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# FEBUXOSTAT-LOADED CHITOSAN/PEG TRANSDERMAL PATCHES CONTAINING ROSEMARY OIL AS A NATURAL PENETRATION ENHANCER: FORMULATION, RELEASE KINETICS AND EX VIVO SKIN PERMEATION

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*Febuxostat; transdermal patch; chitosan; polyethylene glycol; rosemary oil; skin permeation enhancer; SDG 3; SDG 9*

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**Abstract**

***Background:*** *Febuxostat, a selective xanthine oxidase inhibitor used in gout-related hyperuricemia, is normally given orally. A skin patch could offer steady drug input without gastrointestinal exposure or hepatic first-pass loss, but the stratum corneum limits passive uptake.*
***Objective:*** *To prepare matrix-type febuxostat patches from chitosan and polyethylene glycol (PEG), to examine how the polymer ratio shapes drug release, and to test rosemary oil as a plant-derived permeation enhancer.*
***Methods:*** *Patches were cast by solvent evaporation on a polyvinyl alcohol backing layer, with di-n-butyl phthalate as plasticizer. Polymer-ratio batches (FFB1–FFB6) were compared for in vitro release and fitted to zero-order, first-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models. A second series (FFBR1–FFBR6) held the chitosan:PEG ratio at 3:1 and varied rosemary oil from 1% to 10% w/w. Patches were assessed for weight, thickness, drug content, hardness, flatness, folding endurance and moisture uptake/loss. Permeation across excised rabbit skin was measured in Franz diffusion cells.*
***Results:*** *The patches were smooth, transparent and uniform, with thickness of 0.23–0.28 mm, weight of 35–40 mg and drug content of 97.34–99.36%. A higher PEG share accelerated release, with burst release at higher PEG levels. All formulations followed non-Fickian release (n = 0.634–0.678), and the 3:1 batch (FFB3) gave*

*the best-fitting kinetics. Rosemary oil raised permeation in a concentration-dependent manner: the 10% patch (FFBR6) gave the highest flux (242.89 ± 4.23 µg/cm²·h) and the shortest lag time (1.56 ± 0.012 h), compared with 21.53 ± 1.72 µg/cm²·h and 3.87 ± 0.006 h for the control.*

***Conclusion:*** *A chitosan/PEG matrix combined with rosemary oil is a feasible route to sustained, enhanced transdermal delivery of febuxostat. Both the polymer ratio and the enhancer level should be tuned together.*

## INTRODUCTION

Transdermal delivery moves a drug through the skin so that it can reach the systemic circulation at a controlled rate [1,2]. For suitable molecules it sidesteps gastrointestinal degradation and hepatic first-pass metabolism, smooths out the peaks and troughs of repeated oral dosing, and allows non-invasive self-administration, which may help adherence [3]. The main obstacle is the stratum corneum, whose corneocytes and intercellular lipids restrict passage of most compounds. Molecular size, lipophilicity, solubility, partition coefficient and applied concentration all determine whether a drug can cross passively [3]. Febuxostat is a non-purine selective inhibitor of xanthine oxidase. By blocking conversion of hypoxanthine and xanthine to uric acid it lowers serum urate, and it is an established alternative to allopurinol in chronic gout [4,5]. It is administered orally, so a patch might provide prolonged input while avoiding gastrointestinal exposure, provided enough drug can be driven across the skin.

The polymer matrix of a patch governs film formation, strength, hydration and diffusion. Chitosan, obtained by deacetylation of chitin, is biocompatible, biodegradable, hydrophilic and film-forming [6]. PEG is a hydrophilic excipient that adds flexibility and alters hydration and release [6]. The ratio between the two can therefore be used to steer release kinetics.

Chemical penetration enhancers temporarily loosen the barrier by disturbing intercellular lipids, improving partitioning into skin or changing the diffusion path [7,8]. Terpene-rich essential oils are attractive natural alternatives [7,9], and rosemary oil has been reported to improve permeation of selected drugs [10]. Their effect depends on oil level, drug and matrix, so the concentration has to be optimized without compromising patch quality [9,10].

To our knowledge, the combined effect of chitosan:PEG ratio and rosemary oil level on febuxostat patches has not been systematically reported. We therefore prepared febuxostat patches on a chitosan/PEG matrix, tested the influence of polymer ratio on release and its kinetics, and quantified how rosemary oil concentration affects *ex vivo* permeation through rabbit skin. By supporting new delivery options for a widely used gout drug, the work relates to SDG 3 (Good Health and Well-being) and, through formulation innovation, SDG 9 (Industry, Innovation and Infrastructure).

## 2. Materials and Methods

### 2.1 Materials

Febuxostat (Leads Pharma, Islamabad); rosemary oil (Marhaba Laboratories, Lahore); PEG and chitosan (Dow Chemical Company, USA); polyvinyl alcohol and di-n-butyl phthalate (Sigma-Aldrich, Germany); methanol and ethanol (Merck, Germany). Equipment: pH meter (Denver 215), analytical balance (Shimadzu AX200/220), dissolution tester (Pharma Test PTWS-II), UV/Vis spectrophotometer (Shimadzu 1795), water distillation unit (IM100 IRMECO) and Vernier caliper (Nagarjuna Engineering).

### 2.2 Preparation of patches

A backing layer was made from 4% w/v PVA in distilled water (80 °C with stirring, cooled to room temperature, degassed by sonication); 12 mL was poured into Petri dishes and dried at room temperature. Febuxostat was blended with chitosan and PEG by magnetic stirring, then di-n-butyl phthalate (15% w/w of polymer) and rosemary oil were added (Table 1). The matrix was cast onto the dried backing film, covered with an inverted funnel to slow evaporation, and the dried composite cut into 1.7 cm² patches (six per 10 cm² dish).

**Table 1. Composition of febuxostat patches with different rosemary oil levels (fixed chitosan:PEG 3:1).**

| Code | Febuxostat (mg) | Chitosan (mg) | PEG (mg) | Rosemary oil (% w/w) | Plasticizer | Ethanol (mL) |
|---|---|---|---|---|---|---|
| FFBR1 | 120 | 60 | 20 | 1 | 15% of polymer | 10 |
| FFBR2 | 120 | 60 | 20 | 2 | 15% of polymer | 10 |
| FFBR3 | 120 | 60 | 20 | 3 | 15% of polymer | 10 |
| FFBR4 | 120 | 60 | 20 | 4 | 15% of polymer | 10 |
| FFBR5 | 120 | 60 | 20 | 5 | 15% of polymer | 10 |
| FFBR6 | 120 | 60 | 20 | 10 | 15% of polymer | 10 |

The FFB1–FFB6 series (Section 3.3) contained no enhancer and differed only in chitosan:PEG ratio.

**2.3 Physicochemical evaluation**

**FTIR.** Components were ground, mixed into the matrix and scanned; peaks were compared with reference spectra to identify functional groups and judge drug–excipient compatibility [11].

**Thickness and weight.** Thickness was measured at several points with a micrometer screw gauge, and ten patches per batch were weighed individually to obtain mean ± SD [12].

**Folding endurance.** A patch was folded repeatedly at one spot until it cracked or broke; the number of folds was recorded [13].

**Moisture uptake and loss.** Three patches per batch were weighed and kept three days either in a desiccator over saturated salt solution (high humidity; uptake) or over anhydrous calcium chloride under vacuum at 37 °C (loss). Percentage change was calculated against initial weight [14].

**2.4 In vitro release and kinetics**

Release was measured with the USP dissolution apparatus at 32 ± 0.5 °C and 50 rpm; aliquots were withdrawn at set times and analysed by UV spectrophotometry [15]. Data were fitted to zero-order ($Q = k_1t$), first-order ($\ln(100 - Q) = \ln 100 - k_2t$), Higuchi ($Q = k_3t^{1/2}$), Hixson–Crowell ($W_0^{1/3} - W_t^{1/3} = k_4t$) and Korsmeyer–Peppas ($M_t/M_\infty = k_5t^n$) models [16–18]. The model with the highest $R^2$ was taken as best fit, and the exponent n was used to classify the mechanism.

**2.5 Ex vivo permeation**

Permeation through excised rabbit skin was studied in Franz diffusion cells for the six rosemary oil levels (1, 2, 3, 4, 5 and 10%) and an enhancer-free control. Flux, permeability coefficient (Kp), lag time ($Tl_{ag}$) and enhancement ratio (ER) were derived. skin source and ethics approval, receptor medium, temperature, stirring speed, sampling schedule, number of replicates, and statistical test used for the $p < 0.05$ comparison.]

**3. Results**

**3.1 FTIR**

Febuxostat showed characteristic bands at 3453.99, 3291, 2877 and 2354.2 $cm^{-1}$. Chitosan bands appeared at 3453.99, 2964, 2877 and 2231 $cm^{-1}$; rosemary oil at 2958.48, 2927.75 and 2879.2 $cm^{-1}$; and PEG at 2878, 1464 and 1240 $cm^{-1}$ (Figure 1). The spectra indicated no marked chemical interaction among the components.

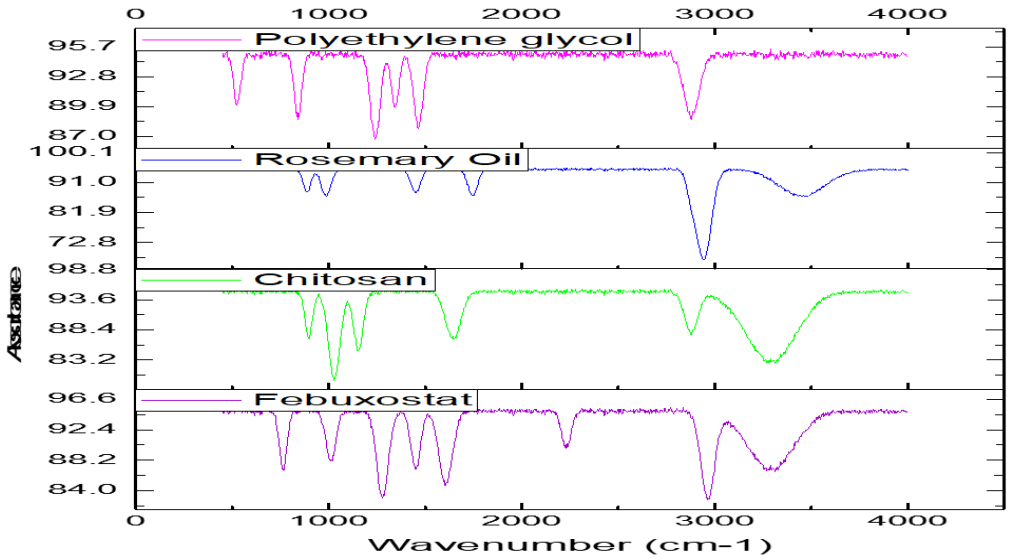



**Figure 1. FTIR spectra of febuxostat, rosemary oil, chitosan and PEG.**

### 3.2 Physical properties

Patches were smooth, transparent and homogeneous. Thickness ranged from 0.23 to 0.28 mm and weight from 35 to 40 mg, with small standard deviations (Table 2). Patches resisted repeated folding without breaking and showed essentially complete flatness (99.97–100%). Drug content was 97.34–99.36% across batches.

**Table 2. Physical parameters and drug content of febuxostat patches with rosemary oil.**

| Code | Weight (mg ± SD) | Drug content (% ± SD) | Thickness (mm ± SD) | Moisture uptake (%) | Moisture loss (%) | Hardness (g) | Flatness (%) |
|---|---|---|---|---|---|---|---|
| FFBR1 | 39.23 ± 0.03 | 99.35 ± 0.00 | 0.27 ± 0.008 | 10.4 ± 1.2 | 6.9 ± 1.9 | 245 ± 2.1 | 99.97 |
| FFBR2 | 39.45 ± 0.021 | 98.21 ± 0.043 | 0.26 ± 0.005 | 9.9 ± 1.5 | 6.5 ± 1.5 | 252 ± 2.8 | 100 |
| FFBR3 | 35.17 ± 0.029 | 98.32 ± 0.021 | 0.25 ± 0.004 | 8.2 ± 1.3 | 7.3 ± 2.1 | 243 ± 1.9 | 99.98 |
| FFBR4 | 37.56 ± 0.047 | 99.36 ± 0.00 | 0.28 ± 0.005 | 9.9 ± 1.5 | 7.8 ± 1.8 | 236 ± 1.7 | 100 |
| FFBR5 | 38.21 ± 0.08 | 97.34 ± 0.023 | 0.23 ± 0.008 | 8.4 ± 1.8 | 6.2 ± 1.9 | 234 ± 2.3 | 99.97 |
| FFBR6 | 39.19 ± 0.035 | 98.54 ± 0.012 | 0.24 ± 0.003 | 9.1 ± 1.3 | 7.3 ± 1.6 | 238 ± 1.9 | 100 |

### 3.3 In vitro release and kinetics

Without enhancer, raising the PEG proportion relative to chitosan sped up release (Figure 2). Burst release was seen at higher PEG levels, and also in batches with a comparatively high chitosan share. Kinetic fitting for the FFB batches is given in Table 3. All batches had n between 0.634 and 0.678, indicating non-Fickian (anomalous) transport. FFB3 (3:1) produced the highest $R^2$ values overall (0.989–0.995). First-order and Higuchi models described most of the other batches best.

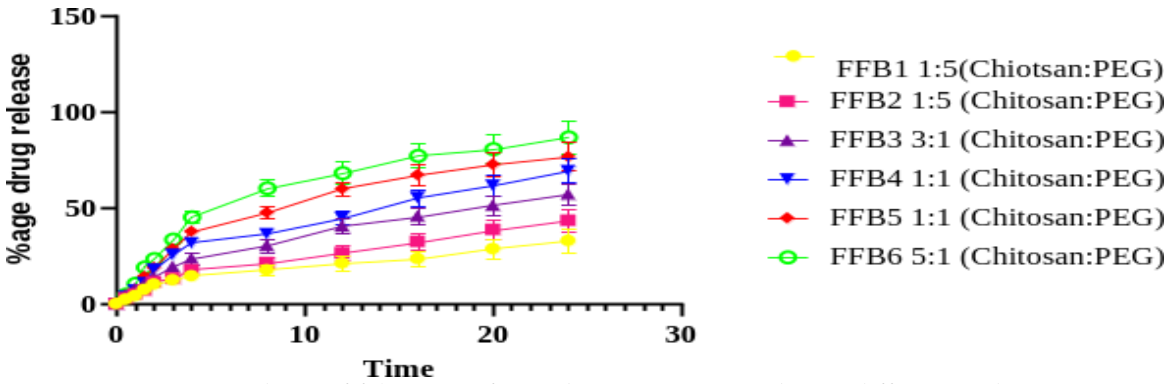



**Figure 2. In vitro release of febuxostat from chitosan/PEG patches at different polymer ratios, without enhancer.**

**Table 3. Release-model fitting for patches with varying chitosan:PEG ratios (no enhancer).**

| Code | Zero-order $R^2$ | First-order $R^2$ | Higuchi $R^2$ | Hixson–Crowell $R^2$ | Korsmeyer–Peppas $R^2$ | n | Mechanism |
|---|---|---|---|---|---|---|---|
| FFB1 | 0.945 | 0.956 | 0.956 | 0.934 | 0.967 | 0.678 | Non-Fickian |
| FFB2 | 0.913 | 0.934 | 0.943 | 0.945 | 0.935 | 0.634 | Non-Fickian |
| FFB3 (3:1) | 0.989 | 0.995 | 0.990 | 0.995 | 0.989 | 0.634 | Non-Fickian |
| FFB4 | 0.943 | 0.978 | 0.986 | 0.965 | 0.934 | 0.678 | Non-Fickian |
| FFB5 | 0.912 | 0.967 | 0.945 | 0.935 | 0.967 | 0.634 | Non-Fickian |
| FFB6 | 0.932 | 0.923 | 0.934 | 0.932 | 0.923 | 0.652 | Non-Fickian |

### 3.4 Ex vivo permeation

Permeation rose steadily with rosemary oil concentration (Figure 3, Table 4). The 10% patch (FFBR6) showed the greatest flux, permeability coefficient and enhancement ratio and the shortest lag time; FFBR3–FFBR6 differed significantly from the control ($p < 0.05$).

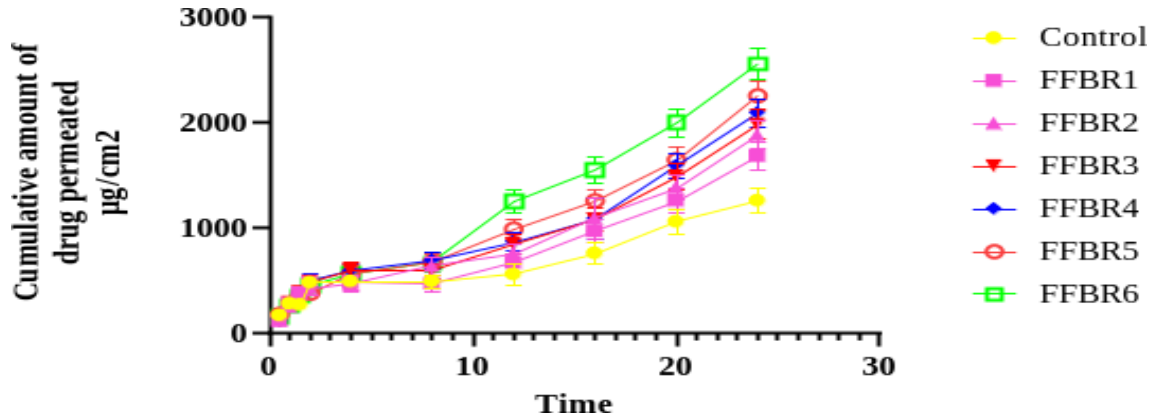



**Figure 3. Cumulative febuxostat permeated through rabbit skin at different rosemary oil concentrations**

**Table 4. Ex vivo permeation parameters through rabbit skin.**

| Code | Flux (μg/cm²·h ± SD) | Kp (cm/h ± SD) | ER | Tlag (h ± SD) |
|---|---|---|---|---|
| Control | 21.53 ± 1.72 | 0.689 ± 0.002 | 1.00 | 3.87 ± 0.006 |
| FFBR1 | 32.67 ± 2.12 | 0.934 ± 0.006 | 1.45 | 3.07 ± 0.004 |
| FFBR2 | 49.27 ± 2.72 | 1.632 ± 0.003 | 2.78 | 3.45 ± 0.003 |
| FFBR3 | 87.78 ± 1.93 | 2.998 ± 0.023* | 4.89 | 2.87 ± 0.006 |
| FFBR4 | 117.45 ± 3.54 | 4.221 ± 0.034* | 5.39 | 2.34 ± 0.008 |
| FFBR5 | 182.78 ± 3.22 | 5.112 ± 0.052* | 7.12 | 2.03 ± 0.011 |
| FFBR6 | 242.89 ± 4.23 | 5.473 ± 0.004* | 8.22 | 1.56 ± 0.012 |

*$p < 0.05$ versus control.

## 4. Discussion

**Polymer ratio and release.** The ratio of chitosan to PEG clearly shaped how febuxostat left the patch. PEG is strongly hydrophilic; as the medium enters the film it hydrates the matrix, promotes swelling and opens water-filled channels through which dissolved drug can move. Batches richer in PEG therefore released faster [19]. The same mechanism explains the burst effect at high PEG: drug lying near the surface escapes quickly through the freshly hydrated network, which can undermine prolonged delivery. PEG content therefore has to be balanced against the need for sustained release. A burst was also noticed in some chitosan-rich batches, plausibly from surface-bound drug dissolving before the matrix was fully hydrated.

**Kinetics.** FFB3 (3:1) was the best-fitting batch. A larger chitosan share probably gives the film enough structure to resist diffusion, while a smaller PEG share keeps the matrix hydrated and the drug mobile. Most other batches were best described by first-order or Higuchi models, which points to release depending on both the drug remaining in the matrix and diffusion through the hydrated network. Notably, the first-order and Hixson–Crowell coefficients of FFB3 were equal, so model choice alone should not be read as proof of a single mechanism; the n values (0.634–0.678) support anomalous transport in which diffusion and polymer relaxation both contribute.

**Comparison with other patches.** Polymeric matrices have been used to prolong delivery of other drugs, for example a chitosan/PVA-based zolmitriptan patch [19] and chitosan/PEG systems for other actives [6]. Although the drugs differ, these reports and our data agree that matrix composition is a primary lever for controlling release and permeation.

**Plasticizer and film quality.** Di-n-butyl phthalate lowers intermolecular forces between polymer chains and raises chain mobility, which gave films that were flexible, formed well and dried faster. The patches therefore handled without cracking. The uniform weight, thickness and drug content (Table 2) suggest that the casting method was reproducible. The best formulation should be chosen not on release alone but on the whole profile of content, integrity, release and permeation.

**Enhancer effect.** Rosemary oil raised flux, Kp and enhancement ratio and shortened lag time in a concentration-dependent way, with 10% the most effective of the levels tested. Terpene-rich oils are thought to fluidize the ordered lipid lamellae of the stratum corneum and thus lower diffusional resistance [8,9], consistent with the earlier appearance of febuxostat in the receptor compartment. Because the highest level tested was also the most effective, an optimum may lie at or above 10%, which remains to be explored together with irritation potential.

**Complementary roles.** The matrix mainly controls loading, hydration and release from the patch, whereas rosemary oil helps the released drug cross the skin. Fast release with poor permeation would not deliver drug effectively, and strong enhancement without control of release could produce unwanted rapid input; the best system needs both elements tuned together.

**Limitations.** Rabbit skin is generally more permeable than human skin, so fluxes will probably be lower in humans. Results of stability and skin-irritation studies, if performed, and *in vivo* data are needed to confirm suitability.

## 5. Conclusion

Febuxostat patches on a chitosan/PEG matrix were uniform and flexible. Polymer ratio-controlled release and kinetics, with the 3:1 batch fitting best, and rosemary oil at 10% gave the largest increase in permeation across rabbit skin. These results show that matrix composition and enhancer level should be optimized jointly when designing transdermal febuxostat systems, and they justify further stability, irritation and *in vivo* work.

## Declarations

**Informed consent:** Not applicable.

**Data availability:** Data supporting this study are contained within the article. **Acknowledgments:** The authors thank their Faculty of Pharmacy, IBADAT Interntaional University Islamabad, Pakistan

**Conflicts of interest:** The authors declare no conflict of interest.

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