



FORMULATION AND IN-VITRO EVALUATION OF CELECOXIB-LOADED NIOSOMAL MATRIX-TYPE TRANSDERMAL PATCHES FOR THE MANAGEMENT OF OSTEOARTHRITIS

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ABSTRACT

Celecoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor widely prescribed for the symptomatic management of osteoarthritis, is a Biopharmaceutics Classification System (BCS) Class II drug whose poor aqueous solubility and cardio-gastrointestinal liabilities on chronic oral dosing limit its clinical utility. The present study aimed to formulate and evaluate celecoxib-loaded niosomal matrix-type transdermal patches as a non-invasive alternative capable of sustaining drug release and reducing systemic exposure. Niosomes were prepared by the thin-film hydration technique using Span 60 and cholesterol at three molar ratios (1:1:1, 1:2:1 and 1:2:2); the 1:1:1 formulation (F1) showed the highest entrapment efficiency (93.24%), a mean particle size of 616.0 nm, a polydispersity index of 0.315 and a zeta potential of -32.7 mV, and was selected for patch fabrication. Matrix-type transdermal patches were prepared by the solvent-casting method using HPMC K100 and PVP K30 as film-forming polymers, optimised through a 3^2 factorial design (nine batches, F1–F9). Fourier-transform infrared spectroscopy confirmed the absence of significant drug–excipient interaction. The optimised patch (F3, high HPMC K100 and high PVP K30) exhibited satisfactory physicochemical properties (weight 192.6 ± 2.1 mg, thickness 0.53 ± 0.01 mm, folding endurance 290 ± 6 , surface pH 5.86 ± 0.04 , drug content $98.40 \pm 0.45\%$) and released 71.0% of celecoxib over 12 h *in-vitro*, compared with 85% released from a plain (non-vesicular) patch over the same period, confirming that vesicular entrapment sustained drug release. Release data best fitted the Higuchi model ($R^2 = 0.992$), with a Korsmeyer–Peppas exponent ($n = 0.68$) indicative of non-Fickian (anomalous) transport combining diffusion and polymer relaxation. These findings suggest that incorporating niosomes into a matrix-type transdermal patch is a promising controlled-release approach for transdermal delivery of celecoxib in osteoarthritis management and warrants further *ex vivo* permeation and *in vivo* evaluation.

KEYWORDS: Celecoxib; Niosomes; Transdermal patch; Osteoarthritis; Matrix system; Controlled drug release; 3^2 factorial design.

INTRODUCTION

Osteoarthritis (OA) is a chronic, progressive, whole-joint disease and the most common form of arthritis worldwide, characterised by progressive breakdown of articular cartilage, subchondral bone remodelling, osteophyte formation and low-grade synovial inflammation, producing pain, stiffness and functional impairment.^[1] It represents a leading global cause of

disability, and its prevalence continues to rise with the ageing population, obesity and sedentary lifestyles.^[2] Key catabolic mediators implicated in its pathophysiology include interleukin-1 β (IL-1 β), tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), cyclo-oxygenase-2 (COX-2)-derived prostaglandin E₂, and matrix metalloproteinases.^[3,4]

Celecoxib is a diaryl-heterocyclic, highly selective COX-2 inhibitor used for the symptomatic relief of pain and inflammation in osteoarthritis and rheumatoid arthritis. By selectively inhibiting the inducible COX-2 isoform, celecoxib suppresses prostaglandin E₂-mediated sensitisation of nociceptors and synovial inflammation while sparing COX-1-dependent gastric mucosal protection, thereby offering a more favourable gastrointestinal safety margin than traditional non-selective NSAIDs.^[5,6] Nevertheless, celecoxib carries a boxed warning for cardiovascular thrombotic risk on chronic administration and shares the class-related gastrointestinal and renal liabilities of NSAIDs.^[7,8] Furthermore, celecoxib is a practically water-insoluble, lipophilic molecule (aqueous solubility ~5 µg/mL; log P ≈ 3.5) and is classified as a BCS Class II drug, in which dissolution is often rate-limiting to oral absorption.^[9]

Transdermal drug delivery systems (TDDS) offer a well-recognised, non-invasive alternative to oral and parenteral therapy, permitting sustained and controlled drug input, avoidance of hepatic first-pass metabolism and gastrointestinal degradation, improved patient compliance, reduced dosing frequency, and the option of terminating drug administration simply by removing the patch.^[10,11] Matrix-type transdermal patches, in which the drug is homogeneously dispersed within a polymeric film, are amongst the simplest and most robust TDDS configurations, with release generally following classical Higuchi (square-root-of-time) kinetics governed by drug diffusivity and loading within the polymer matrix.^[12,13]

A major limitation of simple matrix patches for lipophilic, poorly soluble drugs such as celecoxib is inefficient partitioning into, and diffusion across, the lipophilic stratum corneum. Vesicular carriers such as niosomes self-assembled bilayer vesicles formed from non-ionic surfactants (e.g. Span 60) in combination with cholesterol have emerged as chemically stable, low-cost and biodegradable alternatives to liposomes for enhancing the effective solubility, skin partitioning and cutaneous residence of lipophilic drugs.^[14–16] Niosomes act by establishing a high local drug concentration gradient at the skin surface, adsorbing onto and fusing with the stratum corneum, and disrupting the ordered intercellular lipid lamellae, thereby improving transdermal flux without invasive physical disruption of the skin.^[17,18] Incorporation of niosomes within the polymer matrix of a transdermal patch can combine the permeation-enhancing and drug-reservoir properties of the vesicle with the mechanical robustness, dose uniformity and patient acceptability of a conventional patch.^[19,20]

Several previous reports have described niosomal or nanoparticulate systems for celecoxib and other NSAIDs, and matrix-type transdermal patches for a range of drugs, but a niosome-in-matrix-patch platform combining Span 60/cholesterol vesicles with an HPMC K100–PVP K30 film for sustained transdermal delivery of celecoxib in

osteoarthritis has not been extensively characterised.^[21,22] The present investigation was therefore undertaken with the aim of formulating and evaluating celecoxib-loaded niosomal matrix-type transdermal patches, optimising the vesicle composition and the polymer matrix using a 3² factorial design, and comparing the in-vitro release performance of the optimised niosomal patch against a conventional (non-vesicular) celecoxib patch.

MATERIALS AND METHODS

Materials

Celecoxib was obtained ex-gratis from Prudence Pharma Chem. Span 60, cholesterol, hydroxypropyl methylcellulose (HPMC K100), polyvinylpyrrolidone (PVP K30), polyethylene glycol 400 (PEG 400), propylene glycol, oleic acid and glycerine were procured through institutional stores. Methanol and ethanol (analytical grade) were obtained from commercial suppliers. All other reagents used were of analytical grade.

Equipments

A UV–Visible double-beam spectrophotometer, Fourier-transform infrared (FTIR) spectrophotometer, digital melting point apparatus, rotary evaporator, probe sonicator, refrigerated centrifuge, dynamic light scattering (DLS)/zeta potential analyser (Zetasizer), transmission electron microscope (TEM), digital weighing balance, magnetic stirrer with hot plate, vortex mixer and a laboratory refrigerator/temperature-controlled incubator were used for formulation and characterisation.

Preformulation studies

The organoleptic properties, melting point (capillary method), aqueous and organic solubility, and λ_{max} of celecoxib were determined. A calibration curve of celecoxib was constructed in phosphate-buffered saline (PBS, pH 7.4) over the 2–10 µg/mL range by UV spectrophotometry at the determined λ_{max}. Drug–excipient compatibility was assessed by FTIR (KBr pellet, 4000–400 cm⁻¹) for the pure drug, individual excipients, and physical mixtures, examining the retention of principal characteristic absorption bands without new peak formation or shift exceeding 10–20 cm⁻¹.^[23,24]

Preparation of celecoxib-loaded niosomes

Niosomes were prepared by the thin-film hydration method. Celecoxib, Span 60 and cholesterol were dissolved in a chloroform: methanol mixture (2:1 v/v) in a round-bottom flask, and the organic solvent was removed under reduced pressure using a rotary evaporator to deposit a thin, dry lipid film on the flask wall. The film was hydrated with 10 mL phosphate-buffered saline (pH 7.4) with gentle agitation above the surfactant phase-transition temperature to yield a multilamellar niosomal dispersion, which was subsequently probe-sonicated to reduce and homogenise vesicle size. Three formulations were prepared by

varying the Span 60: cholesterol molar ratio (F1, 1:1:1; F2, 1:2:1; F3, 1:2:2, drug: surfactant: cholesterol), and each was evaluated for entrapment efficiency, particle size, polydispersity index (PDI), zeta potential, surface morphology (TEM) and *in vitro* drug diffusion through a dialysis membrane.

Preparation of celecoxib-loaded niosomal transdermal patches

Matrix-type transdermal patches were prepared by the solvent-casting technique. PVP K30 was dissolved in a hydroalcoholic solvent system (ethanol: distilled water) under continuous stirring, followed by gradual addition and hydration of HPMC K100 to obtain a homogeneous polymeric gel. The optimised celecoxib-loaded niosomal dispersion (equivalent to 100 mg celecoxib) was incorporated into the polymer solution, together with PEG 400 (plasticiser), oleic acid (penetration enhancer) and glycerine (humectant). The casting solution was poured into a 9.5 cm glass Petri dish lined with a backing membrane and dried at room temperature ($25 \pm 2^\circ\text{C}$) for 24 h, or in a hot-air oven at $40 \pm 2^\circ\text{C}$, until a dry, uniform film formed. The dried patch was peeled off, wrapped in aluminium foil, and stored in a desiccator until further evaluation. A plain (non-vesicular) celecoxib patch of identical polymer composition was prepared as a comparator.

Optimisation by 3^2 factorial design

A 3^2 full factorial design was employed to optimise the patch matrix, with HPMC K100 (Factor A: 100, 150, 200 mg) and PVP K30 (Factor B: 100, 150, 200 mg) as independent variables at three levels each, yielding nine formulations (F1–F9) with celecoxib-loaded niosomal suspension (equivalent to 100 mg celecoxib), PEG 400 (1 mL), oleic acid (0.5 mL) and glycerine (0.25 mL) held constant. F5 represented the centre-point formulation.

Physicochemical characterisation of niosomes

Entrapment efficiency was determined by separating untrapped drug from the niosomal dispersion, lysing the vesicles with methanol, and estimating total and free drug spectrophotometrically. Mean particle size, Z-average diameter and PDI were measured by dynamic light scattering, and zeta potential was determined by laser Doppler electrophoresis using a folded capillary cell, both in triplicate at 25°C .^[25] Vesicle morphology was examined by transmission electron microscopy. *In-vitro* drug diffusion from the niosomal dispersion was studied using the dialysis-bag method, with samples withdrawn at predetermined intervals and analysed by UV spectrophotometry at 252 nm.^[26]

Evaluation of transdermal patches

Patches were evaluated for weight uniformity, thickness (screw gauge), folding endurance (repeated folding at the same point until visible crack/break), surface pH (aqueous swelling method), percentage moisture absorption, percentage moisture loss, and drug content

uniformity (spectrophotometric estimation of an extracted patch aliquot).^[27]

In-vitro drug release and kinetic analysis

In-vitro release from the optimised niosomal patch and the plain comparator patch was studied using the dialysis-membrane diffusion-cell method in PBS (pH 7.4): ethanol (80:20 v/v) receptor medium maintained at $37 \pm 0.5^\circ\text{C}$ with continuous stirring over 12 h, with samples withdrawn at fixed intervals (0.5–12 h) and replaced with fresh medium. Cumulative percentage drug release (%CDR) was calculated after correcting for sample withdrawal. Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas kinetic models using DD-Solver software, and the coefficient of determination (R^2) of each model, together with the Korsmeyer–Peppas release exponent (n), was used to elucidate the predominant release mechanism.^[28,29]

RESULTS AND DISCUSSION

Preformulation studies

Celecoxib was obtained as a white to off-white, odourless crystalline powder with a melting point and characteristic FTIR spectrum consistent with reference values, confirming the identity and purity of the drug sample. The drug showed negligible aqueous solubility ($<5\ \mu\text{g/mL}$, pH-independent) but was freely soluble in methanol, ethanol and DMSO, consistent with its classification as a BCS Class II, highly lipophilic molecule ($\log P \approx 3.5$). The λ_{max} of celecoxib in PBS (pH 7.4) was determined at 252 nm, and the calibration curve was linear over the 2–10 $\mu\text{g/mL}$ range ($y = 0.1179x - 0.0563$; $R^2 = 0.9911$), confirming compliance with the Beer–Lambert law and validating the method for subsequent quantification, in accordance with ICH Q2(R1) linearity requirements.^[28]

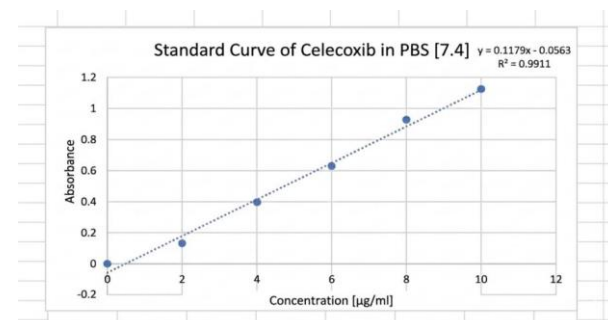


Figure 1: Standard calibration curve of celecoxib in PBS pH 7.4 at 252 nm.

Drug–excipient compatibility

FTIR spectra of pure celecoxib, individual excipients (Span 60, cholesterol, HPMC K100, PVP K30, PEG 400, oleic acid) and their physical mixtures showed retention of all principal characteristic absorption bands (N–H and S=O sulfonamide stretching, C–F stretching, aromatic C=C stretching of celecoxib; ester carbonyl of Span 60; O–H of cholesterol; lactam carbonyl of PVP K30; ether C–O–C of PEG 400; carboxylic C=O of oleic acid), with

no new peaks and no shifts exceeding the 10–20 cm^{-1} threshold indicative of chemical interaction. These findings confirm good physicochemical compatibility

between celecoxib and all excipients used in the niosomal and patch formulations.^[23,24]

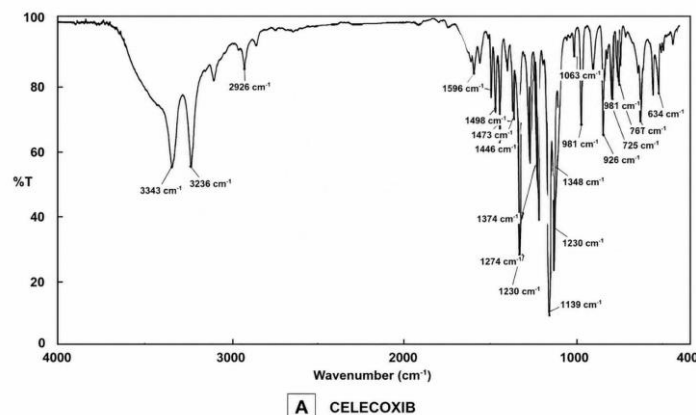


Figure 2: FTIR spectrum of pure celecoxib.

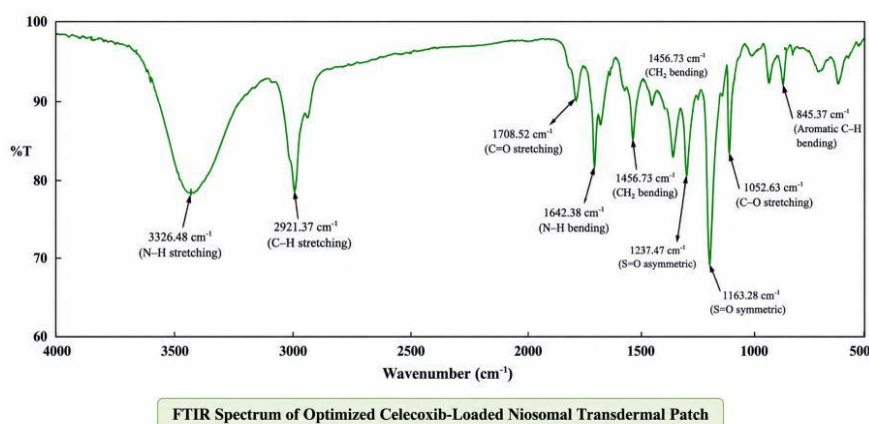


Figure 3: FTIR spectrum of the optimised celecoxib-loaded niosomal transdermal patch (F3).

Formulation and characterisation of niosomes

Table 1 summarises the physicochemical characteristics of the celecoxib-loaded niosomal formulations (F1–F3). Formulation F1 (Span 60:cholesterol, 1:1:1) exhibited the highest entrapment efficiency (93.24%), the smallest

mean particle size (616.0 nm) and the highest absolute zeta potential (–32.7 mV) among the three formulations, and was therefore selected as the optimised niosomal dispersion for patch fabrication.

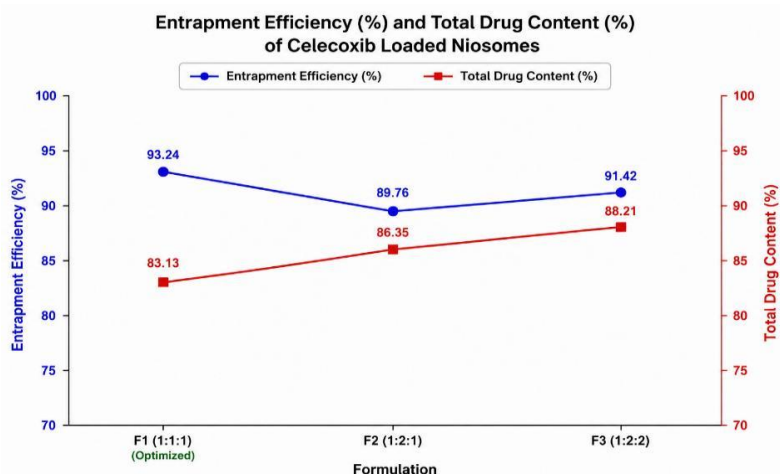


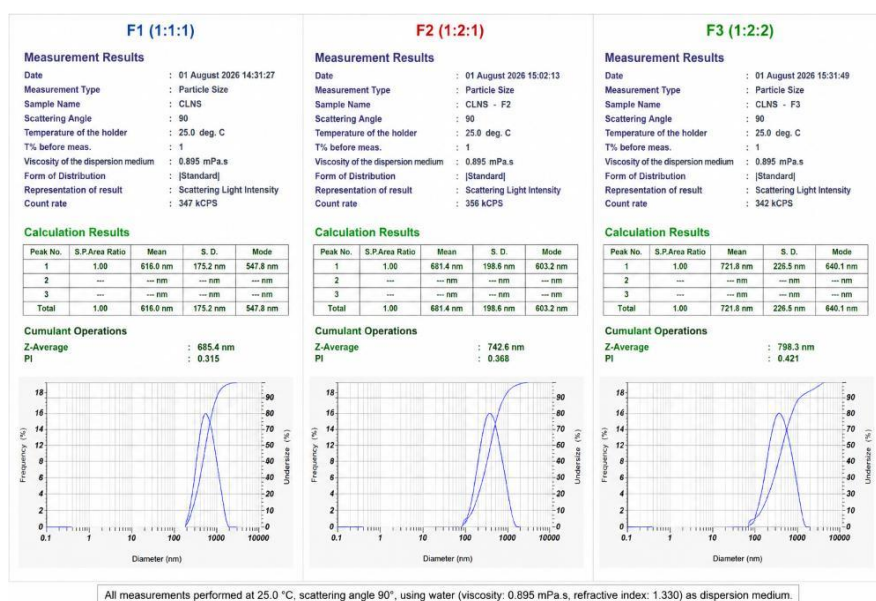
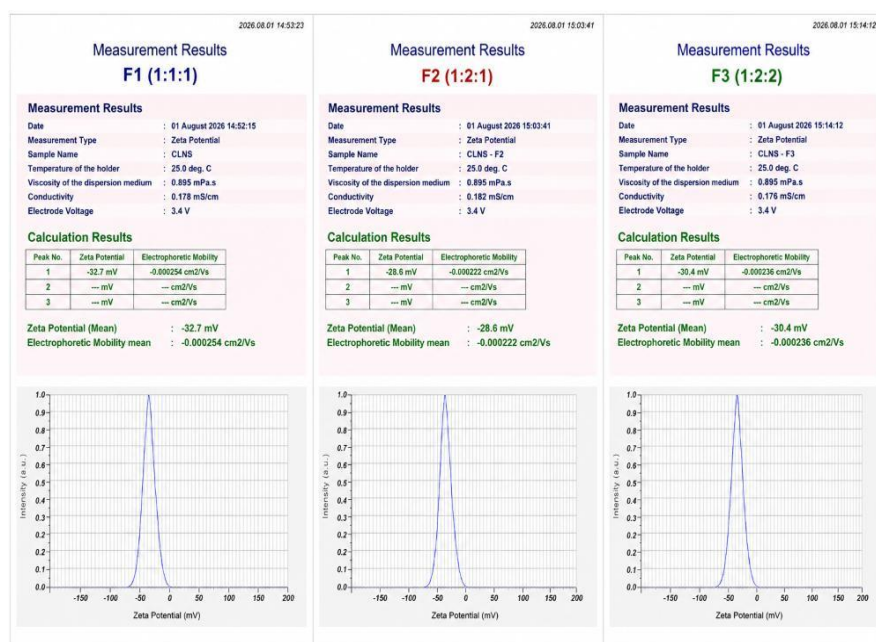
Figure 4: Entrapment efficiency (%) and total drug content (%) of celecoxib-loaded niosomes (F1–F3).

Table 1: Physicochemical characterisation of celecoxib-loaded niosomal formulations, mean $\pm$ SD (n = 3).

Parameter	F1 (1:1:1)	F2 (1:2:1)	F3 (1:2:2)
Entrapment efficiency (%)	93.24	89.76	91.42
Total drug content (%)	83.13	86.35	88.21
Z-average particle size (nm)	685.4	742.6	798.3
Mean particle size (nm)	616.0	681.4	721.8
Polydispersity index (PDI)	0.315	0.368	0.421
Zeta potential (mV)	-32.7	-28.6	-30.4

An increase in the surfactant: cholesterol ratio (F2, F3) was associated with a progressive increase in mean particle size and PDI, likely reflecting altered vesicle packing and bilayer rigidity at higher cholesterol loading,

while F1 provided the most favourable combination of small vesicle size, high entrapment and good colloidal stability, consistent with reports on Span 60/cholesterol niosomal systems.^[14,25]

**Figure 5: Particle size and polydispersity index (PDI) of celecoxib-loaded niosomal formulations F1–F3.****Figure 6: Zeta potential distribution of celecoxib-loaded niosomal formulations F1–F3.**

TEM examination of the optimised formulation (F1) revealed predominantly spherical, well-formed vesicles ranging from the sub-micron to nanometre scale, corroborating the DLS particle-size data and supporting the successful development of the optimised niosomal

formulation. In-vitro dialysis-bag diffusion studies of the niosomal dispersion demonstrated a gradual, sustained release of celecoxib, consistent with a vesicular reservoir effect.

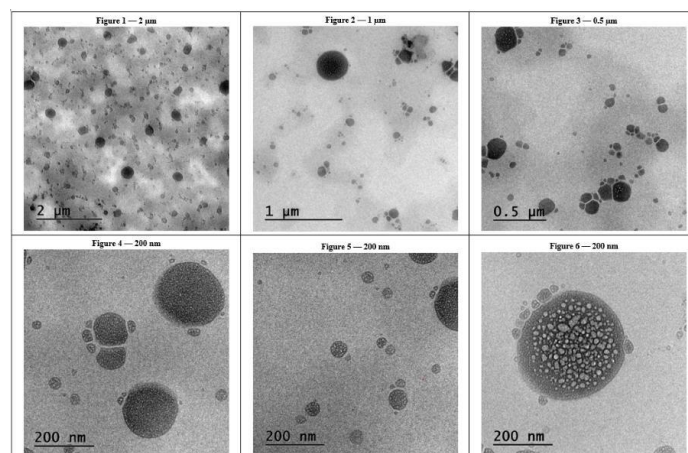


Figure 7: Transmission electron micrographs of the optimised celecoxib-loaded niosomes (F1) at increasing magnification.

Physical evaluation of optimised niosomal transdermal patches

Table 2 presents the physicochemical characteristics of the nine 3^2 factorial patch formulations (F1–F9). All formulations showed acceptable weight uniformity (182–193 mg), thickness (0.46–0.53 mm), folding endurance (220–290 folds) and surface pH (5.72–5.86), the latter being close to normal skin pH and therefore unlikely to

cause skin irritation. Formulation F3 (high HPMC K100, high PVP K30) showed the highest folding endurance (290 ± 6) and drug content ($98.40 \pm 0.45\%$), together with the lowest moisture absorption (4.68%) and moisture loss (2.24%), indicating a mechanically robust, physically stable film, and was therefore selected as the optimised patch formulation.

Table 2: Physical evaluation of celecoxib niosomal transdermal patches (representative formulations; mean $\pm$ SD, n = 3).

Formulation	Weight (mg)	Thickness (mm)	Folding endurance	Surface pH	Drug content (%)
F1	182.4 ± 3.2	0.46 ± 0.02	220 ± 6	5.72 ± 0.04	96.10 ± 0.45
F2	188.7 ± 2.8	0.50 ± 0.01	258 ± 6	5.79 ± 0.04	97.00 ± 0.45
F3	192.6 ± 2.1	0.53 ± 0.01	290 ± 6	5.86 ± 0.04	98.40 ± 0.45
F5 (centre point)	193.1 ± 2.5	0.53 ± 0.01	285 ± 6	5.83 ± 0.04	97.50 ± 0.45

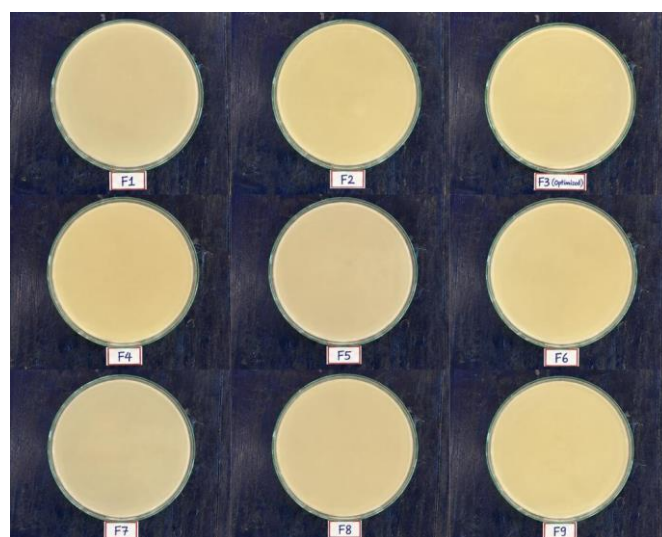


Figure 8: Physical appearance of celecoxib-loaded niosomal transdermal patches (F1–F9) after solvent casting.

***In-vitro* drug release and release kinetics**

All nine formulations exhibited a gradual, continuous increase in cumulative percentage drug release over 12 h, characteristic of controlled release from a matrix system. Increasing the HPMC K100 concentration generally decreased drug release, consistent with the higher gel-

layer viscosity retarding drug diffusion, whereas increasing PVP K30 concentration increased drug release, consistent with its pore-forming, hydrophilic character. Formulation F3 demonstrated the highest cumulative release at 12 h (71.0%) among the niosomal patches and was confirmed as the optimised batch.

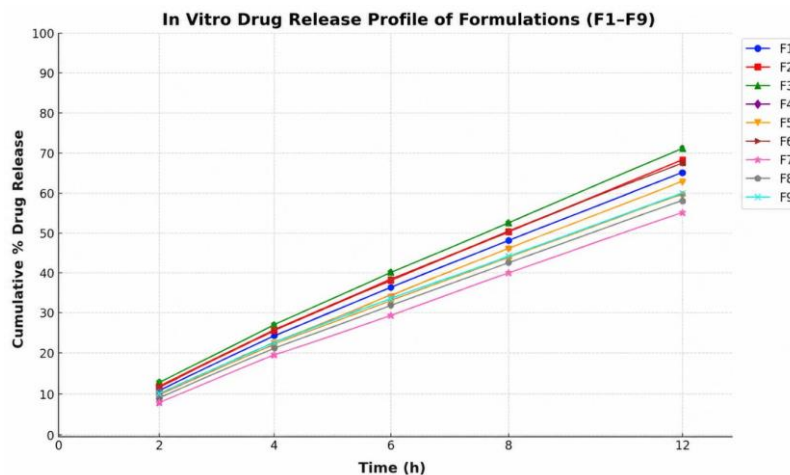


Figure 9: *In-vitro* cumulative percentage drug release profile of celecoxib niosomal transdermal patches (F1–F9).

Kinetic modelling of the release data (Table 3) showed R^2 values ranging from 0.948–0.963 (zero-order), 0.969–0.981 (first-order), 0.982–0.992 (Higuchi) and 0.977–0.987 (Korsmeyer–Peppas) across F1–F9. The Higuchi model provided the best fit for all formulations (highest R^2), indicating that drug release from the niosomal patch matrix was predominantly diffusion-controlled.^[30] The

Korsmeyer–Peppas release exponent (n) ranged from 0.64 to 0.68 across formulations, falling within the $0.45 < n < 0.89$ range characteristic of non-Fickian (anomalous) transport, in which drug release is governed by a combination of diffusion through, and relaxation/swelling of, the hydrophilic polymer matrix.^[31]

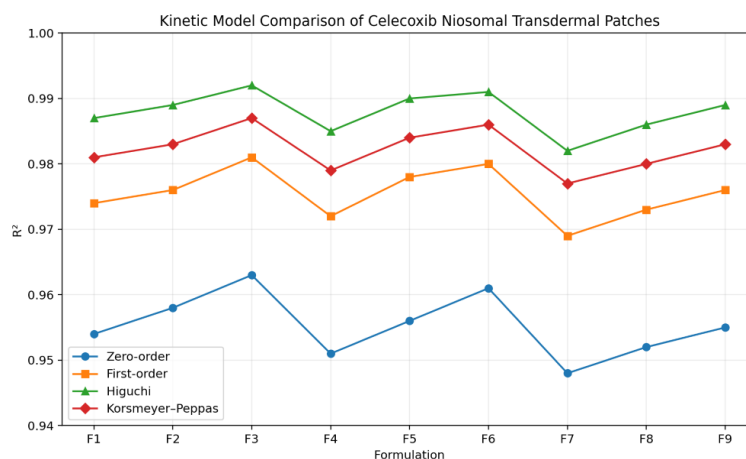


Figure 10: Comparison of zero-order, first-order, Higuchi and Korsmeyer–Peppas model fits (R^2) for celecoxib niosomal transdermal patches (F1–F9).

Table 3: Release-kinetic model fitting of celecoxib niosomal transdermal patches (F1–F9)

Formulation	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer–Peppas R^2	n
F1	0.954	0.974	0.987	0.981	0.65
F2	0.958	0.976	0.989	0.983	0.66
F3	0.963	0.981	0.992	0.987	0.68
F5	0.956	0.978	0.990	0.984	0.67
F6	0.961	0.980	0.991	0.986	0.68

Comparative release: plain patch versus optimised niosomal patch

The plain (non-vesicular) celecoxib patch released drug considerably faster, reaching approximately 85% cumulative release at 12 h, compared with 71.0% for the optimised F3 niosomal patch over the same period. The slower, more sustained release from the niosomal patch is attributable to the additional diffusional barrier imposed by the niosomal bilayer, which the drug must first partition out of before diffusing through the

surrounding polymer matrix, confirming that vesicular entrapment provides an additional level of release control beyond that of the polymer matrix alone.^[19,20] This sustained-release behaviour is pharmaceutically desirable for a chronic, once-daily or alternate-day transdermal regimen in the symptomatic management of osteoarthritis, potentially reducing dosing frequency and fluctuations in systemic drug concentration relative to conventional oral celecoxib therapy.^[7]

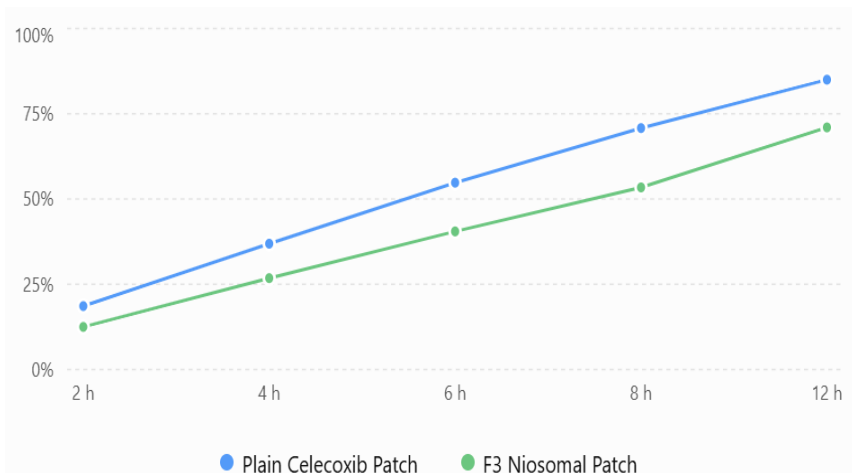


Figure 11: Comparative *in-vitro* release of the plain celecoxib patch versus the optimised (F3) celecoxib niosomal transdermal patch over 12 h.

CONCLUSION

Celecoxib-loaded niosomes were successfully prepared by the thin-film hydration method, with the 1:1:1 Span 60: cholesterol formulation (F1) providing optimal entrapment efficiency, particle size and colloidal stability. Incorporation of this optimised niosomal dispersion into an HPMC K100–PVP K30 matrix, optimised through a 3^2 factorial design, yielded a mechanically robust, skin-compatible transdermal patch (F3) that released celecoxib in a sustained, predominantly diffusion-controlled (Higuchi), non-Fickian manner over 12 h, markedly slower than a conventional non-vesicular patch. These results support niosomal matrix-type transdermal patches as a promising, non-invasive, controlled-release platform for celecoxib in the management of osteoarthritis. The present findings are based on laboratory-scale, *in-vitro* data; further *ex-vivo* skin permeation, *in-vitro*–*ex-vivo* correlation, dermal tolerability, stability, and *in-vivo* pharmacokinetic/ pharmacodynamic studies are warranted before clinical translation.

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Conflict of Interest: The authors declare no conflict of interest.

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