



Cubosomal Hydrogels in Topical Drug Delivery: Formulation Strategies, Characterization and Therapeutic Applications

Akash. A ^[1], S. Mohan Kumar ^[2], Dr. J. Karthi ^[3], Dr. S. Swarnalatha ^[4], Santhosh Kumar. G ^[5]

^[1]-8th Semester B.Pharm-Pallavan Pharmacy College.

^[2]-Department Of Pharmaceutics, Assistant Professor- Pallavan Pharmacy College.

^[3]-Department Of Pharmacognosy, Professor Cum Principal-Pallavan Pharmacy College.

^[4]-Department Of Pharmacology, Vice Principal And Head Of The Department- Pallavan Pharmacy College.

^[5]-Department Of Pharmacology, Assistant Professor- Pallavan Pharmacy College.

E-mail: sansanthosh997@gmail.com

ABSTRACT

Cubosomes are self-assembled, bicontinuous cubic liquid crystalline nanoparticles built from polar lipids such as glyceryl monooleate and phytantriol, dispersed in water with the aid of an amphiphilic stabiliser. Their internal architecture, comprising curved lipid bilayers folded around two interpenetrating aqueous channels, gives them a very large internal surface area and an unusual capacity to house hydrophilic, lipophilic and amphiphilic actives within the same particle. When these dispersions are embedded into a hydrophilic polymer network to yield a semisolid cubosomal hydrogel, or "cubogel", the resulting system combines the nanostructural advantages of cubosomes with the ease of application, spreadability and residence time expected of a conventional topical gel. This review brings together the current understanding of cubosome self-assembly and phase behaviour, the top-down and bottom-up routes used to manufacture them, the polymeric strategies used to convert them into hydrogels, and the physicochemical toolbox, ranging from dynamic light scattering to small-angle X-ray scattering, cryogenic electron microscopy and Franz-cell permeation studies, that is used to characterise them. The therapeutic applications discussed span antifungal and antimicrobial cubogels, anti-inflammatory and analgesic formulations, wound and burn dressings, antioxidant and cosmeceutical preparations, and emerging anticancer and receptor-targeted topical systems. Safety, stability and scale-up considerations that continue to limit clinical translation are also examined, together with directions in which the field appears to be moving, including stimuli-responsive and ligand-decorated cubogels.

1. Introduction

Topical drug delivery remains one of the most attractive non-invasive routes for treating localised cutaneous and mucocutaneous disease, largely because it allows a therapeutic concentration to be built up directly at the site of pathology while sparing the rest of the body from unnecessary drug exposure. Conventional creams, ointments and gels have served this purpose for decades, yet they are frequently let down by the same handful of problems: poor aqueous solubility of many actives, inconsistent and often shallow penetration across the stratum corneum, rapid wash-off or evaporation from the skin surface, and a need for frequent reapplication that erodes patient adherence. These shortcomings have pushed formulation scientists toward nanostructured carriers, liposomes, niosomes, transfersomes, solid lipid nanoparticles and, more recently, cubosomes, that can be engineered to overcome one or more of these barriers simultaneously.[1]

Among these carriers, cubosomes occupy a distinctive niche. They are dispersed fragments of a bicontinuous cubic lyotropic liquid crystalline phase, a thermodynamically stable, highly ordered lipid-water mesophase that forms spontaneously when certain amphiphilic lipids are hydrated beyond a critical water content. Because the resulting particles are optically isotropic, mechanically rigid relative to vesicular carriers, and possess an extraordinarily large internal interfacial area, they have attracted growing interest not only in pharmaceuticals but also in the cosmeceutical industry, where the same structural features are exploited to improve the delivery of actives used in skin care.[2]

A cubosomal dispersion on its own, however, is a low-viscosity, free-flowing fluid, which is rarely convenient for application to skin, mucosa or a wound bed. Incorporating the dispersion into a hydrogel matrix, most often using Carbopol, hydroxypropyl methylcellulose, chitosan, xanthan gum, or a thermoreversible poloxamer network, converts it into a semisolid "cubogel" that can be spread, retained at the site of application, and that releases the encapsulated drug in a controlled fashion from a reservoir of intact cubic nanoparticles. This review focuses specifically on this cubosomal hydrogel format, tracing the formulation logic from lipid selection through to the hydrogel matrix, summarising the analytical methods used to confirm that the intended nanostructure has actually been achieved, and surveying the therapeutic areas in which cubogels have been investigated over the past decade.

2. The Skin Barrier and the Rationale for Liquid Crystalline Carriers

The stratum corneum is the principal obstacle to topical drug absorption. Its brick-and-mortar arrangement of corneocytes embedded in a lamellar lipid matrix of ceramides, cholesterol and free fatty acids is deliberately built to keep hydrophilic and many amphiphilic molecules out, while only modestly lipophilic, low-molecular-weight compounds are able to partition through it at an appreciable rate. Several authors working on cubosomal wound-healing and burn formulations have pointed out that the internal lipid organisation of a cubosome bears a structural resemblance to the lamellar packing of stratum corneum lipids, and have proposed that this similarity facilitates fusion or intimate contact between the cubosome bilayer and the skin lipids, thereby promoting drug entry into and across the epidermis.[3,4]

Beyond this structural argument, the bioadhesive character of the cubic phase, its viscosity and stickiness relative to a simple aqueous solution, allows cubosomal formulations to remain in contact with the skin or mucosal surface for longer than a conventional cream, reducing wash-off and, in principle, the frequency of reapplication needed to sustain a therapeutic effect. The very large internal surface area created by the two interpenetrating aqueous channels of the cubic phase also gives these carriers an unusually high loading capacity for both water-soluble and lipid-soluble drugs, which is of particular value for actives that are otherwise difficult to formulate because of poor solubility in either phase alone.

3. Cubosomes: Origin, Composition and Structural Organisation

3.1 Lipid Building Blocks: Monoolein and Phytantriol

Cubosome formation depends on the use of an amphiphilic lipid capable of adopting a bicontinuous cubic mesophase on hydration. In practice, the field has converged almost entirely on two materials: glyceryl monooleate (GMO, also called monoolein) and phytantriol.[5,6] GMO is an unsaturated monoglyceride derived from oleic acid that is inexpensive, generally regarded as safe and widely used as a food and pharmaceutical excipient, but its ester linkage renders it susceptible to enzymatic hydrolysis by esterases and lipases, which can compromise the integrity of the cubic phase in biological environments over time. Phytantriol, an isoprenoid triol used extensively in cosmetics, lacks this ester bond and is therefore chemically more robust, maintaining its liquid crystalline structure across a wider range of conditions and storage times, although it tends to be more costly and, being of non-glyceride structure, is not always interchangeable with GMO in an existing formulation.[6,7] Both lipids exhibit closely related phase behaviour in water: at low hydration they form a lamellar phase, and as water content increases they pass through one or more cubic phases before eventually reaching a hexagonal or micellar phase at very high dilution and temperature.

3.2 Cubic Mesophases and Their Symmetry

Three cubic space groups are most commonly reported for GMO- and phytantriol-based systems: Pn3m (the double-diamond structure), Ia3d (the gyroid structure) and Im3m (the primitive structure). Each of these arrangements consists of a continuous, curved lipid bilayer folded into a triply periodic surface that separates two non-intersecting, interwoven aqueous channel networks, hence the description of cubosomes as bicontinuous. This honeycomb-like internal geometry, confirmed principally by small-angle X-ray scattering and cryogenic transmission electron microscopy, is what gives cubosomes their exceptionally large internal surface-to-volume ratio compared with lamellar vesicular systems such as liposomes.[8,9] The particular cubic phase that forms, and the lattice parameter of that phase, depend on the lipid used, the water content, temperature, and the presence of the stabiliser and any solubilised drug, all of which can subtly swell or shrink the unit cell and, in some cases, drive a transition from one cubic symmetry to another.[10] Because the dispersed cubosome particles are prepared by fragmenting this bulk cubic gel phase (or by assembling it directly from a precursor solution) in the presence of a colloidal stabiliser, the resulting nanoparticles retain the internal cubic order of the parent mesophase while behaving, at the macroscopic level, as a pourable colloidal dispersion rather than a rigid gel.

4. Preparation of Cubosomes

Two broad manufacturing philosophies are used to convert the bulk cubic phase into a stable, sub-micron colloidal dispersion suitable for pharmaceutical use: top-down fragmentation of the pre-formed cubic gel, and bottom-up self-assembly directly from a molecularly dissolved precursor.

4.1 Top-Down Approaches

The most widely used top-down method begins by melting the lipid, or heating it together with the drug, and mixing it with an aqueous solution of the stabiliser to form a coarse, viscous cubic gel. This bulk gel is then broken down into nanoparticles by applying high mechanical energy, typically through high-pressure homogenisation, probe sonication, or a combination of the two. In the preparation of flurbiprofen-loaded ocular cubosomes, for example, hot high-pressure homogenisation was used to yield particles of roughly 150 nm with a bicontinuous cubic P-type structure confirmed by cryo-TEM and SAXS.[11] Amphotericin B-loaded phytantriol cubosomes intended for oral administration were likewise optimised by systematically varying homogenisation pressure and cycle number, with 1200 bar and nine cycles giving the narrowest particle size distribution around 257 nm.[12] For dermatological actives, simple emulsification of the melted lipid and stabiliser followed by probe sonication is common, as illustrated by the preparation of clotrimazole cubosomal dispersions from glyceryl monooleate and poloxamer 407.[13] Top-down methods are attractive because they are conceptually

simple and scale reasonably well to laboratory and pilot-plant volumes, but the high shear and, in some variants, elevated temperatures involved make them less suitable for fragile biological payloads such as peptides, proteins or nucleic acids.

4.2 Bottom-Up Approaches

Bottom-up strategies avoid the harsh mechanical step altogether by dissolving the lipid in a water-miscible solvent or hydrotrope, such as ethanol, polyethylene glycol 200 or propylene glycol, and then diluting this precursor solution into an aqueous phase containing the stabiliser. As the solvent disperses into the bulk water, the lipid self-assembles directly into cubic nanoparticles without the need for sonication or homogenisation, a solvent precursor dilution approach that has been used successfully to encapsulate the fragile protein antigen ovalbumin within phytantriol and GMO cubosomes for vaccine delivery research.[14] More recently, microfluidic platforms have been used to generate lyotropic liquid crystalline nanoparticles from monoolein and phytantriol under precisely controlled, continuous flow conditions, offering better batch-to-batch reproducibility, narrower particle size distributions and, in principle, a more scalable route than either conventional top-down or solvent-dilution bottom-up methods.[15] Bottom-up methods generally produce smaller and more uniform particles at the laboratory scale, but residual organic solvent, and the comparatively low throughput of some microfluidic set-ups, remain practical concerns.

4.3 Role of Colloidal Stabilisers

Regardless of the manufacturing route chosen, an amphiphilic polymeric stabiliser is essential to prevent the nascent cubic nanoparticles from aggregating or coalescing back into the bulk gel phase. The triblock copolymer poloxamer 407, chemically identical to Pluronic F127, is by far the most frequently used stabiliser; its central hydrophobic poly(propylene oxide) block anchors into the outer lipid layer of the cubosome while the flanking hydrophilic poly(ethylene oxide) chains extend into the surrounding water, providing steric stabilisation and, to some extent, a stealth-like surface that can reduce opsonisation.[16] Optimising the ratio of lipid to stabiliser, and the stabiliser concentration itself, has repeatedly been shown to influence both particle size and encapsulation efficiency, as demonstrated in a full factorial study of phycocyanin-loaded cubosomes in which the lipid-to-poloxamer ratio was tuned to obtain particles of approximately 183 nm with an encapsulation efficiency above 87%.[17] It is worth noting that concerns have emerged in the wider nanomedicine literature about pre-existing anti-polyethylene glycol antibodies in some patients, which has prompted exploratory work on alternative, non-PEG stabilisers, although poloxamer- and Pluronic-based systems remain the default choice in almost all of the topical cubosome literature reviewed here.[16]

5. From Cubosomal Dispersions to Cubosomal Hydrogels (Cubogels)

5.1 Rationale for Gelling Cubosomal Dispersions

A freshly prepared cubosomal dispersion is, in most cases, a thin, milky, low-viscosity liquid. While this is entirely acceptable for parenteral or ocular use, where drops or thin films are the norm, it is poorly suited to application on intact skin, an open wound or a mucosal surface, all of which benefit from a semisolid vehicle that resists gravity-driven run-off, spreads evenly, and stays where it is placed for long enough to deliver a meaningful dose. Embedding the cubosomal dispersion within a hydrophilic polymer network converts it into a cubogel that behaves, on application, much like a conventional hydrogel, while the drug itself remains sequestered within the intact cubic nanoparticles distributed throughout the gel matrix. This arrangement is generally reported to provide slower, more sustained drug release than either a plain drug-loaded hydrogel or a simple cubosomal dispersion applied directly, because the drug must first diffuse out of the cubic lattice before it can partition into and across the gel network.[4,18]

5.2 Common Gel-Forming Systems

Carbopol 940, a cross-linked polyacrylic acid polymer, is the most frequently reported gelling agent for cubogels intended for cutaneous use, owing to its favourable rheological profile, ease of neutralisation to a skin-compatible pH, and long track record as a topical excipient. It has been used, for instance, to convert silver N-heterocyclic carbene-loaded cubosomes into a burn-wound cubogel and to gel an N-alkylated benzimidazole cubosomal formulation developed for the same indication.[18,19] Other polymers reported in the literature include hydroxypropyl methylcellulose, chitosan (including mannosylated chitosan used for active targeting, discussed further below), xanthan gum and combinations of these, the choice generally being guided by the desired viscosity, mucoadhesive strength, and compatibility with the intended anatomical site. For mucosal and ocular applications, thermosensitive or ion-sensitive in situ gelling systems built from poloxamer and hyaluronic acid have also been combined with cubosomes, allowing a formulation that is a free-flowing liquid at room temperature to gel spontaneously on contact with the warmer, ionically richer environment of the eye or vaginal mucosa.[22]

5.3 Representative Cubogel Formulations

A useful illustration of the format comes from work on simvastatin, where cubosomes prepared by a top-down method and characterised for particle size, entrapment efficiency and sustained release were subsequently incorporated into a cubogel using different gelling agents; the optimised cubogel displayed pseudoplastic rheological behaviour and achieved considerably higher ex vivo skin flux than a conventional simvastatin hydrogel.[4] A comparable strategy was used for hesperidin, where the resulting cubogel supported near-complete closure of full-thickness wounds in an animal model within two

weeks, outperforming the untreated control.[21] Silver-based organometallic complexes loaded into cubosomes and gelled with Carbopol 940 produced a burn-wound cubogel with high entrapment efficiency, sustained drug release over 24 hours, and superior healing outcomes relative to two marketed burn products in an in vivo comparison.[18] Vaginal and ocular mucosal cubogels built around fenticonazole and voriconazole, respectively, further demonstrate how the same underlying platform, an emulsified GMO- or phytantriol-based cubosomal core stabilised with poloxamer, can be adapted to very different anatomical targets simply by changing the gel-forming excipient and the route-specific characterisation panel applied to it.[22,23] Perhaps the most sophisticated example to date combines a cubosomal core with an active-targeting ligand: berberine hydrochloride cubosomes coated with mannosylated chitosan were designed so that the mannose units on the particle surface would be recognised by mannose receptors on activated wound-site macrophages, in principle directing the anti-inflammatory and antibacterial payload preferentially to the cells most responsible for driving chronic wound inflammation.[24]

6. Characterization of Cubosomes and Cubosomal Hydrogels

Because the therapeutic promise of a cubosomal hydrogel rests entirely on the assumption that an intact, bicontinuous cubic nanostructure has actually formed and survived incorporation into the gel, a fairly extensive analytical panel is routinely applied at both the cubosome and the cubogel stage.

6.1 Particle Size, Polydispersity and Zeta Potential

Dynamic light scattering is the standard first-pass technique for estimating the hydrodynamic diameter and polydispersity index of a cubosomal dispersion, with reported mean sizes for topical formulations typically falling somewhere between 50 and 300 nm, depending on lipid-to-stabiliser ratio and the energy input used during manufacture.[13,17,36] Because DLS assumes spherical, non-interacting scatterers and can be misled by even a small population of larger aggregates or vesicular by-products, its results are usually cross-checked against microscopy, and its practical detection limits relative to complementary techniques such as UV-visible spectroscopy have themselves been the subject of dedicated methodological study.[25] Zeta potential, measured by electrophoretic light scattering, provides an indirect measure of surface charge and, by extension, the electrostatic contribution to colloidal stability; most GMO- and phytantriol-based cubosomes carry a moderate negative charge, typically in the range of minus 15 to minus 30 millivolts, sufficient to resist aggregation when combined with the steric stabilisation provided by the poloxamer corona.[11,26]

6.2 Morphological Analysis

Polarised light microscopy is often used as an early, low-cost screen, since an isotropic cubic phase should appear dark under crossed polarisers, in contrast to the characteristic birefringence of a lamellar or hexagonal phase; this test was applied, for example, to confirm cubic phase formation in dexamethasone acetate cubosomes before more detailed structural work was undertaken.[10] Transmission electron microscopy and, more informatively, cryogenic TEM are used to visualise individual particles without the drying artefacts associated with conventional negative staining, typically revealing faceted particles with the characteristic internal honeycomb texture expected of a bicontinuous cubic structure.[9,11] Atomic force microscopy has also been used as a complementary surface-imaging technique, as in the characterisation of flurbiprofen cubosomes, where AFM-measured particle heights were consistent with the sizes obtained independently by DLS and cryo-TEM.[11]

6.3 Internal Nanostructure by Small-Angle X-Ray Scattering

Small-angle X-ray scattering is generally regarded as the definitive method for confirming which cubic space group, Pn3m, Ia3d or Im3m, is actually present in a given formulation, since the ratios of the Bragg peak positions in a SAXS pattern are diagnostic of a specific crystallographic symmetry and allow the lattice parameter of the mesophase to be calculated directly. SAXS is typically used alongside cryo-TEM, with the X-ray data providing a statistically averaged, bulk view of the ordered structure across the whole sample while cryo-TEM offers a real-space view of individual particles, the two techniques together giving a much more convincing structural picture than either alone.[9,26] SAXS has also proved useful for confirming that structural order is retained, or has changed, on storage or after encapsulation of a new active, as shown in a study of porphyrin-loaded cubosomes in which repeated SAXS measurements over a two-week period showed no change in diffraction pattern, supporting the structural stability of the formulation.[26]

6.4 Thermal and Spectroscopic Analysis

Differential scanning calorimetry is commonly used to detect any thermal transitions associated with the lipid, the drug, or a drug-lipid interaction, and can provide indirect evidence that a drug has been successfully incorporated into the lipid bilayer rather than remaining as free, untrapped crystalline material. Fourier-transform infrared spectroscopy is used in a similar, complementary role, screening for shifts in characteristic absorption bands that would indicate chemical interaction, or the absence of interaction, between drug and excipients; both techniques were applied together in the characterisation of dexamethasone acetate cubosomes and their gel.[10]

6.5 Entrapment Efficiency and Drug Loading

Entrapment efficiency is usually determined by separating untrapped drug, by ultracentrifugation, dialysis or filtration, from the cubosomal fraction and quantifying the free fraction by an appropriately validated HPLC or UV-spectrophotometric assay, with the entrapped percentage then calculated by difference. Reported entrapment efficiencies for topical cubosomal actives are frequently very high, often exceeding 85 to 95%, reflecting the large internal lipid volume available for lipophilic drug solubilisation and, for surface-active or amphiphilic molecules, the additional binding available at the extensive lipid-water interface.[4,18,23]

6.6 Rheology and Textural Properties

Once the cubosomal dispersion has been incorporated into a gel base, rheological characterisation becomes essential, both to confirm that the semisolid has the flow behaviour expected of a topical product and to relate that behaviour to expected in-use performance. Most cubogels display pseudoplastic, shear-thinning flow with a measurable yield stress, a profile that is generally considered favourable for topical use because it allows the product to be extruded and spread easily under the shear applied during application while resisting flow and remaining in place once shear is removed.[4,38] Spreadability, extrudability, and, where relevant to the intended use, mucoadhesive strength are also frequently assessed as part of the same evaluation package.[18]

6.7 In Vitro Release and Ex Vivo Permeation

Drug release from cubogels is typically studied using a Franz diffusion cell fitted with a synthetic dialysis membrane, generating a cumulative release profile that is then fitted to kinetic models such as zero-order, first-order, Higuchi or Korsmeyer-Peppas equations to infer the dominant release mechanism. Ex vivo skin permeation studies, most often performed with excised rat, rabbit or porcine skin mounted in a Franz cell, extend this analysis to measure steady-state flux and cumulative drug permeated across a biological membrane, and are usually accompanied by a parallel measurement of drug retained within the skin itself, a parameter of particular interest for topical, as opposed to transdermal, therapeutic goals. In the simvastatin cubogel study, for example, ex vivo permeation through excised rat skin gave a flux roughly 1.8-fold higher than that of a conventional simvastatin hydrogel.[4] Similar Franz-cell approaches were used to demonstrate enhanced transcorneal flux for voriconazole cubosomes and enhanced cutaneous flux for felbinac cubosomal gel relative to their respective plain-drug comparators.[22,36]

6.8 Stability, pH and Skin Tolerability

Physical stability is generally monitored over weeks to months by tracking changes in particle size, polydispersity, zeta potential and, where SAXS access is available, the persistence of the original diffraction pattern, since aggregation, Ostwald ripening or a mesophase transition can each compromise performance without necessarily being visible to the naked eye.[17,26] For cutaneous and mucosal cubogels, formulation pH is adjusted to match, as closely as practicable, the physiological pH of the intended application site, and skin or mucosal tolerability is assessed either through the Draize test in animal models or through histopathological examination of treated tissue, both of which have generally reported cubogels to be at least as well tolerated as, and in several comparative studies better tolerated than, the corresponding marketed cream or plain gel.[11,13,18]

7. Therapeutic Applications of Cubosomal Hydrogels in Topical Delivery

7.1 Antifungal and Antimicrobial Applications

Superficial and mucocutaneous fungal infections have been one of the most consistently studied applications for cubosomal delivery, largely because so many antifungal actives, azoles in particular, are poorly water-soluble and benefit from the solubilising lipid environment a cubosome provides. Clotrimazole, formulated as a skin-retentive cubosomal dispersion from glyceryl monooleate and poloxamer 407, achieved markedly higher skin retention than a marketed clotrimazole cream while producing superior in vivo antifungal activity against *Candida albicans* in a rat model, with no greater irritation than the comparator cream.[13] Itraconazole and fluconazole have each been formulated as cubosomal gels for candidiasis, with the fluconazole work demonstrating that cubosomal encapsulation could improve cutaneous antifungal performance relative to conventional fluconazole delivery.[28,29,30] Beyond the skin, the same platform has been extended to other mucosal surfaces: a voriconazole cubosome incorporated into a hyaluronic acid-poloxamer in situ gel produced a substantial increase in transcorneal flux and antifungal inhibition zone relative to a simple voriconazole dispersion, addressing the considerable unmet need for effective topical therapy of fungal keratitis, while a fenticonazole nitrate cubogel developed for vaginal candidiasis achieved high entrapment efficiency and favourable particle characteristics after formal optimisation.[22,23] These results sit within a broader clinical context in which azole and allylamine antifungals such as miconazole and terbinafine remain first-line topical therapy for dermatophyte and candidal skin infections, but where inconsistent cutaneous retention and the emergence of resistant strains continue to motivate the search for improved delivery vehicles.[31,32]

7.2 Anti-Inflammatory and Analgesic Applications

Non-steroidal anti-inflammatory drugs were, historically, among the earliest actives explored in cubosomal form, with an early study on indomethacin-loaded cubosome dispersions establishing the feasibility of percutaneous cubosomal delivery for this drug class.[33] Diclofenac sodium and ketorolac

have subsequently been formulated as cubosomes for percutaneous and ocular anti-inflammatory use respectively, while capsaicin, a lipophilic counter-irritant used for topical analgesia, was shown to achieve targeted, sustained transdermal delivery when incorporated into a cubosomal carrier.[34,35,39] More recent work has moved specifically into the cubogel format for localised pain and soft-tissue injury: a felbinac-loaded cubosomal gel produced significantly greater cutaneous drug flux and faster functional recovery, measured using the sciatic function index, than a plain felbinac gel in a rat model of soft-tissue injury, with corroborating histological evidence of reduced tissue damage.[36] A separate felbinac cubosomal hydrogel developed specifically for inflammatory pain showed anti-inflammatory activity persisting for up to 24 hours after a single application, compared with roughly six hours for a conventional felbinac gel, alongside histological evidence of reduced polymorphonuclear infiltration.[37] Nimesulide has also been optimised as a cubosomal gel using a factorial design approach, achieving sustained release over 24 hours and superior ex vivo absorption through goat skin compared with a commercial nimesulide gel.[38] Collectively, these studies suggest that the sustained-release character of the cubogel format may be particularly well suited to conditions, such as localised musculoskeletal pain, where prolonged drug residence at the site of inflammation is more valuable than a rapid initial burst of drug release.

7.3 Wound Healing and Burn Management

Wound and burn care has emerged as one of the most active areas of cubogel research, in part because the moist, occlusive environment provided by a hydrogel dressing is independently beneficial to healing, and in part because many of the actives under investigation, statins, silver complexes, flavonoids and alkaloids among them, are otherwise difficult to deliver effectively to a wound bed. Simvastatin, repurposed for its pro-angiogenic and wound-healing properties, was formulated into a cubogel that achieved significantly greater wound closure than both a plain simvastatin hydrogel and an untreated control in a rat wound model.[4] A silver(I) N-heterocyclic carbene complex loaded into a Carbopol-gelled cubosomal system produced superior burn-wound healing and reduced infection compared with two marketed burn treatments in an in vivo comparison, with sustained drug release over 24 hours.[18] An N-alkylated benzimidazole compound formulated as a cubogel similarly achieved complete closure of experimental burn wounds within 12 to 16 days in a rabbit model, outperforming clotrimazole and a marketed polymyxin-based ointment, and was reported to cause less irritation than either comparator.[19] Hesperidin, a citrus-derived flavonoid with recognised anti-inflammatory and antioxidant activity, achieved a wound closure rate approaching 99% after 14 days when delivered as a cubogel, compared with roughly 89% in the control group, in a full-thickness wound model.[21] The most mechanistically ambitious of these systems combines berberine hydrochloride cubosomes with a mannosylated chitosan coating designed to target mannose receptors on wound-associated macrophages, an approach intended to concentrate the anti-inflammatory and antimicrobial payload precisely at the immune cells that govern the transition from the inflammatory to the proliferative phase of healing, and one that illustrates how surface functionalisation is beginning to move cubogel design beyond simple passive drug encapsulation.[24]

7.4 Antioxidant, Anti-Ageing and Cosmeceutical Applications

The cosmeceutical industry adopted cubosomal technology relatively early, drawn by the same large internal surface area and controlled-release character that appeals to pharmaceutical formulators, but applied here to actives intended to improve skin appearance and resist oxidative and photo-ageing damage. Alpha-lipoic acid formulated as a liquid crystalline nanostructured dispersion has been evaluated clinically for anti-wrinkle cosmeceutical use, illustrating the crossover between pharmaceutical-grade characterisation and cosmetic product development in this space.[40] More recently, phycocyanin, a hydrophilic, oxidation-sensitive protein antioxidant derived from cyanobacteria, was encapsulated in GMO-poloxamer 407 cubosomes to protect it from degradation and improve its transdermal permeation; the resulting cubosomes not only achieved sustained release and enhanced ex vivo skin permeation but also protected cultured keratinocytes from hydrogen peroxide-induced oxidative damage in vitro, supporting the concept of cubosomal delivery as a strategy for stabilising and delivering fragile natural antioxidants topically.[17] For context, other nanocarrier platforms, including niosomal gels developed for curcumin, have pursued broadly similar anti-inflammatory and antioxidant goals for topical use, underscoring that cubosomes compete within a wider and increasingly crowded field of lipid-based nanocarriers rather than occupying an entirely unique therapeutic space.[41]

7.5 Anticancer and Targeted Topical Applications

Topical and locoregional application of cubosomal carriers has also been explored for oncological indications affecting accessible epithelial surfaces. Curcumin, a poorly soluble polyphenol with well-documented antiproliferative activity in vitro, was loaded into cubosomes intended for topical treatment of cervical cancer, an application that depends on the carrier's ability to improve both the solubility and the local tissue penetration of the drug across mucosal epithelium.[42] Targeting strategies originally developed for systemic oncology applications are also beginning to inform topical cubogel design: cubosomes surface-functionalised with Affimer proteins directed against carcinoembryonic antigen showed preferential accumulation in antigen-expressing colorectal cancer cells both in vitro and in a mouse xenograft model, with low off-target toxicity, demonstrating that active targeting ligands can be successfully conjugated to the cubosome surface without disrupting the underlying cubic nanostructure, a principle that is directly transferable to receptor-targeted topical cubogels for cutaneous and mucosal malignancies.[43]

7.6 Other Applications Illustrating Platform Versatility

A number of additional studies, while not always targeting classical topical indications, illustrate the breadth of drug classes that have been successfully accommodated within cubosomal or cubogel systems. Atazanavir, an antiretroviral protease inhibitor, has been formulated as a cubosomal gel and evaluated both in vitro and ex vivo.[44] Resveratrol, a lipophilic polyphenol with antioxidant and chemopreventive properties, has been developed as a

topical cubosomal nanoformulation.[45] Gliclazide, an oral antidiabetic sulfonylurea, has been formulated as a cubosomal nanoparticle system to improve its oral bioavailability, a non-topical application included here to underline that the fundamental cubosome platform is adaptable well beyond the skin, with the gel-forming step being the principal formulation lever that redirects the same underlying nanoparticle toward a cutaneous, mucosal, ocular or oral therapeutic goal.[46] A corticosteroid cubosomal formulation developed for ocular drug delivery further reflects this cross-route adaptability, extending the platform's reach into anti-inflammatory ophthalmic therapy using the same lipid and stabiliser chemistry described throughout this review.[47]

8. Safety, Toxicity and Biocompatibility Considerations

The lipids most commonly used to build cubosomes, glyceryl monooleate and phytantriol, are both established pharmaceutical and cosmetic excipients with long histories of topical and, in the case of GMO, oral use, and are generally regarded as biocompatible and biodegradable.[6] Direct toxicological data specific to cubosomal formulations remain comparatively sparse relative to the volume of formulation and efficacy work, but the skin irritation, Draize and histopathological assessments incorporated into most of the studies discussed above have consistently reported cubogels to be at least as well tolerated as, and frequently better tolerated than, the corresponding marketed comparator product, an encouraging if still preliminary signal.[13,18,19] The principal chemical liability specific to GMO-based systems is the ester bond's susceptibility to esterase- and lipase-mediated hydrolysis, which could in principle compromise formulation integrity in the presence of skin surface lipases or wound exudate enzymes, a consideration that has motivated the increasing use of phytantriol, or of GMO-phytantriol blends, in formulations intended for prolonged residence on compromised or wounded skin.[6] At the excipient level, the poloxamer 407 stabiliser that dominates the cubosome literature is itself well characterised pharmacologically and generally considered safe at the concentrations used, although the broader nanomedicine literature has begun to flag the theoretical possibility of pre-existing anti-polyethylene glycol antibodies affecting the pharmacokinetics or tolerability of PEGylated nanocarriers in a subset of patients, a consideration that will likely need to be addressed as cubosomal products move closer to clinical and regulatory scrutiny.[16,27]

9. Translational and Regulatory Challenges

Despite an increasingly large and favourable body of preclinical evidence, no cubosomal hydrogel product has yet achieved widespread clinical or regulatory approval as a prescription topical medicine, and the gap between laboratory-scale formulation success and a commercially viable, regulator-ready product remains considerable. Scale-up is one recurring obstacle: high-pressure homogenisation and probe sonication, the two most commonly used top-down manufacturing steps, are well suited to small research batches but require careful re-engineering, and consistent quality-by-design validation, to be reproduced reliably at pilot and commercial scale, while microfluidic bottom-up methods, though promising for reproducibility, currently offer more limited throughput.[15,16] Long-term physical stability is a second concern, since the metastable, sterically stabilised colloidal state of a cubosome is inherently more susceptible to particle growth, aggregation or an unwanted mesophase transition over extended storage than is, for example, a simple polymeric solution, making robust accelerated and real-time stability data an essential, and sometimes underreported, part of any translational package.[16,26] Finally, the analytical burden associated with confirming and monitoring the cubic nanostructure, particularly the reliance on small-angle X-ray scattering, which requires specialised synchrotron or laboratory SAXS instrumentation not routinely available in a standard quality-control laboratory, adds cost and complexity to batch release testing relative to conventional semisolid dosage forms, and will need to be addressed through the development of simpler, validated surrogate release or structural specifications before cubogels can be manufactured and released under standard pharmaceutical quality systems.

10. Future Perspectives

Several directions currently emerging in the literature seem likely to shape the next phase of cubosomal hydrogel development. Active targeting, already demonstrated with mannosylated chitosan-coated berberine cubosomes directed at wound macrophages and with Affimer-functionalised cubosomes directed at tumour-associated antigens, is likely to be extended to other receptor systems relevant to cutaneous disease, including targets expressed on activated keratinocytes in psoriasis or on specific immune cell populations in chronic inflammatory dermatoses.[24,43] Stimuli-responsive cubosomes, engineered to alter their release profile in response to a local trigger such as pH, temperature or an enzyme characteristic of infected or inflamed tissue, represent a second promising avenue, offering the possibility of on-demand rather than purely passive sustained release.[16] On the manufacturing side, continued refinement of microfluidic and other continuous bottom-up processes, potentially supported by quality-by-design and machine-learning-assisted formulation optimisation, may help close the scale-up gap that currently separates most cubogel research from commercial reality.[15] Finally, broader adoption of complementary, side-by-side structural and biological characterisation, combining SAXS or cryo-TEM confirmation of nanostructure with rigorous, standardised ex vivo permeation and in vivo efficacy comparisons against currently marketed products, will be necessary to build the kind of consistent, comparable evidence base that regulators and clinicians will ultimately need before cubosomal hydrogels can move from an active academic research topic to an established topical dosage form.

11. Conclusion

Cubosomal hydrogels bring together two well-established but previously separate ideas, the bicontinuous cubic liquid crystalline nanoparticle and the conventional semisolid hydrogel, into a single delivery platform that appears to offer genuine, measurable advantages for topical therapy: high drug

loading and entrapment efficiency regardless of a drug's polarity, sustained and often prolonged release relative to plain drug or plain hydrogel comparators, and improved cutaneous or mucosal retention that has translated, across a wide range of studies spanning antifungal, anti-inflammatory, wound-healing, antioxidant and anticancer applications, into better ex vivo permeation and, where tested, better in vivo therapeutic outcomes than existing marketed products. The manufacturing toolkit available to build these systems, spanning simple emulsification through to high-pressure homogenisation, solvent precursor dilution and microfluidics, together with an increasingly sophisticated analytical panel built around SAXS, cryo-TEM and Franz-cell permeation studies, has matured considerably over the past decade. What remains is the harder work of translation: demonstrating robust, reproducible manufacturing at scale, generating the long-term stability and safety data that regulators will require, and simplifying the analytical burden associated with routine quality control, all of which will determine whether cubosomal hydrogels move from a productive academic research theme into a genuinely new class of topical medicine.

Acknowledgments:

I would like to acknowledge the Tamil Nadu chemists and druggist educational trust (TNCDE) and Pallavan pharmacy college for their extended support.

Disclosure of conflict of interest:

There is no conflict of interest.

Author contribution:

AKASH. A had principal responsibility for the conception, design of the study and drafting of manuscript. Santhosh Kumar.G was responsible for the revision of the manuscript for important intellectual content, S. Mohan Kumar, Dr. J. Karthi, Dr. S. Swarnalatha contributed towards reviewing of the literature. All authors agreed on the final version of manuscript.

References

1. Chandrakala V. Cubosomes: a boon for cosmeceuticals and topical drug delivery. *Int J Pharm Pharm Sci*. 2022.
2. Nath B, et al. Recent advances in the use of cubosomes as drug carriers with special emphasis on topical applications. *J Lipids*. 2024;2024:2683466. doi:10.1155/2024/2683466.
3. Sivadasan D, Sultan MH, Alqahtani SS, Javed S. Cubosomes in drug delivery—a comprehensive review on its structural components, preparation techniques and therapeutic applications. *Biomedicines*. 2023;11(4):1114. doi:10.3390/biomedicines11041114.
4. Formulation and evaluation of simvastatin cubosomal nanoparticles for assessing its wound healing effect. *Sci Rep*. 2023. doi:10.1038/s41598-023-44304-2.
5. Development of N-alkylated benzimidazole based cubosome hydrogel for topical treatment of burns. *RSC Adv*. 2024. doi:10.1039/D4RA04816D.
6. Phytantriol-based lyotropic liquid crystal (latanoprost cubosomes) as a transdermal/ocular delivery system. *Int J Pharm*. 2018.
7. Design and manufacturing of monodisperse and malleable phytantriol-based cubosomes for drug delivery applications. *Int J Pharm X / Colloids Surf B*. 2020.
8. Cubosomes: remarkable drug delivery potential. *Drug Discov Today*. 2016.
9. A versatile nanocarrier—cubosomes, characterization, and applications. *Pharmaceutics*/PMC9268278. 2022.
10. Cubosome topologies at various particle sizes and crystallographic symmetries; dexamethasone acetate cubosomes as a potential transdermal delivery system for treating skin inflammation.
11. Novel vehicle based on cubosomes for ophthalmic delivery of flurbiprofen with low irritancy and high bioavailability. *Acta Pharmacol Sin*. 2010.
12. Cubosomes as targeted drug delivery systems—a biopharmaceutical approach (Amphotericin B phytantriol cubosomes).
13. Omar S, Ismail A, Hassanin K, Hamdy S. Formulation and evaluation of cubosomes as skin retentive system for topical delivery of clotrimazole. *J Adv Pharm Res*. 2019;3(2):68-82. doi:10.21608/aprh.2019.9839.1079.
14. Preparation of phytantriol cubosomes by solvent precursor dilution for the delivery of protein vaccines. *Int J Pharm*. 2011.
15. Formation of particulate lipid lyotropic liquid crystalline nanocarriers using a microfluidic platform. *Int J Pharm*. 2022.
16. Lipid cubosome nanoparticles for drug delivery. *Nanotoxicology*. 2025. doi:10.1080/17435889.2025.2567841.
17. Improving the stability and transdermal permeability of phycocyanin loaded cubosomes. *Front Nanotechnol*. 2024. doi:10.3389/fnano.2024.1359219.
18. Cubosomes hydrogel containing silver based organometallic compounds for enhanced wound healing of burns: in vitro and in vivo studies. 2024.
19. Development of N-alkylated benzimidazole based cubosome hydrogel for topical treatment of burns. *RSC Adv*. 2024. doi:10.1039/D4RA04816D.

20. Formulation and evaluation of simvastatin cubosomal nanoparticles for assessing its wound healing effect. *Sci Rep*. 2023. doi:10.1038/s41598-023-44304-2.
21. Hesperidin-loaded cubogel as a novel therapeutic armamentarium for full-thickness wound healing. *Colloids Surf B Biointerfaces*. 2023.
22. Development and optimization of hyaluronic acid-poloxamer in-situ gel loaded with voriconazole cubosomes for enhancement of activity against ocular fungal infection. *Pharmaceutics*. 2022;PMC9032757.
23. Development and characterization of fenticonazole nitrate-loaded cubogel for the management of vaginal candidiasis. 2025;PMC12284559.
24. Rupanavar R, Shinde M, Mane V, et al. Mannosylated chitosan-coated berberine hydrochloride cubosomal hydrogel for targeted macrophage-mediated wound healing. *J Pharm Innov*. 2026;21:256. doi:10.1007/s12247-026-10424-1.
25. Tomaszewska E, Soliwoda K, Kadziola K, et al. Detection limits of DLS and UV-Vis spectroscopy in characterization of polydisperse nanoparticle colloids. *J Nanomater*. 2013;2013:e313081.
26. Tuning structure and morphology of lipidic cubosomes by encapsulation of novel porphyrin-derivatives. *Colloids Surf B Biointerfaces*. 2025.
27. A review of poloxamer 407 pharmaceutical and pharmacological characteristics.
28. Nitika, Nikita, KI SY. Formulation, development and optimization of itraconazole cubosomal gel for the treatment of candidiasis. *Int J Pharm Anal Acta*. 2020;3(1):15-9.
29. Ruchi S, Gurvinder K, Deepak NK. Fluconazole loaded cubosomal vesicles for topical delivery. *Int J Drug Dev Res*. 2015;7:32-41.
30. Prajapati V, Jain A, Jain R, et al. Treatment of cutaneous candidiasis through fluconazole encapsulated cubosomes. *Drug Deliv Transl Res*. 2014;4(5-6):400-408.
31. Emerging trends in the use of topical antifungal-corticosteroid combinations. *J Fungi*. 2022;8(8):812.
32. Development of miconazole-loaded microemulsions for enhanced topical delivery and non-destructive analysis by near-infrared spectroscopy. PMC10304693. 2023.
33. Esposito E, Cortesi R, Drechsler M, et al. Cubosome dispersions as delivery systems for percutaneous administration of indomethacin. *Pharm Res*. 2005;22:2163-2173. doi:10.1007/s11095-005-8176-x.
34. Yall Appamaharaj H, Saboji J, Patil S, et al. Preparation and evaluation of diclofenac sodium cubosomes for percutaneous administration. *World J Pharm Pharm Sci*. 2014;3:523-539.
35. Zubair A, Sharma PK, Warsi MH. Fabrication and evaluation of ketorolac loaded cubosome for ocular drug delivery. *J Appl Pharm Sci*. 2016;6(9):204-208.
36. Bhardwaj S, Anshul, Gaur PK, Bhatia S. Potential assessment of topical felbinac-loaded cubosomal gel in soft tissue injury in albino rats. *Assay Drug Dev Technol*. 2022. doi:10.1089/adt.2022.063.
37. Topical felbinac loaded cubosomal hydrogel for promising treatment of inflammatory pain. *J Dispers Sci Technol*. 2024. doi:10.1080/01932691.2024.2440423.
38. Optimizing nimesulide loaded cubosomal gel for enhanced efficacy: a systematic engineering approach with factorial design for topical applications. *J Pharm Innov*. 2024. doi:10.1007/s12247-024-09847-5.
39. Peng X, Zhou Y, Han K, et al. Characterization of cubosomes as a targeted and sustained transdermal delivery system for capsaicin. *Drug Des Devel Ther*. 2015;9:4209-4218.
40. Sherif S, Bendas ER, Badawy S. The clinical efficacy of cosmeceutical application of liquid crystalline nanostructured dispersions of alpha lipoic acid as anti-wrinkle.
41. Curcumin niosomes prepared from proniosomal gels: in vitro skin permeability, kinetic and in vivo studies. *Polymers*. 2021;13(5):791. doi:10.3390/polym13050791.
42. Victorelli FD, Manni LS, Biffi S, et al. Potential of curcumin-loaded cubosomes for topical treatment of cervical cancer. *J Colloid Interface Sci*. 2022;620:419-430. doi:10.1016/j.jcis.2022.04.031.
43. Affimer tagged cubosomes: targeting of carcinoembryonic antigen expressing colorectal cancer cells using in vitro and in vivo models. PMC9007418. 2022.
44. Ananda KC, Madhubabu A, Padmanabha, Vasudha VB, Vinod KY. Design, formulation, in vitro and ex-vivo evaluation of atazanavir-loaded cubosomal gel. *Biointerface Res Appl Chem*. 2021;11(4):12037-54. doi:10.33263/BRIAC114.1203712054.

-
45. Kurangi B, Jalalpure S, Jagwani S. Formulation and evaluation of resveratrol loaded cubosomal nanoformulation for topical delivery. *Curr Drug Deliv.* 2020;18(5):607-19. doi:10.2174/1567201817666200902150646.
46. Nasr M, Almawash S, Al Saqr A, Bazeed AY, Saber S, Elagamy HI. Bioavailability and antidiabetic activity of gliclazide-loaded cubosomal nanoparticles. *Pharmaceuticals.* 2021;14(8):786.
47. Chakorkar SS, Mulla JSA, Chakorkar SS. A novel corticosteroid cubosomes for ocular drug delivery. *Indo Am J Pharm Res.* 2020;10(06):322-8.

Note: reference details above were compiled from openly available bibliographic listings and article records; authors and editors are advised to cross-verify each citation (author list, volume/page, and DOI) against PubMed or the publisher record prior to submission.