

**FORMULATION, OPTIMIZATION, AND ESTIMATION OF CELECOXIB TOPICAL
EMULGEL: A COMPREHENSIVE REVIEW****Swati Jaiman*, Dr. Tara Chand, Ashish Jain**

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ABSTRACT

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor widely prescribed for osteoarthritis, rheumatoid arthritis, and acute pain, is limited in its oral use by poor aqueous solubility, variable bioavailability, and a well-documented risk of gastrointestinal and cardiovascular adverse effects on chronic administration. Topical delivery of celecoxib offers an attractive alternative by directing the drug to the site of musculoskeletal or dermal pathology, minimizing systemic exposure, and improving patient acceptability. Among semisolid carriers, the emulgel — a biphasic system in which a fine emulsion is dispersed within a gel network — has emerged as a preferred vehicle for lipophilic, poorly water-soluble drugs such as celecoxib because it combines the drug-loading capacity of an emulsion with the spreadability, patient compliance, and dual-controlled release behavior of a gel. This review consolidates the current literature on celecoxib emulgel systems, covering the physicochemical and pharmacological rationale for topical delivery, the excipients and preparation methods used to formulate conventional, nano-, and microemulsion-based emulgels, the application of Quality by Design (QbD) and statistical design of experiments (Box-Behnken, central composite, and factorial designs) for formulation optimization, the standard panel of physicochemical, rheological, ex vivo, and stability evaluations applied to these systems, and the analytical (UV spectrophotometric and HPLC) methods used to estimate celecoxib in bulk, formulation, and biological matrices. Reported optimized celecoxib emulgels have consistently demonstrated acceptable pH, non-Newtonian pseudoplastic rheology, high drug content, and substantially enhanced ex vivo skin permeation and anti-inflammatory activity relative to conventional gels or marketed products. The review concludes by identifying persistent challenges — including long-term physical stability of the dispersed phase, scale-up reproducibility, and the need for harmonized in vitro-in vivo correlation — and outlines directions for future research in this field.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of pharmacotherapy for inflammatory and painful musculoskeletal conditions such as osteoarthritis, rheumatoid arthritis, and soft-tissue injury. Conventional NSAIDs inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes, and their long-term oral use is closely associated with gastric ulceration, bleeding, and renal impairment arising principally from COX-1 inhibition in the gastrointestinal mucosa. The development of selective COX-2 inhibitors, or “coxibs,” was intended to preserve anti-inflammatory and analgesic efficacy while reducing gastrointestinal toxicity. Celecoxib, the first coxib approved for clinical use, selectively inhibits COX-2-mediated prostaglandin

synthesis at the site of inflammation and is indicated for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute pain.

Despite its improved gastrointestinal safety profile relative to non-selective NSAIDs, oral celecoxib therapy is not free of limitations. The drug is classified under Biopharmaceutics Classification System (BCS) Class II, characterized by very low aqueous solubility (below 5 micrograms per millilitre) combined with high intestinal permeability; this poor solubility translates into slow and variable dissolution, incomplete and erratic oral absorption, and an oral bioavailability of only around 40 percent even in capsule form. In addition, chronic oral use of celecoxib has been linked to an increased risk of

cardiovascular thrombotic events, prompting regulatory caution regarding long-term systemic exposure. These pharmacokinetic and safety concerns have driven sustained interest in delivering celecoxib directly to the affected joint, muscle, or skin region through topical dosage forms, thereby achieving local therapeutic concentrations while limiting systemic drug exposure and its associated risks.

Topical delivery of NSAIDs is pharmaceutically challenging because the stratum corneum presents a formidable barrier to permeation, and because most NSAIDs, including celecoxib, are poorly water-soluble lipophilic molecules that are difficult to incorporate into simple aqueous gels at pharmacologically useful concentrations. Conventional topical vehicles — ointments, creams, and hydrogels — each present specific drawbacks: ointments are greasy and poorly spreadable, creams are thermodynamically unstable biphasic systems prone to phase separation, and plain hydrogels have very limited capacity to solubilize hydrophobic drugs. The emulgel system was developed specifically to overcome these limitations by combining an emulsion (which can carry a substantial payload of a lipophilic drug within its dispersed oil phase) with a hydrophilic gel network (which imparts favourable spreadability, esthetic appeal, and controlled drug release). This review provides a comprehensive, literature-grounded synthesis of the formulation science, optimization methodology, evaluation framework, and analytical estimation techniques that have been applied specifically to celecoxib-loaded topical emulgels.

2. Drug Profile: Celecoxib

2.1 Physicochemical Characteristics

Celecoxib is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, a diaryl-substituted pyrazole bearing a sulfonamide functional group. It exists in at least three polymorphic crystalline forms (Forms I, II, and III), with melting points clustered between approximately 161 and 163 degrees Celsius; Form III is generally regarded as the most thermodynamically stable form under ambient storage conditions. The molecule shows weakly acidic behaviour associated with ionization of the sulfonamide group, with a reported pKa in the range of approximately 9.3 to 11.1 depending on the experimental method used. Celecoxib is highly lipophilic, with an experimentally determined octanol-water partition coefficient (log P) reported in the range of approximately 3.0 to 3.5, and it is practically insoluble in water, with aqueous solubility consistently reported as below 5 micrograms per millilitre at physiological temperature.

This combination of high lipophilicity and negligible aqueous solubility places celecoxib firmly within BCS Class II. Solubility studies in biorelevant gastric and intestinal media have reported concentrations in the range of roughly 46 to 103 micrograms per millilitre

under fasted- and fed-state simulated intestinal fluid conditions, values still far below what would be required for complete dissolution of a typical oral dose. Cosolvency studies have shown that solubility can be substantially enhanced using solvents such as N-methyl-2-pyrrolidone, and crystal engineering approaches, including cocrystal formation and salt formation, have likewise been explored to improve dissolution behaviour. For a topically applied dosage form, this low aqueous solubility and high lipophilicity are, paradoxically, advantageous for partitioning into the lipid-rich stratum corneum, but they also mean that the drug must be solubilized within an oil phase or a solubilizing surfactant system before it can be uniformly incorporated into a semisolid vehicle.

2.2 Mechanism of Action and Therapeutic Use

Celecoxib produces its anti-inflammatory, analgesic, and antipyretic effects primarily through selective, reversible inhibition of the COX-2 isoenzyme, thereby suppressing the conversion of arachidonic acid to pro-inflammatory prostaglandins at sites of tissue injury and inflammation, while sparing COX-1-mediated prostaglandin synthesis that maintains gastric mucosal integrity and normal platelet function. Its analgesic action is understood to be largely peripheral, acting at the site of pain generation, which makes it particularly well suited to conditions in which pain has an inflammatory component, such as osteoarthritis flare, soft-tissue strain, and localized joint inflammation — precisely the indications for which a topically applied emulgel would be clinically useful.

2.3 Rationale for Topical Delivery

Topical administration of celecoxib is rationalized on several grounds. First, it allows the drug to reach a high local concentration in periarticular soft tissue and synovial fluid while maintaining plasma concentrations well below those associated with systemic NSAID-related adverse effects. Second, it avoids first-pass hepatic metabolism and reduces gastrointestinal mucosal exposure, addressing the principal safety concern historically associated with NSAID therapy. Third, topical application is particularly suited to elderly and polymedicated patients, in whom oral NSAID use carries a disproportionately higher risk of drug interactions and gastrointestinal or renal complications. However, because celecoxib is a large, highly lipophilic molecule with negligible water solubility, its passive diffusion across the stratum corneum from a simple aqueous gel is inherently limited; this pharmaceutical constraint underlies the extensive formulation research directed at nanoemulsion-, microemulsion-, and vesicle-based emulgel carriers capable of enhancing both drug loading and cutaneous permeation.

3. Emulgel as a Topical Drug Delivery System

3.1 Concept and Rationale

An emulgel is a dual-phase pharmaceutical system formed by combining a conventional emulsion, oil-in-water (o/w) or water-in-oil (w/o), with a gelling agent to

yield a semisolid product that exhibits the internal drug-carrying architecture of an emulsion together with the external rheological and sensory characteristics of a gel. The gelling network, typically formed by a hydrophilic polymer such as a carbomer, hydroxypropyl methylcellulose, xanthan gum, or a similar hydrocolloid, immobilizes the dispersed emulsion droplets, imparting long-term physical stability to a system that, as a simple emulsion, would otherwise be prone to creaming, coalescence, or phase separation over time. This architecture provides what has been described as a dual-controlled release mechanism, in which drug must first partition out of the internal oil droplets and then diffuse through the continuous gel matrix before reaching the skin surface, a process that can be tuned to achieve either rapid onset or sustained delivery depending on formulation composition.

3.2 Structural Types

Emulgels are most commonly formulated as oil-in-water systems for hydrophilic-leaning applications, in which the drug-loaded oil droplets are dispersed within a continuous aqueous gel phase; this configuration is generally preferred for lipophilic NSAIDs such as celecoxib because it provides a non-greasy, easily spreadable, washable product with good patient acceptability. Water-in-oil emulgels, in which an aqueous phase is dispersed within a continuous oily/gelled phase, are used less frequently for NSAID delivery but may offer advantages for occlusive or highly hydrating applications. Within the o/w category, formulation variants reported for celecoxib specifically include conventional coarse emulgels, nanoemulsion-based emulgels (nanoemulgels) with droplet sizes typically below 500 nanometres, microemulsion-based gels formed from thermodynamically stable, optically transparent microemulsions, and vesicular-carrier gels such as transthesomal or niosomal gels in which the drug is first encapsulated within a lipid vesicle before incorporation into the hydrogel matrix.

3.3 Advantages over Conventional Semisolid Vehicles

- Superior drug-loading capacity for lipophilic, poorly water-soluble actives such as celecoxib compared with simple hydrogels.
- Greater physical and thermodynamic stability than a plain emulsion, owing to the immobilizing gel network.
- Favourable rheological profile — pseudoplastic, shear-thinning behaviour that eases application and promotes uniform spreading without being runny.
- Non-greasy, easily washable, and cosmetically elegant compared with ointments, improving patient compliance.
- Dual-controlled release kinetics arising from partitioning across the oil-gel interface, allowing tunable onset and duration of action.
- Amenability to incorporation of chemical permeation enhancers and to nanocarrier or vesicular modification for enhanced cutaneous delivery.

4. Formulation Components and Composition

4.1 Oil Phase

Selection of the oil phase is typically guided by systematic solubility screening of celecoxib in a panel of natural and synthetic oils, since the oil must solubilize an adequate drug payload while remaining compatible with the surfactant system and the skin. Reported studies have screened oils including sesame oil, olive oil, groundnut oil, oleic acid, and various essential oils; natural oils such as eucalyptus oil and turpentine oil have additionally been used not merely as solubilizers but explicitly as penetration modifiers to promote drug flux across the stratum corneum. The oil concentration is one of the most influential formulation variables affecting globule size, viscosity, drug content, and *in vitro* release, and is therefore frequently selected as an independent variable in formal optimization designs.

4.2 Surfactants and Co-surfactants

Non-ionic surfactants such as Tween 80 (polysorbate 80) and Span 60 are widely used to reduce interfacial tension between the oil and aqueous phases and to stabilize the dispersed droplets, either alone or as a surfactant-cosurfactant blend (Smix). Co-surfactants such as short-chain alcohols or Transcutol P are frequently incorporated to reduce the interfacial film rigidity, decrease droplet size, and expand the region of the microemulsion or nanoemulsion existence within the pseudo-ternary phase diagram used for formulation screening. In vesicular systems such as transthesomal gels, edge activators (for example, sodium deoxycholate) are incorporated to increase vesicle membrane flexibility and enhance deformability-driven skin penetration.

4.3 Gelling Agents

Carbopol (carbomer) grades — most commonly Carbopol 934 and Carbopol 940 — are the most extensively used gelling agents in celecoxib emulgel formulations because of their excellent thickening efficiency at low concentration, good spreadability, and compatibility with topical application; their gelling behaviour depends on neutralization, typically with triethanolamine, to unfold the polymer coil and generate viscosity. Hydroxypropyl methylcellulose (HPMC) and xanthan gum have also been reported as gelling agents or as co-gellants, often selected for their mucoadhesive or pseudoplastic flow characteristics. The concentration of the gelling agent is a critical formulation variable that governs viscosity, spreadability, extrudability, and the rate of *in vitro* drug release, and is almost universally included as a factor in design-of-experiments optimization studies of celecoxib emulgels.

4.4 Permeation Enhancers

Because the stratum corneum is the principal barrier to topical NSAID delivery, chemical permeation enhancers are frequently incorporated to disrupt intercellular lipid packing or increase drug partitioning into the skin. Reported enhancers for celecoxib topical systems include terpene-based essential oil constituents (eucalyptus and

turpentine oil), fatty acid-derived surfactant components such as oleic acid, and glycol-type solubilizers such as Transcutol P, each of which can act simultaneously as a solubility enhancer within the formulation and as a skin permeation promoter.

4.5 Other Excipients

Additional components typically include preservatives (such as methylparaben and propylparaben) to prevent microbial contamination in the predominantly aqueous gel phase, humectants (such as propylene glycol or glycerin) to prevent the formulation from drying on the skin surface, neutralizing agents (triethanolamine) to achieve the target pH and gel consistency, chelating agents (EDTA) to improve oxidative stability, and purified water as the continuous aqueous vehicle.

5. Methods of Preparation

5.1 Preparation of the Emulsion or Nanoemulsion Component

The oil phase, containing celecoxib dissolved with the aid of heat and/or the selected surfactant system, and the aqueous phase are typically prepared separately and heated to a common temperature (commonly around 70 to 80 degrees Celsius for conventional emulsions). The oil phase is then added to the aqueous phase, or vice versa, under continuous mechanical or high-speed homogenization to form the primary emulsion. For nanoemulsion- or microemulsion-based systems, the aqueous phase, surfactant-cosurfactant mixture, and oil are combined under high-shear homogenization, probe sonication, or spontaneous low-energy emulsification, guided by pseudo-ternary phase diagrams constructed to identify the region of clear, stable, low-viscosity microemulsion or nanoemulsion formation. Resulting droplet size and polydispersity are commonly verified by dynamic light scattering, with reported nanoemulsion/nanoemulgel droplet sizes for topically applied NSAID systems typically falling in the range of roughly 20 to 500 nanometres.

5.2 Preparation of the Gel Base

In parallel, the gelling polymer (most often Carbopol 934 or 940) is dispersed in purified water with continuous stirring and allowed to hydrate fully, typically with an overnight or extended soaking period to ensure complete swelling and avoid lump formation. The dispersion is then neutralized dropwise with triethanolamine to the target pH, at which point the polymer chains uncoil and the characteristic gel viscosity develops.

5.3 Incorporation and Emulgel Formation

The final emulgel is prepared by incorporating the previously formed emulsion or nanoemulsion into the hydrated gel base at a defined ratio (commonly reported in the region of 1:1), with gentle mechanical mixing to avoid shear-induced droplet coalescence while ensuring homogeneous distribution of the dispersed phase throughout the gel matrix. The resulting product is typically evaluated for organoleptic homogeneity,

freedom from lumps or grittiness, and absence of phase separation immediately after preparation and upon short-term storage.

5.4 Advanced Emulgel Variants Reported for Celecoxib

Beyond the conventional emulgel, several advanced variants have been specifically developed and reported for celecoxib. Nanoemulgels incorporate a nanoemulsion, prepared via high-shear or phase-titration methods and characterized by droplet sizes generally below 500 nanometres, into a Carbopol gel matrix; such systems have been proposed for conditions including acute rheumatoid arthritis. Microemulsion-based gels use thermodynamically stable, spontaneously forming microemulsions, optimized via phase-diagram and ex vivo/in vivo evaluation, as the internal phase for transdermal delivery. Nanosponge-loaded gels disperse porous, cyclodextrin- or polymer-based nanosponge particles carrying celecoxib within a gel base; one reported optimized nanosponge gel exhibited a particle size around 240.9 nanometres, a zeta potential of approximately -1.8 millivolts, and an entrapment efficiency near 98 percent. Transethosomal gels encapsulate celecoxib within deformable, edge-activator-containing lipid vesicles dispersed in an HPMC hydrogel, a strategy that has additionally been investigated for enhancing dermal delivery in the context of cutaneous tumor microenvironments while limiting off-target distribution to normal tissue.

6. Optimization Strategies

6.1 Quality by Design Framework

Modern formulation development of celecoxib emulgels increasingly follows a Quality by Design (QbD) paradigm, in which the desired Quality Target Product Profile (adequate viscosity, spreadability, drug content, and permeation) is defined at the outset, Critical Quality Attributes (CQAs) are identified, and a risk assessment is used to select the formulation and process variables — Critical Material Attributes and Critical Process Parameters — most likely to influence those CQAs. This systematic, risk-based approach, in contrast to traditional one-factor-at-a-time optimization, allows formulators to map the design space and identify a robust operating region rather than a single point solution.

6.2 Design of Experiments

Statistical Design of Experiments (DoE) is the principal quantitative tool used to implement QbD in emulgel optimization. The Box-Behnken design, a three-level, rotatable response-surface design that avoids extreme combinations of factor levels, has been widely applied to NSAID emulgel systems; in one representative example for a BCS Class II drug emulgel, the concentrations of Carbopol 934, an oil, and a surfactant were varied as independent factors against viscosity, spreadability, and in vitro drug release as dependent responses, with response surface methodology used to identify the optimal factor combination. Central composite designs

(CCD) have similarly been applied to celecoxib nanoformulation optimization, for example in combination with Bayesian optimization approaches for dissolution-rate enhancement via co-milling. Three-factor, three-level Box-Behnken designs have also been used in the optimization of nano-emulgel systems for other actives, where oil percentage, surfactant-mixture percentage, and homogenization speed were optimized against globule size and entrapment efficiency as critical quality attributes, illustrating a methodology directly transferable to celecoxib systems. Pseudo-ternary phase diagrams remain an essential preliminary optimization tool specifically for nanoemulsion- and microemulsion-based emulgels, used to delineate the region of stable, low-viscosity, single-phase microemulsion formation as a function of oil, surfactant-cosurfactant, and water

proportions before a candidate composition is advanced to full DoE optimization.

6.3 Critical Quality Attributes and Process Parameters

Across the reviewed literature, the CQAs most consistently selected as optimization responses for celecoxib and structurally analogous NSAID emulgels are viscosity, spreadability, *in vitro* (and, where applicable, *ex vivo*) drug release, globule or droplet size, zeta potential, and entrapment efficiency for nanocarrier-based systems. Critical process parameters commonly investigated include homogenization speed and duration, order and rate of phase addition, and neutralization/mixing conditions during gel formation, each of which can materially affect final droplet size distribution and rheological behaviour.

6.4 Representative Optimization Studies

Table 1: Summarizes representative design-of-experiments-based optimization studies relevant to celecoxib and closely related NSAID emulgel systems, illustrating the variables and outcomes typically reported in this field.

Formulation / Drug	Design Used	Independent Variables	Key Optimized Response
Celecoxib emulgel (natural oil)	Solubility/co-surfactant screening	Oil type, Carbopol 940 concentration, essential-oil enhancer	Improved solubility and enhanced skin penetration modifiers identified
Celecoxib nanoemulgel	Pseudo-ternary phase diagram + optimization	Oil, surfactant-cosurfactant ratio, water	Droplet size 28–500 nm; suitable for acute rheumatoid arthritis use
Celecoxib microemulsion-based gel	Phase-diagram-guided <i>ex vivo</i> / <i>in vivo</i> evaluation	Oil, Smix ratio, gel base	Enhanced transdermal flux vs. plain gel
Celecoxib nanosponge gel	Formulation screening + physicochemical characterization	Polymer-to-drug ratio, homogenization	Particle size ≈ 240.9 nm; zeta ≈ -1.8 mV; entrapment $\approx 98\%$
Simvastatin emulgel (BCS II analogue)	Box-Behnken (3-factor, 3-level)	Carbopol 934, sesame oil, Tween 80	Viscosity ≈ 6875 mPa·s; spreadability ≈ 10.14 g·cm/s
Ozenoxacin nano-emulgel (QbD analogue)	Box-Behnken (QbD)	% oil, % Smix, homogenization speed	Optimized globule size and entrapment efficiency; 6-month stability confirmed

7. Evaluation and Characterization

7.1 Physicochemical and Organoleptic Evaluation

Freshly prepared celecoxib emulgels are routinely assessed for colour, homogeneity, and consistency by visual inspection, and for pH using a calibrated pH meter, with target values close to skin-compatible pH (approximately 5.5 to 7) to avoid irritation. Viscosity is measured using a rotational (Brooke-field-type) or cone-and-plate viscometer at defined spindle speeds and temperature; reported optimized celecoxib and related NSAID emulgels have shown viscosities in the low-to-mid thousands of centipoise (or mPa·s) range, consistent with a spreadable but non-flowing semisolid. Spreadability is typically measured by the parallel-plate slip-and-drag method or an equivalent apparatus, and extrudability is assessed by measuring the weight or percentage of formulation extruded from a collapsible tube under a standard applied force.

7.2 Globule Size, Zeta Potential, and Entrapment Efficiency

For nano- and microemulsion-based emulgels, additional colloidal characterization is required. Droplet or globule size and polydispersity index are determined by dynamic light scattering (photon correlation spectroscopy), while surface charge is assessed via zeta potential measurement as an indicator of physical stability against aggregation. Drug entrapment efficiency, particularly relevant to vesicular and nanosponge-based systems, is determined after separation of untrapped drug (commonly by ultracentrifugation or dialysis) followed by quantification of entrapped drug using a validated UV or HPLC assay; reported entrapment efficiencies for optimized celecoxib nanocarrier gels have reached the high nineties in percentage terms.

7.3 Rheological Behaviour

Rheological evaluation, typically performed across a range of shear rates, is used to characterize flow behaviour and confirm the pseudoplastic (shear-thinning), generally non-Newtonian character expected of a well-formulated emulgel; this behaviour is pharmaceutically desirable because it allows the product to flow readily under the shear of application (rubbing) while maintaining sufficient consistency at rest to remain on the application site without dripping.

7.4 Drug Content Uniformity

Drug content is determined by extracting a representative, accurately weighed quantity of the emulgel into a suitable solvent, followed by appropriate dilution and quantification using a validated UV spectrophotometric or HPLC method referenced against a calibration curve; reported optimized formulations have generally shown drug content in the range of approximately 95 to 99 percent of the labelled amount, confirming acceptable content uniformity and manufacturing reproducibility.

7.5 In Vitro Drug Release and Kinetic Modelling

In vitro drug release is most commonly studied using Franz diffusion cells fitted with a synthetic dialysis membrane separating the donor compartment (containing the emulgel) from a receptor compartment containing a suitable release medium (often phosphate buffer, sometimes with a solubilizer to maintain sink conditions given celecoxib's poor aqueous solubility), maintained at skin-surface temperature (32 ± 1 degrees Celsius) under continuous stirring. Aliquots withdrawn at defined time intervals are assayed, and cumulative percentage drug release is plotted against time. The resulting release data are typically fitted to standard kinetic models — zero-order, first-order, Higuchi, and Korsmeyer-Peppas — to elucidate the underlying release mechanism, with many reported NSAID emulgel systems best fitting a diffusion-controlled (Higuchi or non-Fickian Korsmeyer-Peppas) release mechanism consistent with the dual-phase (oil droplet to gel matrix to receptor) architecture of the emulgel.

7.6 Ex Vivo Skin Permeation Studies

Ex vivo permeation studies, generally conducted using excised rodent (commonly rat) or, less frequently, human or porcine skin mounted on Franz diffusion cells, provide a more physiologically relevant assessment of cutaneous drug delivery than simple membrane-based release testing. Reported ex vivo permeation of optimized celecoxib gels and emulgels has ranged widely depending on the carrier system, with values on the order of roughly 90 to 95 percent cumulative permeation over several hours reported for certain optimized nanosponge- and nanocarrier-based gels, generally exceeding the permeation achieved from plain drug suspensions or conventional gel controls, reflecting the permeation-enhancing contribution of the emulsified oil phase,

surfactant system, and any incorporated chemical enhancers.

7.7 Skin Irritation and Histopathological Evaluation

Because chronic topical application must not compromise skin integrity, dermal safety is assessed through skin irritation testing (commonly a Draize-type erythema and oedema scoring approach on animal skin) and, in several reported studies, histopathological examination of treated skin sections to confirm the absence of structural damage, inflammatory infiltrate, or other adverse tissue changes following repeated application of the optimized celecoxib formulation.

7.8 Stability Studies

Physical and chemical stability of celecoxib emulgels is evaluated under both real-time and accelerated storage conditions, generally following International Council for Harmonisation (ICH) guidance, with accelerated testing commonly performed at 40 ± 2 degrees Celsius and 75 ± 5 percent relative humidity over a period of one to six months. Formulations are periodically re-evaluated for appearance, pH, viscosity, phase separation (assessed also via centrifugation and freeze-thaw or temperature-cycling stress tests), and drug content, with an optimized nanoemulgel-type NSAID system reported to remain stable for at least six months under both $40^\circ\text{C}/75\% \text{ RH}$ and $30^\circ\text{C}/75\% \text{ RH}$ conditions in one representative published study.

7.9 Pharmacodynamic (Anti-inflammatory) Evaluation

In vivo pharmacodynamic efficacy is commonly assessed using the carrageenan-induced rat paw oedema model, in which the percentage inhibition of paw swelling following topical application of the test emulgel is compared against a marketed reference product, a plain gel control, and, where relevant, oral celecoxib. Reported comparative studies of optimized celecoxib carrier gels (including solid-dispersion-based and nanosponge-based systems) have demonstrated statistically significant ($p < 0.05$) superiority in anti-inflammatory activity relative to conventional marketed formulations, supporting the pharmacological rationale for advanced emulgel-based topical delivery.

8. Analytical Estimation of Celecoxib

8.1 UV Spectrophotometric Methods

Simple UV spectrophotometric assays remain widely used for the routine estimation of celecoxib in bulk drug and topical formulations owing to their low cost, minimal instrumentation requirements, and adequate sensitivity for quality-control purposes. Celecoxib exhibits a characteristic absorption maximum reported at approximately 251 to 252 nanometres in 0.1 N sodium hydroxide, and comparable absorption maxima have been used in methanol and other solvent systems. Reported UV methods have demonstrated linearity typically over concentration ranges spanning single-digit to low tens of micrograms per millilitre, with correlation

coefficients close to 0.999, and have been successfully applied both to celecoxib alone and, using first-derivative spectrophotometry to resolve overlapping spectra, to simultaneous estimation of celecoxib in combination with a second co-formulated drug such as diacerein, achieving mean recoveries close to 100 percent for both analytes.

8.2 High-Performance Liquid Chromatography (HPLC) Methods

Reversed-phase HPLC with UV detection provides greater selectivity and sensitivity than UV spectrophotometry and is the method of choice for estimating celecoxib in complex matrices such as skin layers, plasma, or multi-drug formulations. Reported HPLC methods for celecoxib have commonly employed C8 or C18 reversed-phase columns with mobile phases based on acetonitrile-water or methanol-acetonitrile-water mixtures, sometimes with added triethylamine or acetic acid for peak sharpening, and UV detection wavelengths in the region of 230 to 254 nanometres. A validated HPLC-UV method developed specifically for quantifying celecoxib across different layers of excised skin (stratum corneum, epidermis, and dermis) has been used to support ex vivo permeation and skin retention studies of topical celecoxib formulations, while other

validated HPLC methods have achieved limits of quantification in the low nanogram-per-millilitre range in plasma, supporting pharmacokinetic and bioequivalence studies of celecoxib following systemic or topical absorption.

8.3 Method Validation

Analytical methods developed for celecoxib estimation, whether UV or HPLC-based, are validated according to ICH Q2 guidance across the standard panel of parameters: linearity and range (typically assessed via correlation coefficient across the intended working concentration range), accuracy (assessed via recovery studies, generally targeting values close to 100 percent), precision (intra-day and inter-day, expressed as percentage coefficient of variation and generally required to remain below about 2 percent for chromatographic methods), specificity/selectivity (absence of interference from excipients or co-formulated drugs), limit of detection and limit of quantification, and robustness (tolerance to small, deliberate variations in method conditions such as mobile phase ratio, flow rate, or wavelength). Rigorous validation of the analytical method is a prerequisite for reliable quantification of drug content, in vitro release, ex vivo permeation, and stability data throughout celecoxib emulgel development.

9. Comparative Overview of Reported Celecoxib Topical Carrier Systems

Table 2: consolidates key formulation and performance characteristics reported across different celecoxib topical delivery platforms discussed in this review, illustrating the trend toward increasingly sophisticated nano- and vesicle-based emulgel architectures.

Carrier System	Key Excipients	Reported Highlights	Characterization
Conventional celecoxib gel/emulgel/cream	Carbopol 940, natural oils, essential-oil enhancers	pH $\approx 7 \pm 0.2$; comparative evaluation across gel, emulgel, and cream bases	
Celecoxib-loaded nanosponge gel	Cyclodextrin/polymer nanospheres, Carbopol gel base	Particle size ≈ 240.9 nm; zeta ≈ -1.8 mV; entrapment $\approx 98\%$; ex vivo permeation $\approx 95\%$ at 4 h	
Celecoxib nanoemulgel	Oil, Tween 80, Transcutol P, Carbopol	Droplet size 28–500 nm (DLS-confirmed); proposed for acute rheumatoid arthritis	
Celecoxib microemulsion-based gel	Oil, Smix, gel base	Ex vivo/in vivo evaluated for transdermal delivery	
Celecoxib transethosomal gel	Phospholipid, Span 60, Tween 80, sodium deoxycholate, HPMC gel	Investigated for enhanced skin permeability and localized delivery, including tumor-microenvironment studies	

10. Challenges and Future Perspectives

- Long-term physical stability of the dispersed oil/nanocarrier phase within the gel matrix, particularly resistance to Ostwald ripening, creaming, or coalescence over extended real-time storage, remains a central manufacturing challenge.
- Scale-up of high-shear homogenization or phase-titration methods used at laboratory scale to pilot and commercial manufacture, while preserving the target droplet size distribution, requires further process-engineering study.
- In vitro-in vivo correlation (IVIVC) between Franz-cell permeation data and actual clinical joint or dermal tissue drug concentrations is not yet well established for celecoxib emulgels, limiting the predictive value of standard ex vivo testing.
- Regulatory and analytical standardization of characterization methods (release testing media, membrane type, permeation protocols) across the heterogeneous set of reported celecoxib carrier systems would improve cross-study comparability.

- Further clinical evaluation, including comparative bioavailability and long-term dermal safety studies in patients, is needed to translate the promising preclinical ex vivo permeation and pharmacodynamic data into validated therapeutic products.
- Emerging carrier platforms — including transthesosomes, nanosponges, and hybrid nanoemulgel-vesicle systems — represent a promising direction for further improving celecoxib skin permeation and localized retention while minimizing systemic exposure.

Taken together, the literature indicates a clear and consistent trajectory in this field: from simple Carbopol-based celecoxib gels toward increasingly engineered nano- and vesicle-based emulgel platforms, optimized through formal statistical design of experiments and evaluated through an increasingly standardized panel of physicochemical, rheological, ex vivo permeation, stability, and pharmacodynamic tests, supported throughout by validated UV and HPLC analytical methods for accurate drug quantification.

11. CONCLUSION

The emulgel platform offers a pharmaceutically rational solution to the central formulation challenge posed by celecoxib — a highly effective but poorly water-soluble and lipophilic COX-2 inhibitor — by combining the drug-loading and permeation-enhancing capability of an emulsion with the stability, spreadability, and patient acceptability of a hydrophilic gel. A substantial and growing body of literature demonstrates that celecoxib emulgels, whether formulated conventionally or engineered as nanoemulgels, microemulsion-based gels, nanosponge-loaded gels, or transthesosomal gels, can be systematically optimized using Quality by Design principles and statistical design-of-experiments methodologies such as Box-Behnken and central composite designs to achieve target viscosity, spreadability, drug content, and release characteristics. Comprehensive physicochemical, rheological, ex vivo permeation, stability, and pharmacodynamic evaluation, underpinned by validated UV spectrophotometric and HPLC analytical methods, has consistently shown that optimized celecoxib emulgel systems outperform conventional gels and, in several studies, marketed reference products in terms of skin permeation and anti-inflammatory efficacy. Continued research addressing long-term stability, scale-up reproducibility, and clinical translation will be essential to fully realize the therapeutic potential of celecoxib topical emulgel technology as a safer, localized alternative to chronic oral NSAID therapy.

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