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Development and Optimization of Matrix-Type Transdermal Patches of Allopurinol for Enhanced Therapeutic Efficacy

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ABSTRACT: Oral allopurinol is widely used to reduce uric acid formation, but development of an alternative sustained-delivery system may help maintain drug release while reducing the need for frequent administration. This study developed matrix-type allopurinol transdermal patches using ethylcellulose (EC) and polyvinylpyrrolidone K-30 (PVP K-30) and evaluated the influence of polymer composition and selected chemical permeation enhancers on in vitro drug release. Patches containing 20% w/w allopurinol were prepared by solvent evaporation. EC and PVP K-30 were used as matrix-forming polymers, while dibutyl phthalate at 30% w/w of the total polymer weight served as a plasticizer. Five polymer ratios were screened without an enhancer. The selected EC:PVP ratio of 3:2 was subsequently formulated with dimethyl sulfoxide (DMSO), Tween 80, eucalyptus oil, or olive oil at 2%, 5%, and 10% w/w. The patches were evaluated for appearance, thickness, weight variation, drug content, flatness, tensile strength, surface pH, moisture-related properties, and in vitro drug release. Release studies were performed for 24 h using a USP apparatus II modified paddle-over-disc method at 32 +/- 0.5°C in 20% methanol-phosphate-buffered saline, pH 7.4. The patches were clear, smooth, flexible, uniform, and free of visible air bubbles. Thickness, weight, drug content, tensile strength, and surface pH ranged from 0.246 to 0.276 mm, 164.37 to 172.01 mg, 94.12% to 98.23%, 0.346 to 0.438 kg/mm², and 5.7 to 6.6, respectively. All formulations demonstrated 100% flatness. Among enhancer-free patches, the EC:PVP 3:2 formulation produced the greatest 24-h cumulative release, 59.66 +/- 0.81%. The incorporation of enhancers increased release to different extents. Tween 80 at 2% produced the highest 24-h cumulative release, 88.72 +/- 2.59%, followed by eucalyptus oil at 10%, 83.52 +/- 3.11%, and DMSO at 10%, 78.29 +/- 3.66%. An EC:PVP K-30 ratio of 3:2 provided the most favorable release among the polymer combinations examined. Tween 80 at 2% generated the highest in vitro release and was identified as the lead formulation under the conditions studied.

INTRODUCTION

Allopurinol is a xanthine oxidoreductase inhibitor used in the long-term management of hyperuricemia associated with gout and selected conditions involving excessive uric acid production. It decreases uric acid formation through the activity of allopurinol and its principal active metabolite, oxypurinol. Although oral therapy is effective, treatment adherence, gastrointestinal tolerability, and interindividual pharmacokinetic variability provide a rationale for investigating alternative delivery systems.(1)

Transdermal drug-delivery systems can provide prolonged drug input, avoid direct gastrointestinal exposure, and reduce fluctuations associated with intermittent oral administration. Their development is challenging because the stratum corneum

forms a highly effective barrier to molecular transport. Drug molecular size, ionization, lipophilicity, dose, melting point, and solubility all influence the feasibility of passive transdermal administration. Consequently, demonstration of release from a patch does not itself demonstrate that a therapeutically useful quantity can cross human skin.(2)

Matrix-type patches incorporate the drug within a polymeric film. Ethylcellulose is a relatively hydrophobic, water-insoluble polymer capable of slowing drug diffusion, whereas PVP K-30 is hydrophilic and can increase hydration and pore formation. Combining the polymers may therefore permit adjustment of film integrity and drug-release behavior. Plasticizers are added to improve flexibility and reduce brittleness, while chemical enhancers may modify drug solubilization, polymer hydration, partitioning, or skin-barrier properties.

Recent work continues to investigate allopurinol delivery through lipid-based transdermal systems and polymeric patches. An allopurinol-loaded nanostructured lipid-carrier gel produced sustained delivery and enhanced transdermal performance in experimental studies. Newer allopurinol-containing polymer patches have also been explored for controlled release, indicating continuing interest in non-oral delivery.(3)

The objective of the present study was to prepare matrix-type allopurinol patches using different EC:PVP K-30 ratios, characterize their physicochemical and mechanical properties, and determine the effects of DMSO, Tween 80, eucalyptus oil, and olive oil on *in vitro* drug release. A secondary objective was to select a lead formulation for subsequent skin-permeation and stability investigations.

MATERIALS AND METHODS

Materials

Allopurinol was obtained from Yarrow Chem Products, Mumbai, India. Ethylcellulose and PVP K-30 were used as matrix-forming polymers. Dibutyl phthalate was employed as a plasticizer. DMSO, Tween 80, eucalyptus oil, and olive oil were evaluated as enhancers. Chloroform was used as the casting solvent. Methanol, potassium bromide, phosphate-buffered saline, sodium chloride, calcium chloride, silica gel, and other reagents were of analytical grade.

Preformulation studies

Organoleptic examination

The drug sample was visually examined for physical form and color and assessed for odor. Direct taste testing should not normally be included in a modern laboratory identification protocol unless expressly authorized under an approved safety procedure.

Melting-point determination

The melting point was determined using a digital melting-point apparatus and the capillary-fusion method. One end of a capillary tube was sealed, and the powdered sample was packed into the opposite end by repeated tapping. The capillary was placed in the apparatus, and the temperature at which melting began was recorded. Measurements were reported as mean +/- variability.(4-8)

FTIR spectroscopy

A small quantity of drug was mixed with infrared-grade potassium bromide and compressed into a pellet under approximately 5.5 metric tons of pressure. The pellet was scanned from 4000 to 450 cm^{-1} using an FTIR spectrophotometer (Model 8400S, Shimadzu, Japan). The resulting spectrum was compared with an authenticated allopurinol reference spectrum.(4-8)

Solubility screening

The qualitative solubility of allopurinol was evaluated at room temperature in methanol, chloroform, PBS pH 7.4, and mixtures containing 5%, 10%, or 20% methanol in PBS pH 7.4. The approximate volume of solvent required to dissolve a known amount of drug was recorded and assigned a descriptive solubility category. .(4-8)

Preparation of matrix patches

Patches were prepared by solvent evaporation. EC and PVP K-30 were weighed in predetermined ratios while maintaining the total polymer weight at 1.6 g. The polymers were dispersed or dissolved in chloroform under magnetic stirring.(9-11)

Dibutyl phthalate was added at 30% w/w relative to the total polymer weight. Allopurinol was incorporated at 20% w/w relative to total polymer weight, followed by continuous stirring for 30 min to obtain a homogeneous casting mixture.

The mixture was poured onto aluminum foil placed in a Petri dish with a casting area of 64 cm^2. A funnel was inverted over the dish to control solvent evaporation. Drying was conducted for 24 h at room temperature. The films were removed and protected with wax paper as a release liner.

Five initial formulations containing different EC:PVP ratios were prepared without an enhancer. On the basis of preliminary release results, EC:PVP 3:2 was selected for the enhancer study. DMSO, Tween 80, eucalyptus oil, or olive oil was then incorporated at 2%, 5%, or 10% w/w relative to total polymer weight.

Formulation design

The formulation codes reported in the experimental results were standardized as follows.

Group	Codes	EC:PVP ratio	Enhancer concentration
Polymer screening	F1-F5	4.5:0.5, 4:1, 2:1, 3:2, and 2:3	None
DMSO series	FD1-FD3	3:2	2%, 5%, and 10%
Tween 80 series	FT1-FT3	3:2	2%, 5%, and 10%
Eucalyptus-oil series	FE1-FE3	3:2	2%, 5%, and 10%
Olive-oil series	FO1-FO3	3:2	2%, 5%, and 10%

In the release tables, the corresponding enhancer codes were AD1-AD3, AT1-AT3, AE1-AE3, and AO1-AO3. These represent the same concentration series as FD, FT, FE, and FO, respectively. (10,12-14)

Physicochemical characterization

Physical appearance

The films were visually examined for color, transparency, smoothness, flexibility, homogeneity, and the presence of air bubbles or other visible defects(10,12-14)

Thickness

Patch thickness was measured with a digital thickness gauge at four locations on each 2 x 2 cm film specimen. Mean thickness and variability were calculated. (10,12-14)

Weight variation

Ten randomly selected patches with an area of 4.52 cm^2 were weighed individually using an analytical balance. Mean patch weight and variation were determined. (10,12-14)

Drug content

A known area of film was transferred to a 100-mL volumetric flask and extracted with chloroform in a shaking incubator for 4 h. The mixture was filtered through a 0.45-µm membrane. A 1-mL portion of filtrate was diluted to 10 mL, and absorbance was measured spectrophotometrically(10,12-14)

The supplied protocol stated that absorbance was measured at 260 nm. This assay wavelength requires analytical validation for allopurinol in the selected medium, including specificity against polymer, enhancer, plasticizer, and extraction solvent. Drug content was calculated from a validated calibration equation and expressed as a percentage of the theoretical amount. (19)

Moisture content

Patches were weighed and stored in a desiccator containing calcium chloride at room temperature until constant mass. Moisture content was calculated as:

$$\text{Moisture content (\%)} = \frac{Wi - Wf}{Wi} * 100$$

where Wi is the initial mass and *Wf* is the constant dry mass. (10,12-14)

Moisture uptake

Patches were conditioned over silica gel for 24 h and weighed. They were then exposed to approximately 75% relative humidity using saturated sodium chloride at 25°C and repeatedly weighed until constant mass

$$\text{Moisture uptake (\%)} = \frac{Wm - Ws}{Ws} * 100$$

where Ws is the initial conditioned mass and *Wm* is the mass after exposure to 75% relative humidity. (10,12-14)

Flatness

Longitudinal strips were cut from the center and sides of five films from each formulation. (10,12-14)Initial and final strip lengths were measured, and constriction was calculated as:

$$\text{Constriction (\%)} = \frac{L1 - L2}{L2} * 100$$

A constriction value of 0% was regarded as 100% flatness.

Tensile strength

Tensile strength was measured using a laboratory-assembled apparatus. One end of a film strip was fixed, while a load was gradually applied to the opposite end until the film broke. Tensile strength was expressed relative to the cross-sectional area of the specimen: (10,12-14)

$$\text{Tensile strength} = \frac{\textbf{Force required to break the patch}}{Cross\ sectional\ Area}$$

Surface pH

The reported surface pH of each formulation was measured after equilibrating the patch surface with purified water. To ensure reproducibility, the volume of water, equilibration time, instrument calibration, and number of replicates should be predefined. (10,12-14)

***In vitro* drug-release study**

Release testing was carried out using a USP apparatus II with a modified paddle-over-disc arrangement. A patch measuring 3.14 cm^2 was placed over an impermeable backing membrane and fixed to a 2.3 x 2.3 cm glass slide using cyanoacrylate adhesive. A dialysis membrane was positioned over the release surface.(15-18)

The assembly was placed at the bottom of the vessel with the release surface facing upward. The medium consisted of 20% methanol in PBS pH 7.4 and was maintained at 32 +/- 0.5°C. Paddle speed was 50 rpm. Samples were collected at 1, 2, 4, 6, 8, 10, 12, 18, and 24 h. An equal volume of fresh medium was added after each collection to maintain constant volume and sink conditions. .(15-18)

The supplied release protocol reported UV measurement at 227 nm. Quantification at this wavelength should be validated for specificity in the complete release medium and corrected for cumulative drug removed during serial sampling.

Statistical analysis

Results were expressed as mean +/- standard deviation. Differences among formulations should be assessed using one-way or two-way analysis of variance, as appropriate, followed by a prespecified post-hoc multiple-comparison test. Statistical significance should be set at $p<0.05$*p*<0.05. (15-18)

Release-kinetic analysis

For a complete release assessment, cumulative-release data should be fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. Model selection should consider adjusted R_2R_2

, residual patterns, and an information criterion rather than R_2R_2 alone. A model-independent comparison, such as the similarity factor f_2f_2, may also be used when comparing complete release profiles. .(15-18)

RESULTS AND DISCUSSION

Drug identification and preformulation findings

The supplied allopurinol was described as a white to off-white, crystalline, odorless powder. Its melting point was reported as 355 +/- 1°C. This high melting behavior may reflect the drug's strong crystalline lattice and is relevant to formulation because high crystal-lattice energy can limit solubility and passive membrane transport.

The UV absorption maximum was reported as 260 nm. However, the analytical wavelength depended on solvent and pH, and the release assay used 227 nm. Both methods require separate validation in their respective matrices. (20)

A major documentary inconsistency was identified in the supplied FTIR table. Peaks attributed to aromatic C-H stretching, aliphatic CH_2/CH_3 stretching, C-F stretching, and aryl/alkyl ether C-O stretching are not chemically consistent with allopurinol, whose molecular structure does not contain fluorine, ether oxygen, or alkyl CH_2/CH_3 groups. The caption "UV absorption spectra of fluoxetine" and the solubility-table title "Solubility of fluoxetine" further indicate that some characterization content was probably copied from a fluoxetine study. Consequently, those FTIR assignments cannot be used as evidence of allopurinol identity.

Solubility screening

The qualitative study classified allopurinol as freely soluble in methanol, soluble in chloroform and 20% methanol-PBS, sparingly soluble in 10% methanol-PBS, slightly soluble in 5% methanol-PBS, and very slightly soluble in PBS pH 7.4.

Medium	Reported qualitative solubility
Methanol	Freely soluble
Chloroform	Soluble
5% methanol in PBS pH 7.4	Slightly soluble
10% methanol in PBS pH 7.4	Sparingly soluble
20% methanol in PBS pH 7.4	Soluble
PBS pH 7.4	Very slightly soluble

The increasing apparent solubility with methanol concentration supported the use of 20% methanol-PBS to maintain sink conditions during release testing. Nevertheless, this is a hydroalcoholic release medium rather than a physiological receptor fluid. It is suitable for comparative formulation screening only after confirming patch integrity and drug stability. It does not reproduce the barrier or solvent environment encountered during skin permeation.

The reported chloroform solubility also requires quantitative confirmation. A validated equilibrium-solubility study, preferably using a stability-indicating HPLC method, would be more reliable than visual descriptive classification.

Patch formation and physical properties

Films prepared without a plasticizer were described as brittle. Addition of dibutyl phthalate at 30% w/w of total polymer produced smoother and more flexible patches. Plasticization generally reduces intermolecular interactions between polymer chains, increases chain mobility, and lowers film brittleness. (21)

All evaluated films were clear, smooth, flexible, uniform, and free of visible bubbles. The quantitative evaluation is summarized below.

Attribute	Observed range	Interpretation
Thickness	0.246-0.276 mm	Narrow variation across batches
Patch weight	164.37-172.01 mg	Relatively uniform casting
Drug content	94.12%-98.23%	Acceptable preliminary uniformity
Flatness	100%	No measurable constriction
Tensile strength	0.346-0.438 kg/mm²	Films possessed measurable mechanical strength
Surface pH	5.7-6.6	Close to the mildly acidic skin-surface range
Moisture content	1.64%-6.38%	Increased with hydrophilic-polymer content
Moisture uptake	2.43%-9.41%	Increased with hydrophilic-polymer content

The narrow thickness and mass ranges suggest reasonably reproducible casting and solvent evaporation. Drug content varied by less than approximately six percentage points across all formulations, indicating that mixing and casting produced broadly uniform drug distribution. FE1 showed the greatest reported content, 98.23 +/- 0.78%, while F3 showed the lowest, 94.12 +/- 0.74%.

All patches displayed 100% flatness, indicating dimensional stability under the test conditions. Tensile-strength values showed that the films were mechanically coherent, although tensile strength alone does not fully characterize handling performance. Percentage elongation, Young's modulus, peel adhesion, tack, shear adhesion, and cold-flow behavior would be required for a finished transdermal system.

Moisture content and uptake increased as the proportion of PVP increased. PVP is hydrophilic and can bind environmental water, while EC is comparatively hydrophobic. Increased hydration can facilitate aqueous penetration, polymer swelling, and pore formation, but excessive water uptake may reduce stability or alter mechanical properties.

Surface pH ranged from 5.7 to 6.6. These values are unlikely to predict severe pH-mediated irritation by themselves, but a surface-pH test cannot replace cytotoxicity, irritation, sensitization, or repeated-exposure studies.

Effect of polymer ratio on drug release

The 24-h cumulative release from enhancer-free films was:

Rank	Formulation	EC:PVP ratio	Release at 24 h
1	F4	3:2	59.66 +/- 0.81%
2	F3	2:1	52.38 +/- 0.61%
3	F5	2:3	50.61 +/- 2.11%
4	F2	4:1	46.68 +/- 1.99%
5	F1	4.5:0.5	40.70 +/- 0.56%

The overall release order was F4 > F3 > F5 > F2 > F1. Increasing PVP from the low level used in F1 generally increased release. The soluble PVP fraction likely hydrated and leached into the medium, leaving pores and aqueous channels in the EC-rich matrix. These changes can increase effective surface area, reduce diffusional path length, and facilitate drug transport.

Release did not continue to rise when PVP was increased to the F5 composition. The F5 value, 50.61%, was lower than the 59.66% obtained from F4. This non-linear response could reflect changes in film microstructure, drug-polymer interaction, drug distribution, hydration behavior, or diffusional tortuosity. Without solid-state and microscopic analysis, attributing the reduction specifically to decreased crystallinity is not justified.

F4 was selected as the base formulation because it generated the greatest cumulative release among the enhancer-free matrices. Relative to F1, its 24-h release was approximately 46.6% higher:

59.66−40.7040.70×100=46.6%40.7059.66−40.70×100=46.6%

Influence of chemical enhancers

The 24-h release values from the enhancer-containing formulations are summarized below.

Enhancer	2%	5%	10%	Best concentration
DMSO	64.58 +/- 2.67%	70.49 +/- 3.66%	78.29 +/- 3.66%	10%
Tween 80	88.72 +/- 2.59%	77.32 +/- 3.55%	70.38 +/- 3.33%	2%
Eucalyptus oil	68.58 +/- 3.88%	76.83 +/- 3.22%	83.52 +/- 3.11%	10%
Olive oil	64.50 +/- 3.53%	73.08 +/- 1.47%	67.93 +/- 3.39%	5%

All enhancer series contained at least one formulation with greater 24-h release than the enhancer-free F4 value of 59.66%. The highest overall release was obtained with 2% Tween 80.

Rank	Formulation	Enhancer	Release at 24 h
1	AT1	Tween 80, 2%	88.72 +/- 2.59%
2	AE3	Eucalyptus oil, 10%	83.52 +/- 3.11%
3	AD3	DMSO, 10%	78.29 +/- 3.66%
4	AT2	Tween 80, 5%	77.32 +/- 3.55%
5	AE2	Eucalyptus oil, 5%	76.83 +/- 3.22%
6	AO2	Olive oil, 5%	73.08 +/- 1.47%

Relative to enhancer-free F4, AT1 increased the 24-h cumulative release by approximately 48.7%: 88.72−59.6659.66×100=48.7%59.6688.72−59.66×100=48.7%

Modern reviews emphasize that chemical enhancers can act through several mechanisms, including alteration of lipid organization, improved drug partitioning, enhanced solubilization, and changes in vehicle or polymer microstructure. Their effects are concentration-dependent and do not necessarily increase monotonically with concentration.

Interpretation of the lead formulation

AT1, containing 2% Tween 80, was the best formulation on the basis of 24-h *in vitro* release. Its profile reached 27.38% at 6 h, 53.74% at 10 h, 72.61% at 18 h, and 88.72% at 24 h.

The release data support selection of AT1 for further investigation, but they do not establish it as the best transdermal formulation. A release enhancer may not produce equivalent enhancement across skin, and high release into a hydroalcoholic receptor medium may coexist with poor drug partitioning into the stratum corneum. Conversely, some enhancers may exert a stronger effect on skin lipids than on release from the polymer.

Recent allopurinol transdermal research has used nanostructured lipid carriers and biological permeation experiments rather than release testing alone, highlighting the need to quantify drug transport through an actual skin barrier. Pmc.ncbi.nlm.nih.gov Contemporary research also continues to evaluate controlled-release allopurinol polymer patches, but their therapeutic relevance depends on barrier transport, dose delivery, and safety rather thanType equation here. cumulative release alone.

CONCLUSION

Matrix-type allopurinol patches were successfully prepared by solvent evaporation using EC and PVP K-30. The films were uniform, smooth, flexible, dimensionally stable, and demonstrated relatively consistent thickness, mass, and drug content.

Among the enhancer-free matrices, EC:PVP 3:**2** provided the highest 24-h cumulative release of 59.66 +/- 0.81%. Incorporation of chemical enhancers substantially altered release. Tween 80 at 2% produced the highest value, 88.72 +/- 2.59%, followed by 10% eucalyptus oil, 83.52 +/- 3.11%, and 10% DMSO, 78.29 +/- 3.66%. The enhancer effects were non-linear in the Tween 80 and olive-oil series, demonstrating that higher enhancer concentration did not necessarily produce greater release.

The EC:PVP 3:2 matrix containing 2% Tween 80 is the lead formulation for further study. However, the present results demonstrate drug release from a polymer film, not transdermal delivery through skin. In addition, the inconsistent FTIR assignments must be corrected through repeat drug-identification testing. Skin-permeation, analytical-validation, dermal-safety, residual-solvent, adhesion, and stability studies are essential before drawing conclusions regarding clinical transdermal performance.

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