evaluation of transdermal patch

- **Physical appearance:** The patches were evaluated for color, odor, texture and appearance. The prepared patches underwent a visual inspection, assessing attributes such as color, clarity, flexibility, and smoothness.
- **Thickness:** The thickness of the formulated patch was measured at three different points using a digital vernier caliper and the average thickness was determined from these readings. The standard deviation was calculated to ensure uniformity in the thickness of the prepared patch.
- **Weight uniformity:** The prepared patch was cut into three 1x1 cm² sections and each section was weighed using a digital balance. The average weight was then calculated.
- **Surface PH:** To determine the surface pH of the patch, 1x1 cm² sections were cut from three different areas of the patch and these sections were placed in 0.5 ml of distilled water and allowed to swell for 1 hour. The surface pH was then measured using a digital pH meter and the average pH value was calculated [30].
- **Percentage of moisture content:** The patches were accurately weighed and then placed inside a desiccator containing anhydrous calcium chloride. After 3 days, the patches were removed from the desiccator and reweighed. The moisture content (%) of the transdermal patches was then calculated using the formula mentioned [31].

$$\%Moisture\ content = \frac{Initial\ weight - final\ weight}{Initial\ weight} \times 100$$

- **Folding endurance:** The efficacy of the plasticizer was evaluated using a folding endurance test. This involved manually folding the prepared patches repeatedly at the same spot until they broke. The number of times each transdermal patch could be folded at the same position without breaking was recorded as the folding endurance [32].
- **Estimation of curcumin content in the transdermal patch:** A 1x1 cm² section of the patch was placed in a 10 ml test tube, and 10 ml of methanol was added. The mixture was shaken for 2 hours and then left to stand overnight. Afterward, the solution was filtered using filter paper. From the filtered solution, 1 ml was transferred into a 10 ml volumetric flask and diluted to the mark with methanol. The absorbance was measured at 425 nm using a UV spectrometer and the concentration was calculated using a slope value of 0.1228.

Results and Discussion

The goal of the study was to develop a transdermal patch that would create a matrix-type patch using the solvent casting method. HPMC E15 was used as the polymer in the preparation of the patch, additionally, polyvinyl alcohol was used as a plasticizer and polyethylene glycol as a permeation enhancer. Ethanol and water were used as the solvents in the formulation of the transdermal patch with varying ratios of PVA and HPMC E15, total nine transdermal patch were prepared.

The formulated patches exhibited a yellow color and were odorless. The texture of patches F2, F3, F6, F7, and F8 was uniform, while patches F1, F4, F5, and F8 displayed non-uniform textures. The physiochemical characteristics of these patches, which include uniformity, color, odor, thickness, folding endurance, weight variation, moisture content, and pH were assessed. The results are depicted in Table 2.

Table 2: Physiochemical evaluation of transdermal patch

Formulation code	Folding endurance	Thickness (mm)	Weight variation (mg)	Percentage of moisture content (%)	pH
F1	6	0.22	49.33±0.47	18.92±1.05	6.9
F2	55	0.15±0.02	45±1.63	31.08±0.68	6.8
F3	55	0.21±0.24	55±0.81	24.84±0.57	6.8
F4	>300	0.55	60±0.81	15±0.20	6.9
F5	>300	0.51±0.02	50.2.44	19.30±1.12	6.9
F6	>300	0.46	65±1.63	10.24±0.52	6.9
F7	206	0.57	76.33±1.24	17.03±0.27	7
F8	>300	0.45±0.05	60±0.81	13.35±1.54	6.7
F9	>300	0.41±0.05	72±2.44	15.27±0.98	6.8

Since plasticizer was used in the formulation, the transdermal patches F4, F5, F6, F8, and F9 showed folding endurance of more than 300. It is necessary for the patch's mechanical strength and long-life. Greater folding endurance is a strong indicator of greater strength and stress resistance [33]. Each patch was measured three different positions to ensure thickness uniformity and the average was computed. Measurements of thickness is shown in Table 2, with F7 being the thickest (0.57mm) and F2 being the thinnest (0.15±0.02 mm). Variations ranged from 0.15mm to 0.57mm, as the polymer and plasticizer content increased, so did the

thickness increased. The patch evaluation for weight variation revealed good uniformity with a low standard deviation, suggesting that the mixture was distributed uniformly throughout the prepared patches matrix. The prepared patches have a weight variation of 45 mg to 76 mg. This indicates that the weight increases with increase in polymer content. The transdermal patch's thickness and weight variation are essential properties that affect the patch overall efficacy and rate of drug release. Low residual solvent content (between 31.08 and 10.24%) contributed to the stability of the patches. The F2 patch had the highest moisture content (31.08%±0.68%), while the F6 patch had the lowest moisture content (10.24±0.52%). Formulation 6, with its low moisture content, is better for stability and longer shelf life [34].

To assure that the transdermal patch pH is within the acceptable ranges for skin compatibility and to reduce skin irritation, a pH test is required [35]. Each formulation pH is within the range of physiological skin pH, making it safe for external application. The process ensured that the potent active pharmaceutical ingredient, aloe vera and turmeric, would continue to function as intended.

Conclusion

Among all the formulated patches, the formulation 6 was chosen had all the desired properties such as, a smooth surface with uniform thickness and weight, an ideal surface pH, folding endurance more than 300, the least amount of moisture content (10.246±0.527%), and 7.31±0.139 mg of curcumin. In the present study we could formulate herbal transdermal patch containing Aloe vera and Turmeric for wound healing and evaluated for all the desired properties. Further studies are need to be carried out to confirm its wound healing efficiency.

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