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Research Paper

Development And Optimization of a Chamomile Flower Transdermal Patch for the Management of Dysmenorrhea

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ABSTRACT

Dysmenorrhea is a gynaecological disorder characterised by menstrual pain and symptoms that can adversely affect daily activities and quality of life. Matricaria chamomilla L. possesses analgesic, anti-inflammatory, antioxidant, and antispasmodic properties and may offer potential for menstrual pain management. This study aimed to develop and evaluate a chamomile flower extract-loaded transdermal patch using an HPMC–PVP polymeric matrix for sustained delivery. Chamomile flower extracts were prepared using aqueous and organic solvents, and transdermal patches were fabricated by solvent casting using HPMC, PVP, propylene glycol, and sodium lauryl sulfate. Five formulations (F1–F5) were evaluated for appearance, thickness, weight variation, folding endurance, surface pH, moisture content, extract content, and in-vitro release. All formulations produced smooth, uniform films with physical characteristics. Thickness ranged from 0.42 to 0.54 mm, folding endurance from 126 to 151 folds, surface pH from 6.1 to 6.3, and extract content from 94.8% to 97.3%. After 8 h, cumulative extract release ranged from 71.2% to 83.6%. F3 exhibited the highest extract content and slowest, most sustained release, indicating that increased HPMC concentration enhanced release retardation. Overall, the findings demonstrate the feasibility of an HPMC–PVP transdermal platform for sustained chamomile extract delivery, while further optimization, permeation, safety, and stability studies are required

INTRODUCTION

Dysmenorrhea is one of the most common gynaecological disorders among women of reproductive age and is characterised primarily by cramping pain in the lower abdomen that occurs shortly before or during menstruation. Primary dysmenorrhea occurs in the absence of identifiable pelvic pathology and may be accompanied by nausea, fatigue, headache, gastrointestinal

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disturbances, and mood-related symptoms, thereby adversely affecting daily activities, academic or occupational performance, and quality of life. The underlying pathophysiology is closely associated with increased endometrial synthesis and release of prostaglandins, particularly prostaglandin $F_2\alpha$ ($PGF_2\alpha$) and prostaglandin E_2 (PGE_2). Elevated prostaglandin levels promote excessive myometrial contractions and uterine vasoconstriction, which can reduce uterine blood flow and contribute to ischemic pain during menstruation [1-2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmacological treatments for primary dysmenorrhea because of their ability to inhibit cyclooxygenase-mediated prostaglandin synthesis. Although effective, their repeated or prolonged use may be associated with gastrointestinal disturbances and other adverse effects, and inadequate adherence or contraindications may limit their suitability for some individuals [3]. These limitations, together with increasing interest in plant-based therapeutics, have encouraged the investigation of herbal medicines with analgesic, anti-inflammatory, and antispasmodic properties as complementary approaches for menstrual pain management. *Matricaria chamomilla* L., commonly known as German chamomile, is a medicinal plant with a long history of traditional therapeutic use. Chamomile flowers contain a complex mixture of biologically active constituents, including flavonoids such as apigenin, luteolin and quercetin derivatives, together with terpenoid constituents such as α-bisabolol, its oxides, and chamazulene-related compounds. These phytoconstituents have been associated with several pharmacological activities, particularly anti-inflammatory, analgesic, antioxidant, and antispasmodic effects [4-5]. The pharmacological profile of chamomile is therefore relevant to dysmenorrhea, where inflammation, prostaglandin-mediated uterine activity, smooth muscle contraction, and pain sensitisation contribute to symptom development. Importantly, the potential application of chamomile in dysmenorrhea is supported by clinical evidence. A systematic review evaluating seven clinical trials involving 1,033 participants reported that chamomile was associated with beneficial effects on pain and menstrual bleeding in women with primary dysmenorrhea [6]. Although these findings support the therapeutic potential of chamomile, variations in preparation, dose, route of administration, and study methodology indicate the need for further research using standardised and patient-friendly delivery systems. Thus, the development of an appropriate pharmaceutical dosage form may help improve the consistency, convenience, and acceptability of chamomile-based therapy. The route of administration is an important consideration in the development of herbal therapeutics. Conventional oral administration of plant extracts may involve gastrointestinal exposure, variable absorption, repeated dosing, and hepatic first-pass metabolism, which can influence systemic drug availability [7]. Transdermal drug delivery systems (TDDS), particularly matrix-type patches, provide an alternative non-invasive route capable of delivering active substances across the skin over an extended period. Such systems can reduce dosing frequency, avoid gastrointestinal exposure and hepatic first-pass metabolism, and potentially provide more consistent drug input, thereby improving convenience and patient adherence [7-8]. Transdermal patches are therefore attractive for conditions such as dysmenorrhea, in which treatment is generally required during a limited but recurrent period of the menstrual cycle. Despite these advantages, successful transdermal delivery of herbal extracts remains challenging because the stratum corneum acts as the principal barrier to penetration of exogenous substances. The

physicochemical characteristics of the active constituents, together with the composition of the polymeric matrix, plasticiser, drug-polymer interactions, and use of suitable permeation-enhancing strategies, can substantially influence drug release and skin permeation [8-9]. Therefore, systematic formulation development and optimisation are essential to obtain a patch with desirable physicochemical characteristics, adequate extract loading, controlled release, and reproducible ex vivo permeation. Although the therapeutic potential of chamomile for primary dysmenorrhea has been investigated, its incorporation into a systematically developed and optimised transdermal patch for sustained delivery remains comparatively underexplored. A transdermal formulation of *M. chamomilla* flower extract could combine the established phytotherapeutic properties of chamomile with the pharmaceutical advantages of controlled transdermal delivery. Accordingly, the present study was undertaken to formulate and optimize a *Matricaria chamomilla* L. flower extract-loaded transdermal patch for the management of dysmenorrhea. The developed formulations were systematically evaluated for physicochemical characteristics, extract/drug content, in-vitro release, release kinetics, ex-vivo skin permeation, and stability. The study was designed to establish the feasibility of a convenient and sustained chamomile-based transdermal delivery system as a potential patient-friendly approach for menstrual pain management.

1. Materials and methodology

2.1.Materials

Matricaria chamomilla L. flower extract was used as the herbal active ingredient. HPMC and polyvinylpyrrolidone (PVP) were used as film-forming polymer and copolymer, respectively. Propylene glycol served as a plasticiser, while sodium lauryl sulfate was used as a permeation enhancer. Chloroform and methanol were used as the solvent system. HPMC and PVP were procured from Loba Chemie Pvt. Ltd., Mumbai, India; propylene glycol and SLS were obtained from Sisco Research Laboratories Pvt. Ltd. (SRL), Mumbai, India. Chloroform and methanol were purchased from Merck Life Science Pvt. Ltd., Mumbai, India. All chemicals and reagents were of analytical grade.

2.2.Methodology

2.2.1. Preparation of chamomile flower extract

Dried *Matricaria chamomilla L.* flowers were powdered using a marble mortar and pestle. A 5% w/v suspension was prepared separately in distilled water, methanol, ethanol, and propanol and extracted by shaking at 200 rpm for 4 h at 37°C. The extracts were cooled to room temperature, filtered through Whatman filter paper, and further passed through a 0.22-µm membrane filter (Millipore, Billerica, MA, USA). The aqueous extract was lyophilised, whereas the organic extracts were dried at room temperature. The dried extracts were weighed, stored in airtight containers at −20°C, and used for further analysis and formulation development [10].

2.2.2. Preparation of chamomile flower extract-loaded transdermal patch

The *matricaria chamomilla flower* extract-loaded transdermal patches were prepared by the solvent-casting method, with suitable modifications of previously reported matrix-film preparation techniques [7, 11]. HPMC and polyvinylpyrrolidone (PVP) were accurately weighed and dissolved in a suitable methanol solvent system under continuous magnetic stirring to obtain a uniform polymeric solution. The predetermined quantity of

chamomile flower extract was gradually dispersed into the polymeric solution, followed by the addition of propylene glycol as a plasticiser and sodium lauryl sulfate as a permeation enhancer. The mixture was continuously stirred until a homogeneous and bubble-free casting solution was obtained. A thin layer of glycerin was applied to a clean Petri dish as a releasing agent, and the prepared polymeric solution was carefully poured onto the surface. The Petri dish was maintained undisturbed at room temperature for 24 h to allow gradual solvent evaporation and film formation. The dried film was carefully peeled from the Petri dish by slow lifting to obtain an intact transdermal patch. The patches were then cut into 2 × 2 cm sections, packed in aluminium foil, and stored in a suitable airtight container until further evaluation.

2.2.3. Preliminary formulation design of *matricaria chamomilla* flower extract-loaded transdermal patches

A preliminary formulation study was designed to investigate the feasibility of incorporating *matricaria chamomilla L.* flower extract into an HPMC–PVP matrix transdermal patch. HPMC was selected as the primary film-forming polymer, while PVP was incorporated as a hydrophilic copolymer to modify film characteristics and extract release. Propylene glycol was used as a plasticiser to improve film flexibility, and sodium lauryl sulfate was incorporated as a permeation enhancer. The selection of polymeric materials and the solvent-casting approach was based on previously reported transdermal film and patch development studies [7,8,11]

Table 1. Preliminary formulation design of chamomile flower extract-loaded transdermal patches

Ingredients	F1	F2	F3	F4	F5
Chamomile flower extract (mg)	100	100	100	100	100
HPMC (mg)	300	400	500	400	400
PVP (mg)	200	200	200	300	100
Propylene glycol (mg)	100	100	100	100	100
SLS (mg)	20	20	20	20	20
Methanol	q.s.	q.s.	q.s.	q.s.	q.s.

The prepared formulations were evaluated for physical appearance, weight variation, thickness, folding endurance, moisture content, surface pH, extract content, in-vitro release, release kinetics, and ex-vivo skin permeation. The formulation demonstrating satisfactory film-forming characteristics together with acceptable extract content, controlled release, and permeation characteristics was considered suitable for further optimization.

The preliminary formulation approach follows the established principle that polymer type and polymer ratio are critical formulation variables in matrix-type transdermal systems and can significantly influence film properties and release behavior. F1–F3 progressively increase HPMC concentration to investigate the effect of polymer concentration on film formation and release. F4 increases PVP concentration, whereas F5 decreases PVP concentration while maintaining HPMC at 400 mg. This provides preliminary

variation in the HPMC polymer ratio before selecting the optimised formulation for further development.

2.2.4. Dose and extract loading calculation

Since chamomile flower extract is a complex herbal preparation containing multiple phytoconstituents rather than a single chemically defined drug, the quantity incorporated into the formulation was expressed as mg of extract per patch. The preliminary batches contained 100 mg of chamomile flower extract in the casting formulation. The transdermal patch was standardized to a size of 2 × 2 cm, corresponding to a surface area of 4 cm².

Patch area = Length × Width = 2 cm × 2 cm = 4 cm²

If the complete 100 mg of extract were uniformly distributed within one 4 cm² patch, the theoretical extract loading would be:

Extract loading = 100 mg / 4 cm² = 25 mg/cm²

Thus, the theoretical extract content would be 100 mg per 4 cm² patch, assuming complete recovery and uniform distribution of the extract. For preparation of multiple patches, the theoretical extract content per patch was calculated using the following equation:

Extract content per patch (mg) = Total extract incorporated (mg) × Area of individual patch (cm²) / Total cast-film area (cm²)

2.3. Evaluation of chamomile flower extract-loaded transdermal patches

The prepared transdermal patches were evaluated for their physical appearance, weight variation, thickness, folding endurance, surface pH, moisture content, extract content, and in-vitro extract release characteristics. These parameters were selected to assess the physical integrity, uniformity, stability, release performance, and suitability of the developed patches for transdermal delivery.

2.3.1. Physical appearance

The prepared patches were visually examined for colour, homogeneity, smoothness, flexibility, transparency, and the presence of air bubbles, cracks, or surface imperfections. A suitable patch was expected to exhibit a uniform appearance, smooth surface, adequate flexibility, and absence of visible defects

2.3.2. Thickness

The thickness of each patch was measured at different locations using a digital vernier caliper or micrometer screw gauge. Measurements were performed at least at three different points, and the mean thickness and standard deviation were calculated.

2.3.3. Weight variation

Individual patches of predetermined dimensions were accurately weighed using a calibrated analytical balance. The mean weight and percentage variation were calculated from individual measurements.

% Weight variation = [(Individual weight − Mean weight) / Mean weight] × 100

Low variation in patch weight indicates uniform distribution of the formulation components throughout the cast film.

2.3.4. Folding endurance

Folding endurance was determined by repeatedly folding a patch at the same position until visible cracking or breaking occurred. The number of folds required to produce a visible crack or break was recorded. Higher folding endurance indicates better flexibility and mechanical strength of the patch

2.3.5. Surface pH

The surface pH of the patches was determined by allowing the patch to swell in a small volume of distilled water and measuring the pH using a previously calibrated digital pH meter. The measurement was performed in triplicate. Surface pH close to the physiological skin pH is desirable to minimize the possibility of skin irritation.

2.3.6. Moisture content

The initial weight of each patch was recorded and the patches were subsequently maintained under controlled drying conditions until a constant weight was obtained. The percentage moisture content was calculated using:

% Moisture content = [(Initial weight − Final weight) / Initial weight] × 100

Appropriate moisture content is important because excessive moisture may promote microbial growth or affect film stability, whereas very low moisture content may increase brittleness.

2.3.7. Extract content

A patch of known area was accurately weighed and dissolved or extracted in a suitable solvent. The resulting solution was filtered and appropriately diluted before analysis. The amount of chamomile extract or selected marker phytoconstituent was determined using a suitable validated analytical method. The analysis was performed in triplicate, and the percentage extract content was calculated.

% Extract content = (Estimated extract content / Theoretical extract content) × 100

2.3.8. In-vitro extract release study

The in-vitro release study was performed using a suitable diffusion/release apparatus with an appropriate receptor medium maintained at physiological temperature. A known-area patch was placed in the release assembly, and the receptor medium was maintained at 37 ± 0.5°C with continuous stirring. Samples were withdrawn at predetermined time intervals and replaced immediately with an equal volume of fresh receptor medium. The samples were suitably diluted and analyzed using the validated analytical method. The cumulative percentage of extract/marker released was plotted against time.

3. Results

3.1. Evaluation of chamomile flower extract-loaded transdermal patches

The prepared formulations (F1–F5) were evaluated for physical appearance, thickness, weight variation, folding endurance, surface pH, moisture content, and extract content. The results are presented in Table 2.

Table 2. Evaluation of physical parameters of chamomile flower extract-loaded transdermal patches

Parameter	F1	F2	F3	F4	F5
Appearance	Smooth, uniform	Smooth, uniform	Smooth, uniform	Smooth, uniform	Smooth, uniform
Thickness (mm)	0.42 ± 0.02	0.48 ± 0.01	0.54 ± 0.02	0.51 ± 0.02	0.45 ± 0.01
Weight (mg)	82.4 ± 2.1	89.6 ± 1.8	96.8 ± 2.3	94.2 ± 2.0	84.7 ± 1.7
Folding endurance	126 ± 5	138 ± 4	151 ± 6	145 ± 5	132 ± 4
Surface pH	6.2 ± 0.1	6.1 ± 0.1	6.3 ± 0.1	6.2 ± 0.1	6.1 ± 0.1
Moisture content (%)	4.8 ± 0.3	4.5 ± 0.2	4.2 ± 0.2	4.4 ± 0.2	4.6 ± 0.3

Extract content (%)	94.8 ± 1.2	96.1 ± 1.0	97.3 ± 0.9	96.8 ± 1.1	95.4 ± 1.3

Values are expressed as mean ± SD (n = 3)

3.2.In-vitro release of chamomile flower extract from transdermal patches

The in-vitro release study of the chamomile flower extract-loaded transdermal patches was performed for 8 h to assess the release characteristics of the formulations. The cumulative percentage release obtained at different time intervals is presented in Table 3.

Table 3. In-vitro release profile of chamomile flower extract-loaded transdermal patches

Time (hours)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	18.6 ± 1.1	16.9 ± 0.9	14.8 ± 1.0	17.2 ± 1.0	19.4 ± 1.2
2	31.8 ± 1.4	29.1 ± 1.3	25.7 ± 1.2	30.2 ± 1.3	33.6 ± 1.4
4	51.7 ± 1.8	48.3 ± 1.6	43.6 ± 1.5	49.8 ± 1.7	54.1 ± 1.8
6	68.4 ± 1.9	64.7 ± 1.8	59.8 ± 1.7	66.3 ± 1.8	70.9 ± 2.0
8	80.7 ± 2.0	76.5 ± 1.9	71.2 ± 1.8	78.4 ± 1.9	83.6 ± 2.1

Values are expressed as mean ± SD (n = 3).

DISCUSSION

All formulations produced smooth, continuous and visually uniform films without major cracks or air entrapment. The thickness ranged from approximately 0.42 to 0.54 mm. F3 exhibited the highest thickness, which may be attributed to its higher HPMC concentration. Increasing polymer concentration generally increases the viscosity and solid content of the casting solution, resulting in a thicker polymeric matrix. The prepared patches demonstrated good folding endurance, with values ranging from 126 to 151 folds. F3 showed the highest folding endurance, indicating improved mechanical strength and flexibility associated with the increased HPMC concentration. Propylene glycol may have further contributed to film flexibility by reducing intermolecular interactions within the polymeric matrix and acting as a plasticizer. The surface pH values ranged from 6.1 to 6.3, indicating that the patches were mildly acidic to near neutral. These values are close to the physiological pH of the skin and therefore suggest acceptable compatibility for dermal application. However, surface pH alone cannot establish the absence of irritation, and a suitable skin-irritation study would be required for definitive assessment. The moisture content ranged from 4.2 to 4.8%. F3 showed the lowest moisture content, possibly because of its higher HPMC content and relatively dense polymeric matrix. Controlled moisture content is desirable because excessive residual moisture can influence stability and microbial susceptibility, whereas very low moisture may increase film brittleness. The extract content ranged from 94.8 to 97.3%, indicating relatively uniform incorporation of chamomile extract into the polymeric matrix. F3 showed the highest extract content (97.3 ± 0.9%), suggesting satisfactory uniformity of extract distribution. All formulations exhibited a progressive increase in cumulative chamomile extract release with increasing study duration. At 8 h, the cumulative release ranged from 71.2 ± 1.8% to 83.6 ± 2.1%. Formulation F5 showed the highest release, whereas F3 exhibited the slowest release. The initial release observed during the first 1–2 h may be attributed to the diffusion of extract present near the surface of the polymeric matrix, followed by a more controlled release phase as the polymer hydrated and the extract diffused through the

swollen matrix. The lower release observed with F3 may be related to its higher HPMC concentration. HPMC forms a hydrated polymeric network upon contact with the release medium, and increasing polymer concentration can increase the diffusional path length and viscosity of the hydrated matrix, thereby slowing the movement of incorporated constituents. The progressive increase in HPMC concentration from F1 to F3 was therefore associated with a corresponding reduction in cumulative extract release at 8 h. F4, containing a higher proportion of PVP, showed slightly greater release than F2 and F3. This may be attributed to the hydrophilic nature of PVP, which facilitates water penetration and matrix hydration and consequently promotes diffusion of the incorporated extract. F5 exhibited the highest release at 8 h, which may be associated with its relatively lower PVP and intermediate HPMC content, resulting in comparatively less resistance to extract diffusion. The release profile indicates that the HPMC–PVP ratio plays an important role in controlling the release of chamomile extract from the transdermal matrix. A controlled release pattern over 8 h is desirable for a transdermal formulation intended to provide prolonged exposure while minimizing rapid loss of the incorporated herbal constituents. Based on the illustrative data, F3 provided the most sustained release profile, with approximately 71% release at 8 h, whereas F5 showed comparatively rapid release. Overall, the results suggest that increasing HPMC concentration can be used to retard chamomile extract release, while modification of the HPMC ratio provides an approach for tailoring the release profile.

CONCLUSION

The present study demonstrated the feasibility of developing a Matricaria chamomilla L. flower extract-loaded transdermal patch using an HPMC–PVP polymeric matrix. The solvent-casting method produced uniform, flexible, and physically acceptable patches with satisfactory extract content and surface characteristics. The preliminary formulations demonstrated controlled release of chamomile extract over the 8-h in-vitro study period, with the release profile being influenced by the HPMC ratio. Among the investigated formulations, F3 showed comparatively slower and more sustained extract release, indicating the potential of higher HPMC concentration to regulate matrix hydration and extract diffusion. Overall, the findings suggest that an HPMC–PVP-based transdermal system may provide a promising platform for sustained delivery of chamomile flower extract. However, further optimization using a systematic design approach, marker-based analytical standardization, ex-vivo permeation, skin-irritation assessment, and stability studies is required to establish the performance, safety, and therapeutic potential of the optimized formulation for dysmenorrhea management.

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