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Formulation and evaluation of transdermal patch containing essential oils

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Abstract:

This study investigates the formulation and evaluation of a herbal essential oil-based transdermal drug delivery system (TDDS) with potential anti-inflammatory and analgesic properties. The oils selected—Capsicum oleoresin, Wintergreen oil (methyl salicylate), Mentha oil (menthol), and Thymol oil—are well-known for their therapeutic activities. These oils were incorporated into transdermal patches using suitable polymers and evaluated for physicochemical parameters, and in vitro drug release. Results demonstrated that the herbal essential oil-based TDDS offers a promising alternative for pain and inflammation management with controlled drug delivery and enhanced patient compliance.

Keywords: Transdermal drug delivery system, Essential oils, Capsicum oleoresin, Wintergreen oil, Mentha oil, Thymol, Anti-inflammatory, Analgesic.

Introduction

Pain and inflammation are symptoms of various acute and chronic conditions. Conventional drug delivery methods for managing these symptoms, such as oral NSAIDs and injections, often result in systemic side effects and poor patient adherence. To address these limitations, transdermal drug delivery systems (TDDS) have gained attention as they offer controlled drug release, bypass first-pass metabolism, and improve compliance. (Libby P et al., 2024)

Herbal essential oils possess significant pharmacological activities, including anti-inflammatory and analgesic effects. This study focuses on Capsicum oleoresin (rich in capsaicin), Wintergreen oil (methyl salicylate), Mentha oil (menthol), and Thymol oil—natural agents known for their efficacy in musculoskeletal pain, arthritis, and neuralgia. The goal is to develop and evaluate a TDDS using these oils to determine its potential as a therapeutic alternative.

Materials and Method

Capsicum oleoresin, Wintergreen oil, Mentha oil, and Thymol oil were purchased from Indenta Research & Development Centre, Mumbai. HPMC 100M and HPMC 15M CR were purchased from Panacea

Biotech. All the chemicals and reagents used were of analytical grade.

Formulation of Patches

Transdermal films containing essential oils were casted on glass slide by solvent evaporation method using different grades (K 15 M CR, K 100 M) of HPMC in presence of a plasticizer. PEG 400 (5%) was used as a plasticizer in all cases. Oils were dissolved in water-methanol solvent mixture (7:3). The essential mixture of oil (1%) matrix was prepared by dissolving varying concentrations (1% and 1.5% w/v) of HPMC in the same solvent system. The solution was kept undisturbed for 24 h. Then, with the help of syringe. Thus, in order to study the consequence of responses i.e., drug content of film and drug release and optimization of formulation factors, Box Behnken statistical design was chosen. (Nadpara NP et al., 2012)

Run	Factor 1 A: HPMC K 100 %	Factor 2 B: HPMC K 15 %	Factor 3 C: PEG %
1	1.5	0.5	3.75
2	1	1	3.75
3	1.5	1.5	3.75
4	0.5	0.5	3.75
5	0.5	1	5
6	0.5	1	2.5
7	1	1	3.75
8	1	0.5	2.5
9	1	1.5	2.5
10	0.5	1.5	3.75
11	1.5	1	2.5
12	1	1	3.75
13	1	0.5	5
14	1	1.5	5
15	1.5	1	5

Evaluation of transdermal patches

Percentage moisture content

Moisture content can influence the mechanical strength and drug release behaviour of the transdermal therapeutic systems and therefore, in the present study determination of the moisture of the formulated patch was estimated by keeping the patch under vacuum desiccation until constant weights were obtained. The percentage moisture content of the patch was calculated by the following formula. (Kumar SS et al., 2013)

Percentage moisture content = (Initial weight- Final weight) /Initial weight

pH

Patches were kept in contact with 0.5 ml of double distilled water for 1 h in glass tubes and were allowed to swell. A combined glass electrode was brought near the surface of patch and pH readings were taken after allowing an equilibration period of 1 min. (Khan D et al., 2020)

Swelling Index

The swelling index of the patches was evaluated by submerging pre-weighed 2 × 2

cm2 patches in 50 ml of water. At specified time intervals (5, 10, 30, and 60 minutes), the patches were carefully removed, gently blotted with filter paper to remove excess moisture, and accurately reweighed. The average swelling index was subsequently calculated based on the measurements obtained from all the patches, providing a quantitative assessment of their swelling behavior. (Shivalingam MR et al., 2021)

Drug content

A Pieces of 2 × 2 size were cut from each type of formulation pH 7.4 solution. The contents were magnetically stirred for 2 h. The solution was then filtered through Whatman filter paper (0.45 µ) and diluted suitably with phosphate buffer saline pH 7.4. The solution was then analyzed for its absorbance at spectrophotometrically 280 nm for capsicum oleoresin oil (Capsaicin), 310 nm for wintergreen oil (Methyl salicylate), 498 nm for Menthol and 279 nm for thymol using placebo patch as blank. From the absorbance values, the drug content was determined. (Dhiman S et al., 2011)

***In vitro* drug release studies**

The prepared films were attached onto the dialysis membrane and further adhered to the franz diffusion cell. Consequently, the surface from where the drug permeates having 0.785 cm2 area was facing towards receptor compartment. The receptor compartment contains phosphate buffer of 7.4 pH maintained at 37 ℃ which is magnetically swirled. At programmed timings, 5 mL samples were taken out and equal volume of fresh buffer was replaced. The samples withdrawn were diluted with ethanol and then analysed spectrophotometrically 280 nm for capsicum oleoresin oil (Capsaicin), 310 nm for wintergreen oil (Methyl salicylate), 498 nm for Menthol and 279 nm for thymol. (Hardainiyan SW et al., 2017)

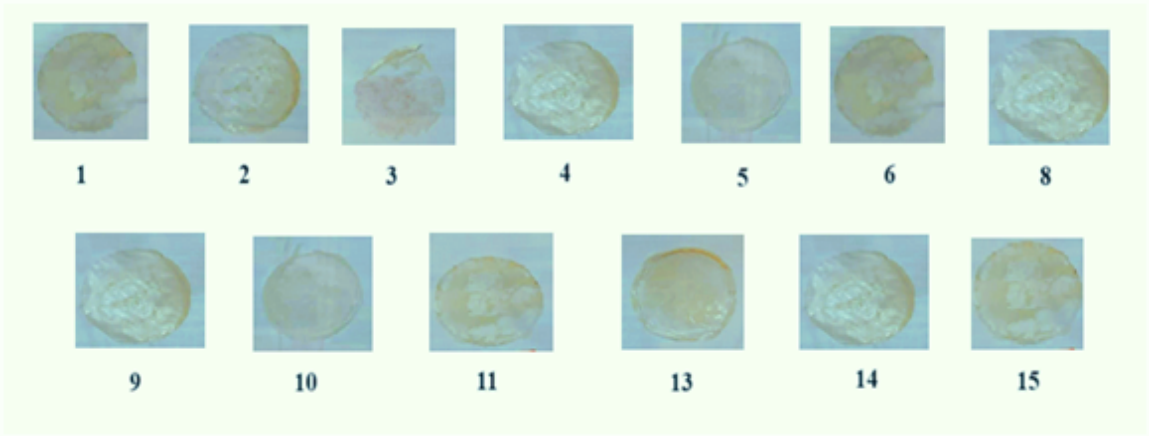

Figure 1: Essential oil patches (Formulation of batches by QbD Software)

Results and discussion

The experimental data illustrates how varying proportions of HPMC K100, HPMC K15, and PEG affect the % moisture content, pH, and swelling index of the transdermal patches. These parameters are critical for ensuring patch stability, skin compatibility, and bioadhesion, ultimately influencing drug release and therapeutic efficacy.

1. **Moisture Content**

Moisture content ranged between 2.4% and 3.9%, indicating the ability of the polymeric matrix to retain water to a certain extent. Higher HPMC K15 content, particularly in runs such as Run 4, 6, 10, and 14, was associated with increased moisture content (≥ 3.9%), which is expected due to the hydrophilic nature of the polymer. Conversely, formulations with higher HPMC K100 and lower PEG (e.g., Run 3 and 9) exhibited lower moisture content, likely due to denser film formation and reduced hygroscopicity. Maintaining moderate moisture content is essential to enhance drug diffusion and prevent brittleness of the patch. Formulations like Run 2, 7, and 12 showed optimal balance with ~2.7% moisture, supporting flexible film formation without compromising integrity.

2. **pH**

The pH of all formulations remained in the range of 6.7 to 6.9, which is within the acceptable range for dermal application and unlikely to cause skin irritation. Slight variations can be attributed to polymer ratios but remain statistically insignificant, suggesting the formulations are skin-compatible and safe.

3. **Swelling Index**

Swelling behavior ranged from 20.6% (Run 8) to 25.4% (Run 4). Swelling is a key indicator of hydration capacity and correlates directly with the release behavior of the drug. Formulations with higher total polymer content (particularly HPMC K15, which is more swellable) exhibited higher swelling indices. For instance, Run 4 and 14, with relatively high levels of HPMC K15, showed swelling indices exceeding 25%.

On the other hand, Run 8, which used lower polymer levels and minimal PEG (2.5%), showed the lowest swelling index (20.6%), likely due to reduced water absorption and gel formation. Notably, PEG acts as a plasticizer and humectant; higher PEG levels (e.g., Run 5, 13, and 15) tended to improve flexibility and swelling.

Overall Trends and Optimization Insight

- A balanced ratio of HPMC K100 and K15 (1:1) with moderate PEG (3.75%) consistently yielded stable patches (e.g., Run 2, 7, 12) with acceptable moisture, ideal pH, and good swelling behavior.
- High HPMC K15 content enhances swelling and moisture uptake, beneficial for drug diffusion but must be controlled to avoid excessive patch hydration or softening.
- PEG at 5% increases plasticity and moisture content, but excessive PEG may lower matrix cohesion, which needs optimization based on drug diffusion goals.

In-vitro drug release

The study aimed to investigate the impact of formulation variables (HPMC K100, HPMC K15, and PEG) on **drug content** and **drug release performance** of four active agents known for their **anti-inflammatory and analgesic** properties. The results reveal several important trends and optimization insights.

Run	Factor 1 A: HPMC K 100 %	Factor 2 B: HPMC K 15 %	Factor 3 C: PEG %	% moisture content	pH	Swelling Index
1	1.5	0.5	3.75	3.4 ± 0.8	6.8± 0.2	23.2 ± 0.5
2	1	1	3.75	2.7 ± 0.6	6.9± 0.3	21.8 ± 0.4
3	1.5	1.5	3.75	2.4 ± 0.4	6.7± 0.3	24.3 ± 0.2

4	0.5	0.5	3.75	3.9 ± 0.2	6.8± 0.4	25.4 ± 0.4
5	0.5	1	5	3.4 ± 0.8	6.9± 0.2	24.1 ± 0.6
6	0.5	1	2.5	3.9 ± 0.1	6.7± 0.3	24.3 ± 0.4
7	1	1	3.75	2.7 ± 0.6	6.9± 0.3	21.8 ± 0.4
8	1	0.5	2.5	3.4 ± 0.8	6.8± 0.2	20.6 ± 1.7
9	1	1.5	2.5	2.4 ± 0.2	6.9± 0.4	21.4 ± 0.8
10	0.5	1.5	3.75	3.9 ± 0.1	6.9± 0.3	22.6 ± 0.6
11	1.5	1	2.5	3.9 ± 0.1	6.8± 0.3	23.2 ± 1.5
12	1	1	3.75	2.7 ± 0.6	6.9± 0.3	21.8 ± 0.4
13	1	0.5	5	3.4 ± 0.8	6.9± 0.2	22.7 ± 0.6
14	1	1.5	5	3.9 ± 0.2	6.7± 0.4	25.3 ± 0.7
15	1.5	1	5	3.9 ± 0.1	6.8± 0.2	24.4 ± 0.5

1. **Drug Content**

All formulations demonstrated **high drug content** for each of the actives, ranging from **94.3% to 99.5%**, which reflects efficient drug incorporation and uniform distribution within the polymeric matrix.

- **Runs 2, 3, 7, 9, and 12** consistently showed drug content above **98%** for most drugs, especially when **HPMC K100 and K15 were used in equal or higher concentrations**, indicating improved matrix stability and drug entrapment efficiency.
- **PEG content** did not significantly influence drug content, although **higher PEG (e.g., Run 5 and 13)** maintained content integrity, suggesting plasticization effects did not interfere with drug loading.

Thus, the drug content results confirm **formulation reproducibility and stability**, essential for therapeutic consistency.

2. **% Drug Release**

Drug release varied significantly across formulations and among the four actives:

Capsaicin:

- The release ranged from **65.9% (Run 11)** to **88.8% (Runs 2, 7, 12)**.
- Highest release occurred in formulations with **1:1 ratios of HPMC K100 and K15 (Runs 2, 7, 12)** and moderate PEG (3.75%).
- Lower PEG or higher HPMC K100 appeared to **restrict diffusion** (e.g., Runs 3 and 11), possibly due to denser film formation.

Methyl Salicylate:

- Exhibited excellent release in most formulations, peaking at **86.9%**, especially in **Run 2, 7, and 12**, again highlighting the effectiveness of balanced polymer ratios.
- Notably, release decreased with increased HPMC K15 and lower PEG (e.g., Run 14), likely due to gel viscosity limiting diffusion.

Menthol:

- Release ranged from **65.9% to 86.6%**, with best results again in **Run 2, 5, and 7**.
- **PEG at 3.75–5%** appeared to enhance Menthol's release, likely due to improved film porosity and drug mobility.
- The **lowest release values** were found in Runs with higher polymer concentration and low PEG (e.g., Run 14).

Thymol:

- Release ranged from **65.9% (Run 14)** to **84.5% (Runs 2, 7, 12)**.
- The formulation parameters affecting Thymol release mirrored those for Capsaicin and Menthol, again favoring balanced HPMC with moderate PEG.

3. **Overall Observations and Optimization**
    - Formulations with **1% HPMC K100, 1% HPMC K15, and 3.75% PEG** (Runs 2, 7, 12) offered **optimum performance**, yielding **high drug content** and **maximum drug release** for all four drugs.
    - Higher **PEG content (5%)** improved drug release marginally but could compromise patch integrity in the long term.

Excess polymer content (Runs 3, 14) reduced drug release due to **increased matrix density**, hindering drug diffusion.

Run	Factor 1 A: HPMC K 100 %	Factor 2 B: HPMC K 15 %	Factor 3 C: PEG %	Drug Content				% Drug Release			
				Capsaicin	Methyl Salicylate	Menthol	Thymol	Capsaicin	Methyl Salicylate	Menthol	Thymol
1	1.5	0.5	3.75	94.3 ± 0.2	98.9 ± 0.3	96.9 ± 0.3	97.3 ± 0.3	71.3	86.1	69.8	78.2
2	**1**	**1**	**3.75**	**99.3± 1.1**	**94.9 ± 0.5**	**98.9 ± 0.3**	**96.4 ± 0.7**	**88.8**	**86.9**	**86.6**	**84.5**
3	1.5	1.5	3.75	98.9 ± 0.3	99.5 ± 0.5	96.8 ± 0.1	95.8 ± 0.3	69.8	86.1	76.1	76.3
4	0.5	0.5	3.75	96.9 ± 0.3	95.9 ± 0.7	99.3± 1.1	97.6 ± 0.5	73.4	77.4	68.9	69.2
5	0.5	1	5	98.9 ± 0.3	94.8 ± 0.5	99.3± 1.1	98.4 ± 0.4	86.1	78.5	86.1	82.5
6	0.5	1	2.5	96.8 ± 0.1	97.3 ± 0.3	94.9 ± 0.5	98.9 ± 0.3	68.9	75.4	77.4	69.8
7	**1**	**1**	**3.75**	**99.3± 1.1**	**94.9 ± 0.5**	**98.9 ± 0.3**	**96.4 ± 0.7**	**88.8**	**86.9**	**86.6**	**84.5**
8	1	0.5	2.5	94.9 ± 0.5	95.8 ± 0.3	94.9 ± 0.5	94.8 ± 0.5	77.4	69.7	75.4	82.1
9	1	1.5	2.5	99.5 ± 0.5	97.6 ± 0.5	99.5 ± 0.5	99.3± 1.1	78.5	70.9	65.9	68.9
10	0.5	1.5	3.75	95.9 ± 0.7	98.4 ± 0.4	95.9 ± 0.7	96.4 ± 0.7	75.4	72.6	69.7	81.1
11	1.5	1	2.5	94.8 ± 0.5	98.9 ± 0.3	95.9 ± 0.7	95.8 ± 0.3	65.9	73.2	70.9	77.4
12	**1**	**1**	**3.75**	**99.3± 1.1**	**94.9 ± 0.5**	**98.9 ± 0.3**	**96.4 ± 0.7**	**88.8**	**86.9**	**86.6**	**84.5**

13	1	0.5	5	96.4 ± 0.7	96.9 ± 0.3	97.3 ± 0.3	98.4 ± 0.4	70.9	86.1	75.4	75.4
14	1	1.5	5	95.8 ± 0.3	98.9 ± 0.3	94.9 ± 0.5	98.9 ± 0.3	72.3	69.8	65.9	65.9
15	1.5	1	5	97.6 ± 0.5	94.9 ± 0.5	95.8 ± 0.3	95.8 ± 0.3	73.2	73.4	69.7	69.7

Conclusion

The evaluation of herbal essential oil-based transdermal drug delivery systems formulated using varying concentrations of HPMC K100, HPMC K15, and PEG demonstrates that polymer ratio and plasticizer content significantly influence the physicochemical properties and drug release behavior of the patches. Optimal formulations—particularly those with balanced HPMC K100 and K15 (1:1) and moderate PEG (3.75%) such as Runs 2, 7, and 12—showed ideal moisture content, pH compatibility, swelling index, high drug content, and enhanced drug release for all four active agents (Capsaicin, Methyl Salicylate, Menthol, and Thymol). These findings support the potential of such transdermal systems for effective anti-inflammatory and analgesic therapy with improved patient compliance.

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