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Review Paper

Enhancement of Solubility and Dissolution of Nepafenac API in Ocular Delivery: A Comprehensive Review

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ABSTRACT

Nepafenac is a topically applied non-steroidal anti-inflammatory prodrug used extensively for pain and inflammation control after cataract surgery and, in several regulatory regions, for prevention of post-operative macular edema in diabetic patients. Its clinical utility is constrained by very low intrinsic aqueous solubility, which has confined marketed products such as Nevanac® and Ilevro® to the suspension dosage form. Suspensions are associated with dosing non-uniformity, ocular irritation, foreign-body sensation and short precorneal residence, all of which can compromise patient compliance and limit corneal drug flux. This review consolidates literature from the sources on the physicochemical basis of the nepafenac solubility problem and on formulation strategies explored to overcome it, including particle-size reduction and nanocrystallisation, amorphous solid dispersion, cyclodextrin complexation, surfactant- and polymer-based micellisation, lipid-based nanocarriers, and combination platforms such as nanoparticle-loaded in-situ gels. Reported apparent-solubility gains, particle size and zeta-potential data, dissolution and ex-vivo/in-vitro corneal permeation outcomes, and stability findings for nepafenac-specific formulations are compared, and characterisation approaches used to evaluate these systems are summarised. The review closes by identifying persistent gaps in the literature-inconsistent reporting of thermodynamic versus apparent solubility, limited in-vitro/in-vivo correlation and scarce use of systematic Quality-by-Design optimisation and outlines directions for future work aimed at translating laboratory-scale, solubility-enhanced nepafenac systems into clinically viable ocular products

INTRODUCTION

Aqueous solubility is one of the most decisive physicochemical determinants of a drug's clinical performance, because dissolution in the biological fluid bathing the site of administration is a prerequisite for absorption, whatever route is

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chosen 17,42. Within the Biopharmaceutical Classification System, a large proportion of drug candidates emerging from contemporary discovery pipelines fall into Class IV, characterised by low membrane permeability and poor aqueous solubility, so that dissolution and permeation becomes rate-limiting for bioavailability 15,19. Poorly water-soluble actives typically dissolve slowly and incompletely, giving erratic absorption and sub-therapeutic tissue concentrations unless the formulation actively compensates for the solubility deficit; solubility enhancement has therefore become a central concern of modern formulation science 16,18.

The consequences of poor solubility are magnified rather than diminished when the intended route is ocular. The eye is protected by an elaborate set of static and dynamic defense mechanisms — the tear film, corneal epithelial tight junctions, reflex blinking and rapid nasolacrimal drainage that together clear most of a topically instilled dose within roughly the first minute after application 25,27. Because typical eye-drop volumes far exceed what the conjunctival sac can retain, and because most of an instilled dose is diluted and washed away within 15-30 seconds, well under five per cent of a topically applied dose is generally considered to reach the intraocular tissues even under favourable conditions 25,28. When the active substance is also poorly soluble, this already narrow absorption window is compressed further, because a drug that has not fully dissolved in the tear fluid or vehicle cannot diffuse across the corneal epithelium at all.

Nepafenac illustrates this dual challenge well. As an amide prodrug of amfenac possessing only weak intrinsic cyclooxygenase-inhibitory activity of its own, nepafenac depends on efficient corneal penetration followed by enzymatic bioactivation in hydrolase-rich ocular tissues (iris-ciliary body, retina and choroid) to exert its anti-inflammatory effect 8,9,11. Its uncharged, moderately lipophilic structure favours rapid corneal transit, and comparative pharmacokinetic work has reported markedly greater ocular bioavailability for nepafenac than for related NSAIDs such as amfenac, ketorolac and bromfenac 8,9. Yet nepafenac's very low aqueous solubility, reported to be on the order of 0.02 mg/mL in water, has confined both marketed products, Nevanac® 0.1% and Ilevro® 0.3%, to the suspension dosage form rather than a true solution 7,62. This review therefore examines why nepafenac is difficult to solubilise, surveys the strategies the literature has explored to enhance its apparent solubility and dissolution for ocular use, compares how these approaches have been evaluated, and considers the research gaps that remain.

2. Nepafenac: Drug Profile

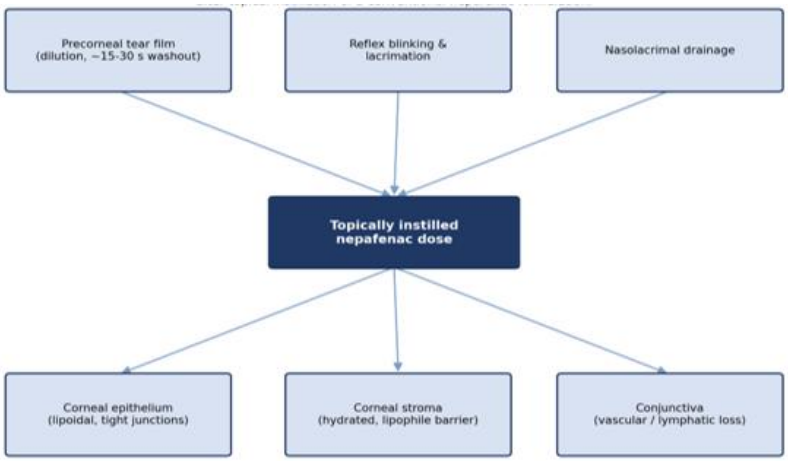
Nepafenac, chemically 2-amino-3-benzoylbenzeneacetamide, has the empirical formula C15H14N2O2 and a molecular weight of approximately 254.28 g/mol 8,10. It is described as a pale yellow crystalline solid with a reported melting point around 184 °C, freely soluble in organic solvents such as ethanol and dimethyl sulfoxide but only sparingly soluble in water 64. Pharmacologically, nepafenac itself shows only weak cyclooxygenase-1 inhibitory activity; after topical ocular instillation it penetrates the cornea and undergoes deamination by intraocular tissue hydrolases to its active metabolite amfenac, a potent non-selective inhibitor of both COX-1 and COX-2 9,11,12. Bioconversion is more extensive in posterior ocular tissues than in the cornea itself, a feature proposed to explain the drug's documented ability to reach the retina and choroid after topical dosing, which is exploited clinically in the prevention of post-surgical macular edema 10,12.

Clinically, nepafenac ophthalmic suspension is indicated for pain and inflammation associated with cataract surgery and, in Europe, for reducing

the risk of postoperative macular edema in diabetic patients undergoing cataract extraction 57,58. Randomised, vehicle-controlled trials of both the 0.1% (three-times-daily) and 0.3% (once-daily) suspensions have reported statistically significant reductions in macular edema incidence and improved best-corrected visual acuity relative to vehicle, with a broadly comparable safety profile across strengths 59,60,61. The requirement for repeated daily dosing of a suspension, however, itself reflects the underlying solubility limitation: a true aqueous solution would in principle allow more uniform dosing, greater comfort, and potentially a lower effective concentration, motivating the substantial body of solubility-enhancement research this review surveys.

3. Ocular Drug Delivery and Formulation Challenges

Effective ocular drug delivery must contend with both static anatomical barriers and dynamic physiological clearance mechanisms. The precorneal tear film, renewed roughly every two to three minutes, is the first line of defense and is responsible for washing away the great majority of an instilled dose within seconds; reflex blinking and lacrimation triggered by an irritant formulation further accelerate this loss 22,25. Once past the tear film, the corneal epithelium presents a lipophilic, tightly-junctioned barrier that restricts paracellular movement of hydrophilic solutes larger than roughly 500 Da, while the underlying stroma, being highly hydrated, poses a reciprocal barrier to excessively lipophilic molecules; a drug therefore needs balanced hydrophilic-lipophilic character to cross the full corneal thickness 28,31. The conjunctiva, in contrast, is far more permeable but is also richly vascularised and lymphatic, so that much of the drug that partitions into conjunctival tissue is lost to systemic and lymphatic clearance rather than reaching the anterior chamber 22,31.



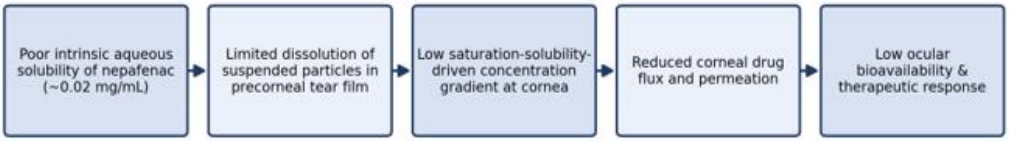
Principle static and dynamic barriers limiting ocular bioavailability after topical instillation of conventional formulation

Nasolacrimal drainage removes a further fraction of the dose within the first minute after instillation, and the small volume of the conjunctival sac (on the order of 7-10 µL) means that a typical eye-drop volume of 30-50 µL is largely spilled or drained regardless of formulation 22,25. Nanocarrier and mucoadhesive-polymer strategies have therefore been developed specifically to prolong precorneal residence time and to promote closer contact between the formulation and the corneal epithelium, thereby improving the fraction of drug ultimately available for absorption 26,30. For a poorly soluble drug such as nepafenac, these general ocular barriers are compounded by the

additional requirement that the drug must first be adequately dissolved, solubilised, or dispersed at sufficiently small particle size before diffusion across the tear film and corneal epithelium can even begin, which is the central formulation problem this review addresses 24,29.

4. Solubility and Bioavailability Limitations of Nepafenac

Nepafenac's ocular formulation challenges stem directly from its physicochemical profile: a moderately lipophilic, essentially non-ionisable amide with reported aqueous solubility around 0.02 mg/mL at 25 °C, well below what is typically required to sustain a saturated diffusion gradient across the cornea from a topically applied volume7,63. Because the marketed suspensions rely on undissolved drug particles acting as a solubility-limited reservoir that slowly re-dissolves in the tear film, the effective driving force for corneal permeation is governed by the drug's saturation solubility rather than by the total dose applied, so that simply increasing suspension concentration (as with Ilevro® 0.3% relative to Nevanac® 0.1%) does not proportionally increase ocular bioavailability 14,63. Suspended particles are also prone to sedimentation, caking and inconsistent resuspension on shaking, raising the risk of dose variability between instillations, while crystal habit and polymorphic form can further influence the true dissolution rate independent of nominal drug concentration 1,7.



An additional complication specific to suspensions is patient tolerability: the presence of solid particles in the tear film has been repeatedly linked to foreign-body sensation, transient blurred vision and reflex lacrimation, each of which can itself accelerate precorneal clearance and further reduce effective ocular exposure, creating a self-reinforcing cycle of poor comfort and poor bioavailability 2,28. These considerations collectively explain why a substantial and growing body of formulation research has targeted the aqueous solubility and dissolution behaviour of nepafenac specifically, seeking to convert the drug from a suspended, solubility-limited system into a molecularly dissolved, nanocrystalline, or complexed form capable of supporting a true or near-true ophthalmic solution with more predictable corneal flux 3,4,29.

5. General Strategies for Solubility Enhancement

Solubility-enhancement approaches described in the pharmaceutical literature are conventionally grouped into physical modifications (which alter particle size, morphology or crystallinity without changing the drug's covalent structure), chemical modifications (such as salt formation or prodrug design), and formulation-based approaches that rely on excipients or carrier systems to solubilise, disperse or entrap the drug 16,18. For a topically instilled ocular product, chemical modification is largely constrained by regulatory and manufacturing considerations (nepafenac itself already represents a deliberately engineered prodrug of amfenac), so the bulk of the reported nepafenac-specific literature falls within the physical and formulation-based categories, summarised below before Section 6 considers their application to nepafenac specifically.

5.1 Particle-size reduction and nanocrystallisation

Particle-size reduction remains the most conceptually direct approach: reducing crystal size increases the surface area available for solvent contact and, per the Noyes-Whitney relationship, proportionally increases the intrinsic dissolution rate; below roughly one micrometre, the Ostwald-Freundlich relationship additionally predicts a modest rise in apparent (kinetic) saturation solubility due to increased surface curvature and interfacial free energy 42,45. Nanocrystal and nanosuspension technologies, produced by top-down (wet media milling, high-pressure homogenisation) or bottom-up (antisolvent precipitation) routes, exploit both effects simultaneously and have become one of the most widely reported platforms for poorly soluble actives across oral, parenteral and ocular routes 43,44,58.

5.2 Amorphisation and solid dispersion

Amorphous solid dispersion converts a crystalline drug into a high-energy amorphous state dispersed within a hydrophilic polymeric carrier (commonly polyvinylpyrrolidone, PVP-vinyl acetate copolymers, or cellulose derivatives), eliminating the lattice energy that must otherwise be overcome for dissolution and thereby markedly increasing apparent solubility and dissolution rate relative to the crystalline drug 38,39,40. First-generation dispersions used crystalline carriers, whereas second- and third-generation systems employ amorphous or surfactant-containing polymeric carriers that additionally improve wettability and physically stabilise the amorphous drug against recrystallisation on storage 40,41.

5.3 Cyclodextrin complexation

Cyclodextrin complexation exploits the toroidal, hydrophilic-exterior/hydrophobic-cavity architecture of cyclic oligosaccharides to form non-covalent inclusion complexes with lipophilic drug molecules, increasing apparent aqueous solubility while often simultaneously improving chemical stability and reducing local irritation 32,36. Chemically modified derivatives such as hydroxypropyl-beta-cyclodextrin (HPbCD), sulfobutylether-beta-cyclodextrin (SBEbCD) and randomly methylated beta-cyclodextrin (RAMEB) show substantially greater intrinsic aqueous solubility than the parent cyclodextrins and are widely favoured in ocular formulations because of their established safety record in approved topical and parenteral products 33,35,37.

5.4 Surfactants, cosolvents and pH-based approaches

Surfactant, cosolvent and pH-based solubilisation strategies rely on micellar solubilisation above the critical micelle concentration, on co-solvency effects from water-miscible solvents such as propylene glycol or PEG 400, or on pH adjustment to favour the ionised (and therefore more soluble) species of an ionisable drug; for ocular use these approaches must be balanced carefully against tear-film tonicity, irritation potential and the buffering capacity of the tear fluid 16,55. Self-nanoemulsifying and microemulsion systems extend this principle by combining oil, surfactant and cosurfactant to spontaneously form nanoscale droplets on aqueous dilution, solubilising the drug within the dispersed oil phase while presenting a very large interfacial area for subsequent release 55,30.

5.5 Lipid-based nanocarriers

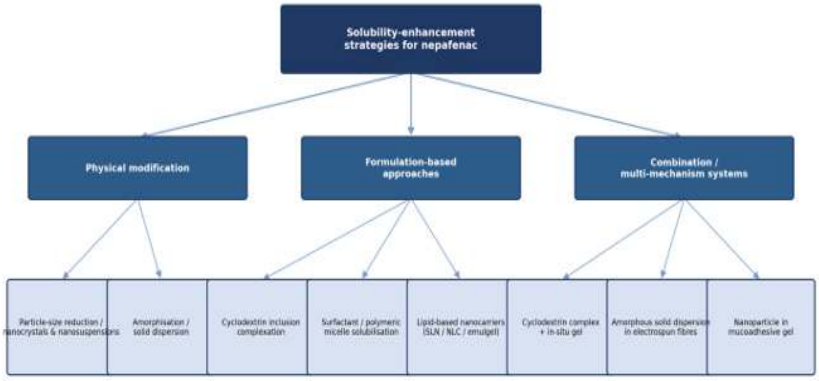
Lipid-based nanocarriers, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), entrap a poorly soluble drug within a biocompatible lipid matrix, combining enhanced apparent solubility with prolonged precorneal residence through mucoadhesive or bioadhesive surface interactions; NLCs, which

incorporate a liquid lipid fraction within the solid matrix, generally show higher drug-loading capacity and reduced drug expulsion on storage compared with first-generation SLNs 65,66,67.

5.6 Polymeric micelles and combination strategies

Polymeric micelles, self-assembled from amphiphilic block copolymers such as Pluronic/poloxamer, TPGS (D-alpha-tocopheryl polyethylene glycol succinate) or Soluplus, solubilise lipophilic drugs within their hydrophobic core while presenting a hydrophilic corona to the aqueous tear film, producing optically clear, low-viscosity systems well suited to eye-drop administration without the vision-blurring associated with particulate suspensions 47,48,49. Because many of these carrier classes act simultaneously as solubilisers and as penetration or residence-time enhancers, combination strategies that layer two or more of the above approaches (for example, nanocrystals incorporated into an in-situ gelling vehicle, or a cyclodextrin complex loaded into a polymeric nanoparticle) have become increasingly common in the recent nepafenac-specific literature discussed next 1,4,29.

6. Specific Solubility-Enhancement Strategies for Nepafenac



Classification of solubility enhancement strategies

6.1 Particle-size reduction and nanosuspensions

Particle-size reduction and nanosuspension approaches have been applied directly to nepafenac. In one representative study, a nepafenac nanosuspension prepared by a solvent-diffusion technique using Pluronic F-127 and HPMC E-5 as stabilisers yielded a mean particle size of 278.3 nm and a zeta potential of -11.1 mV, indicative of an adequately stabilised colloidal system, with a formulation viscosity of about 95 cPs considered supportive of prolonged ocular retention 1. Fourier-transform infrared spectroscopy confirmed the absence of significant drug-excipient interaction, and ex-vivo transcorneal permeation studies reported markedly higher cumulative permeation for the optimised nanosuspension (about 72% over 8 hours) compared with a conventional commercial suspension (about 36% over the same period); accelerated stability testing over one month showed no substantial change in pH or viscosity 1. These findings illustrate the general nanocrystal principle described in Section 5 translating into a measurable ex-vivo permeation benefit specific to nepafenac.

6.2 Cyclodextrin complexation

Cyclodextrin complexation is the most extensively documented nepafenac-specific solubility-enhancement strategy in the accessible literature. Early formulation work established that hydroxypropyl-beta-cyclodextrin (HPbCD) can act simultaneously as a drug carrier, aqueous solubiliser and corneal-penetration enhancer for nepafenac, allowing the drug to bypass rate-limiting tear-film partitioning before releasing at the corneal epithelium for improved bioavailability 2,28. A subsequent study systematically screening cyclodextrins reported that HPbCD performed best in terms of raw solubilisation while gamma-cyclodextrin was most effective at promoting nanoaggregate formation with nepafenac, and identified a mixture of 15% w/v gamma-cyclodextrin and 8% w/v HPbCD, giving aggregate sizes below 1 µm and a viscosity of roughly 10-19 cP, as an optimal combination for further formulation 3. Complex formation in these systems has been confirmed using differential scanning calorimetry, Fourier-transform infrared spectroscopy and proton nuclear magnetic resonance, which together demonstrate loss of the drug's native crystalline thermal signature and characteristic host-guest spectral shifts consistent with inclusion complexation 3,7.

Ternary cyclodextrin-polymer complexes have also been explored to combine solubility enhancement with improved ocular residence. In one study, nepafenac was reported to have an aqueous solubility of only about 0.0197 mg/mL, but apparent solubility rose substantially across a series of cyclodextrin-based microparticle formulations upon addition of hydrophilic polymers such as carboxymethylcellulose (CMC), hyaluronic acid (HA) and sodium alginate (SA), with the best-performing ternary combination reaching roughly 2.6 mg/mL, more than a hundred-fold increase relative to the unmodified drug 7. Rheological characterisation in the same study showed that certain polymer combinations produced gel-like, pseudoplastic behaviour resembling that of the reference commercial suspension, suggesting that solubility enhancement and viscosity-driven residence-time extension can be engineered together within a single cyclodextrin-based platform 7.

6.3 Cyclodextrin-based in-situ gelling systems

Building on this cyclodextrin work, an ion-activated in-situ gelling system for nepafenac was developed using the HPbCD complex combined with sodium alginate (Protanal PH 1033) as the gelling agent, exploiting the interaction between alginate guluronate blocks and divalent cations present in tear fluid to trigger gelation after instillation 2,28. Rheological evaluation showed that the optimised formulation's viscosity increased roughly thirty-fold on exposure to simulated tear fluid at ocular surface temperature, consistent with a genuine sol-to-gel transition intended to extend precorneal residence time and reduce the frequency of repeat dosing required with the conventional suspension 2,28. This combination approach of cyclodextrin-mediated solubilisation coupled to a stimulus-responsive gelling vehicle is a clear illustration of the layered strategies discussed generically in Section 5.

6.4 Micellar and nanoaggregate solubilisation

Micellar and nanoaggregate solubilisation of nepafenac using surfactant or polymer combinations has also been reported as an alternative to solid nanocarriers. A recent formulation study describing a stable micellar system for ocular nepafenac delivery built on the cyclodextrin-aggregate chemistry noted above, reporting favourable in-vitro solubilisation and characterisation outcomes and positioning polymeric drug/cyclodextrin nanoaggregates as an attractive strategy for enhanced topical nepafenac

delivery, consistent with the broader polymeric-micelle literature summarised in Section 5 3,49.

6.5 Amorphous electrospun nanofibrous inserts

Electrospun nanofibrous inserts represent a further physical-platform approach applied specifically to nepafenac. In one study, nine different 0.1% w/w nepafenac-loaded electrospun nanofibrous webs were prepared and evaluated for morphology, physicochemical properties, drug release and in-vitro/ex-vivo permeability; scanning electron microscopy confirmed fibrous, high-surface-area morphology, while Fourier-transform infrared spectroscopy and X-ray diffraction indicated polymer cross-linking together with formation of an amorphous solid dispersion of the drug within the fibre matrix, reflecting the amorphisation principle discussed generically in Section 5 5. Nanofibrous ophthalmic inserts of this type are intended to combine improved apparent solubility (via amorphisation) with a solid, patient-centric dosage form offering more controlled and sustained drug release than a conventional suspension 5.

6.6 Nanoemulsion, emulgel and self-emulsifying systems

Nanoemulsion, emulgel and self-emulsifying platforms have been increasingly applied to nepafenac and to structurally related ocular NSAIDs, exploiting the ability of oil-surfactant-cosurfactant systems to solubilise a lipophilic drug within nanoscale droplets while offering sustained, gel-modulated release upon ocular instillation 30,31. A nepafenac-loaded emulgel intended for controlled ocular delivery has been characterised in vitro and ex vivo, forming part of a wider family of emulsion-based ocular NSAID platforms (including analogous flurbiprofen nanosuspension-in-gel and self-nanoemulsifying systems) that similarly combine solubility enhancement with sustained-release gelling vehicles 30,31,55.

6.7 Polymeric and silica nanoparticle carriers in in-situ gels

Silica and polymeric nanoparticle carriers dispersed within in-situ gelling vehicles have also been reviewed as nepafenac delivery platforms, particularly in the context of uveitis, where amorphous silica nanoparticles have been reported to combine stable structure, ease of surface modification and tolerable biodegradability with efficient corneal penetration when dispersed in poloxamer or poloxamer/chitosan-based in-situ gels, sustaining nepafenac release over periods of up to about twelve hours in reported formulations 29. Ex-vivo porcine perfusion studies of nepafenac nanocarrier systems have additionally reported higher drug retention across cornea, sclera and retina relative to the reference commercial suspension, supporting the broader rationale that nanocarrier-mediated solubility and residence-time enhancement can translate into improved tissue-level drug availability 29,36.

6.8 Combination platforms: an emerging trend

Taken together, the nepafenac-specific literature surveyed above shows a clear technological progression from single-mechanism solubility enhancement (simple nanosuspension or single-cyclodextrin complexation) toward increasingly combined, multi-mechanism platforms that simultaneously address solubility, corneal permeation and precorneal residence time of cyclodextrin complexes embedded in in-situ gels, amorphous solid dispersions formed within electrospun fibres, and nanoparticles dispersed in mucoadhesive or thermosensitive vehicles 2,3,5,7,29. This convergence mirrors trends described more broadly for other poorly soluble ocular NSAIDs and reflects growing recognition

that solubility enhancement alone, without a parallel strategy for prolonging ocular surface contact, is unlikely to translate fully into clinical bioavailability gains 21,24.

7. Comparative Evaluation of Reported Nepafenac Formulations

Table 1 summarises representative reported nepafenac solubility-enhancement formulations drawn from the sources discussed in Section 6, to allow direct comparison of carrier type, preparation method, particle size, and the principal solubility, dissolution or permeation outcome reported for each system. Because studies differ in vehicle composition, testing conditions and outcome measures, the comparison should be read as indicative of relative technological approach rather than as a rigorously controlled head-to-head evaluation.

8. Characterization and Evaluation Parameters

Across the nepafenac-specific and analogous ocular-formulation literature reviewed here, a broadly consistent characterisation workflow is applied to solubility-enhanced systems. Equilibrium (thermodynamic) solubility is typically determined by the shake-flask method, in which excess drug is equilibrated with the vehicle until saturation, whereas apparent or kinetic solubility, more relevant to nanocrystalline and amorphous systems, is often assessed at a fixed, shorter time point and can exceed true thermodynamic solubility due to particle-size-dependent supersaturation effects described by the Ostwald-Freundlich relationship 45,46. Phase-solubility studies, in which apparent solubility is plotted against increasing cyclodextrin or excipient concentration, are used specifically to characterise inclusion-complex stoichiometry and complexation efficiency in cyclodextrin-based nepafenac systems 3,7.

Particle size, polydispersity index (PDI) and zeta potential, measured by dynamic light scattering and electrophoretic mobility respectively, are near-universal descriptors for nanosuspension, nanoparticle, micelle and lipid-nanocarrier systems, providing an indirect indication of colloidal stability against aggregation 1,43,58. Morphological confirmation is generally obtained by scanning or transmission electron microscopy, while the solid-state form of the drug within a carrier (crystalline, amorphous, or complexed) is assessed using differential scanning calorimetry (DSC, to detect loss of the drug's characteristic melting endotherm), powder X-ray diffraction (PXRD, to detect loss of crystalline diffraction peaks), and Fourier-transform infrared spectroscopy (FTIR, to detect shifted or attenuated functional-group vibrations consistent with host-guest or drug-polymer interaction) 3,39,40.

Table 1. Reported solubility-enhancement approaches for nepafenac (representative, non-exhaustive summary).

Formulation type	Carrier / excipient	Preparation method	Reported particle size / viscosity	Key reported outcome	Ref.
Nanosuspension	Pluronic F-127, HPMC E-5	Solvent diffusion	278.3 nm; -11.1 mV zeta; 95 cps	~72% *ex-vivo* transcorneal permeation at 8 h vs ~36% for commercial suspension	1

HPbCD complex	Hydroxypropyl-beta-cyclodextrin	Aqueous complexation	Molecularly dissolved (solution)	Improved aqueous solubility and corneal permeability vs uncomplexed drug	2,28
Cyclodextrin nanoaggregates	gamma-CD 15% w/v + HPbCD 8% w/v	Complexation / self-assembly	<1 micrometre aggregates; 10-19 cps	Optimal solubilising combination identified by DSC/FTIR/NMR	3
Ternary CD microparticles	CD + CMC / HA / sodium alginate	Complexation with polymer addition	Not specified (microparticulate)	Apparent solubility raised to ~2.6 mg/mL (from ~0.02 mg/mL)	7
Ion-activated *in-situ* gel	HPbCD complex + sodium alginate (Protanal PH 1033)	Complexation + gelling polymer	~30-fold viscosity rise on tear-fluid contact	Extended precorneal residence, reduced dosing frequency	2,28
Electrospun nanofibrous insert	Polymer blend, amorphous solid dispersion	Electrospinning	Nanofibre mat	Amorphous conversion (XRD/DSC/FTIR); tunable *in-vitro*/*ex-vivo* release	5
Silica nanoparticle *in-situ* gel	Poloxamer 407 / chitosan / poloxamer 188	Nanoparticle dispersion in thermogelling vehicle	Nanoparticulate	Sustained release up to ~12 h; higher tissue retention (cornea, sclera, retina) vs suspension	29
Emulgel	Oil-surfactant-cosurfactant gel matrix	Emulsification + gelling	Nanoscale globules (emulgel)	*In-vitro*/*ex-vivo* controlled release characterised	30,31

Functional performance is most commonly assessed through in-vitro dissolution testing (often using a modified USP apparatus or dialysis-bag method adapted for the small volumes relevant to ophthalmic products), ex-vivo corneal or corneal-conjunctival permeation studies using excised animal (commonly porcine or rabbit) tissue mounted in Franz-type diffusion cells, and, less frequently, in-vivo ocular pharmacokinetic or pharmacodynamic studies measuring aqueous-humour or tissue drug concentration and anti-inflammatory efficacy 1,29,36. Safety-related endpoints reported across these studies include ocular irritation scoring (Draize-type or histopathological assessment of corneal and conjunctival tissue) and, for cell-based systems, in-vitro cytotoxicity assays, both used to confirm that solubility-enhancing excipients do not themselves compromise ocular tolerability 6,36.

9. Research Gaps and Future Perspectives

Notwithstanding the substantial body of nepafenac-specific formulation work summarised above, several recurring limitations constrain direct comparison and translational progress across studies. First, reporting of solubility outcomes is inconsistent: some studies report thermodynamic (equilibrium) solubility, others report apparent or kinetic solubility measured at a single time point, and few explicitly distinguish between the two, even though the distinction is mechanistically important for nanocrystalline and amorphous systems where apparent solubility can

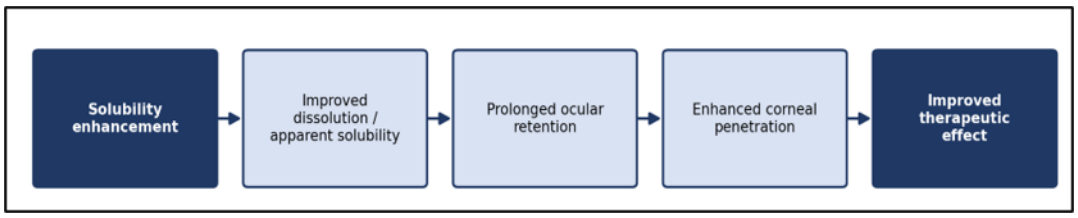
transiently exceed the true thermodynamic value 45,46. Second, standardised, harmonised protocols for in-vitro dissolution and ex-vivo permeation testing of ocular formulations remain limited, so that results obtained with different membrane sources, receptor media, temperatures and sampling intervals are difficult to compare quantitatively across the literature reviewed here 21,24.

Third, correlation between in-vitro or ex-vivo performance and true in-vivo ocular bioavailability (an in-vitro/in-vivo correlation, or IVIVC) is rarely established for nepafenac solubility-enhanced systems, leaving open the question of how faithfully laboratory-scale solubility and permeation gains translate into clinically meaningful improvements in efficacy or dosing frequency 45,59. Fourth, long-term physical and chemical stability data, sterilisation compatibility, and scale-up feasibility are seldom reported in the same depth as initial characterisation, despite being essential for eventual regulatory submission of a sterile ophthalmic product 65,67. Fifth, systematic, statistically-driven optimisation using Quality-by-Design (QbD) principles and Design of Experiments (DoE), now well established for other lipid- and polymer-based ocular nanocarriers, has so far been applied to only a minority of the nepafenac-specific formulations discussed in Section 6, meaning that many reported systems may not represent a formally optimised design space 52,53,55,56.

Finally, excipient tolerability across chronic or repeated ocular dosing, and the potential for multifunctional systems that combine solubility enhancement with sustained release, mucoadhesion and active corneal-penetration promotion within a single, manufacturable platform, remain active areas requiring further systematic investigation before nepafenac solubility-enhanced formulations can be expected to progress from laboratory proof-of-concept toward clinical and regulatory evaluation 21,54.

CONCLUSION

Nepafenac's clinical value in managing postoperative ocular inflammation and, where approved, in preventing diabetes-associated postoperative macular edema is well established, but it’s very low aqueous solubility has confined marketed products to a suspension form with recognised limitations in comfort, dosing uniformity and precorneal residence. The literature surveyed in this review demonstrates that a wide range of solubility-enhancement strategies — particle-size reduction and nanocrystallisation, amorphous solid dispersion, cyclodextrin inclusion complexation, polymeric and lipid-based nanocarriers, and increasingly sophisticated combination platforms such as cyclodextrin-loaded in-situ gels and amorphous nanofibrous inserts have been applied specifically to nepafenac, generally with reported improvements in apparent solubility, dissolution rate, or ex-vivo corneal permeation relative to the unmodified drug or the reference commercial suspension. Realising the full clinical benefit of these approaches, however, will require solubility enhancement to be evaluated together with, rather than separately from, ocular retention, corneal permeation, long-term stability, safety and manufacturability, and would benefit substantially from more consistent, standardised characterisation protocols and from wider adoption of systematic Quality-by-Design optimisation in future nepafenac formulation research.



REFERENCES

1. Umekar MJ. Formulation, Development, and Characterization of Nanosuspension for Uveitis. High Technology Letters30. 2024:269-88.Shelley H, Rodriguez-Galarza RM, Duran SH, Abarca EM, Babu RJ. In situ gel formulation for enhanced ocular delivery of nepafenac. Journal of pharmaceutical sciences. 2018 Dec 1;107(12):3089-97.
2. Vashi R, Sorathia K. Novel stable micellar formulation for ocular delivery of nepafenac: optimization, characterization and in-vitro evaluation. Drug Development and Industrial Pharmacy. 2026 Mar 4;52(3):557-69.
3. Vincze A, Facskó R, Budai-Szűcs M, Katona G, Gyarmati B, Csorba A, Zelkó R, Nagy ZZ, Szente L, Balogh GT. Cyclodextrin-enabled nepafenac eye drops with improved absorption open a new therapeutic window. Carbohydrate Polymers. 2023 Jun 15;310:120717.
4. Omer S, Nagy N, Szőcs E, Kádár S, Völgyi G, Pinke B, Mészáros L, Katona G, Vincze A, Dormán P, Nagy ZZ. Development of innovative electrospun nepafenac-loaded nanofibers-based ophthalmic inserts. International Journal of Pharmaceutics. 2023 Nov 25;647:123554.
5. Racaniello GF, Balenzano G, Arduino I, Iacobazzi RM, Lopalco A, Lopedota AA, Sigurdsson HH, Denora N. Chitosan and Anionic Solubility Enhancer Sulfobutylether-β-Cyclodextrin-Based Nanoparticles as Dexamethasone Ophthalmic Delivery System for Anti-Inflammatory Therapy. Pharmaceutics. 2024 Feb 16;16(2):277.
6. Lorenzo-Veiga B, Diaz-Rodriguez P, Alvarez-Lorenzo C, Loftsson T, Sigurdsson HH. In vitro and ex vivo evaluation of Nepafenac-based cyclodextrin microparticles for treatment of eye inflammation. Nanomaterials. 2020 Apr 9;10(4):709.
7. Walters T, Raizman M, Ernest P, Gayton J, Lehmann R. In vivo pharmacokinetics and in vitro pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac. Journal of Cataract & Refractive Surgery. 2007 Sep 1;33(9):1539-45.
8. Yanni SE, Clark ML, Yang R, Bingaman DP, Penn JS. The effects of nepafenac and amfenac on retinal angiogenesis. Brain research bulletin. 2010 Feb 15;81(2-3):310-9.
9. Chastain JE, Sanders ME, Curtis MA, Chemuturi NV, Gadd ME, Kapin MA, Markwardt KL, Dahlin DC. Distribution of topical ocular nepafenac and its active metabolite amfenac to the posterior segment of the eye. Experimental eye research. 2016 Apr 1;145:58-67.
10. Gamache DA, Graff G, Brady MT, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: I. Assessment of anti-inflammatory efficacy. Inflammation. 2000 Aug;24(4):357-70.
11. Bhatt R, Gurjar M, Alpa Gor DB. Nepafenac eye drops induced unilateral corneal melt. Journal of Health Sciences. 2021;1(01):34.
12. Modi SS, Lehmann RP, Walters TR, Fong R, Christie WC, Roel L, Nethery D, Sager D, Tsorbatzoglou A, Philipson B, Traverso CE.

Once-daily nepafenac ophthalmic suspension 0.3% to prevent and treat ocular inflammation and pain after cataract surgery: phase 3 study. Journal of Cataract & Refractive Surgery. 2014 Feb 1;40(2):203-11.

13. Donnenfeld ED, Holland EJ, Solomon KD. Safety and efficacy of nepafenac punctal plug delivery system in controlling postoperative ocular pain and inflammation after cataract surgery. Journal of Cataract & Refractive Surgery. 2021 Feb 1;47(2):158-64.
14. Varla Y, Joshi V, Patel R, Benival D. Nanosizing of Drugs to Improve the Apparent Dissolution and Bioavailability. Drug Development Approaches for Poorly Soluble Compounds. 2026 Oct 5:81-114.
15. Kumar S, Bhargava D, Thakkar A, Arora S. Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2013;30(3).
16. Sagane R, Erande K. Review on methods of solubility enhancement of BCS class II drugs. Int J Pharm Sci. 2024;2(1):64-76.
17. Zia A. Enhancement of dissolution rate of class II drugs (Hydrochlorothiazide); a comparative study of the two novel approaches; solid dispersion and liqui-solid techniques. Saudi Pharmaceutical Journal. 2015 Jan 1.
18. Bakrey H, Abdu A, Shivgotra R, Soni B, Sharma M, Bakrey A, Jain SK. Innovative strategies and advances in drug delivery systems to address poor solubility: a comprehensive review. Current Drug Targets. 2025.
19. Rusdiana T. Enhancement of solubility BCS class II and IV pharmaceuticals by liqusolid technique: A review. Indonesian Journal of Pharmaceutics. 2020 Jan 1.
20. Santos G, Delgado E, Silva B, Braz BS, Gonçalves L. Topical ocular drug delivery: the impact of permeation enhancers. Pharmaceutics. 2025 Mar 31;17(4):447.
21. Diwan P, Jangde R, Khunte S, Bhardwaj H, Suresh PK. Ocular drug delivery system: Barrier for drug permeation, method to overcome barrier. InDrug Development Life Cycle 2022 Oct 7. IntechOpen.
22. Karmakar S, Manna S, Jana T, Jana S, Nandi G. Unraveling the therapeutic enigma of liposomes in ocular drug delivery. Journal of Bio-X Research. 2025 Sep 30;8(03):176-96.
23. Ahmed S, Amin MM, Sayed S. Ocular drug delivery: a comprehensive review. AAPS pharmscitech. 2023 Feb 14;24(2):66.
24. Zhou HY, Hao JL, Wang S, Zheng Y, Zhang WS. Nanoparticles in the ocular drug delivery. International journal of ophthalmology. 2013 Jun 18;6(3):390.
25. Li H, Dai F, Liu H, Tao Q, Hu J, Zhang Y, Xiao Z, Rupenthal ID, Li H, Yang F, Li W. Physicochemical properties and micro-interaction between micro-nanoparticles and anterior corneal multilayer biological interface film for improving drug delivery efficacy: the transformation of tear film turnover mode. Drug delivery. 2023 Dec 31;30(1):2184312.
26. Löscher M, Seiz C, Hurst J, Schnichels S. Topical drug delivery to the posterior segment of the eye. Pharmaceutics. 2022 Jan 6;14(1):134.
27. Marto-Costa C, Duarte AC, Ekoh E, Vieira S, Salema-Oom M, Silva-Herdade AS, Alvarez-Lorenzo C, Serro AP. Cyclodextrin-based therapeutic contact lenses for improved nepafenac bioavailability. Applied Materials Today. 2026 Oct 1;52:103383.
28. Sangode CM, Tatode AA, Umekar MJ. Nepafenac loaded ophthalmic nanocarriers for treatment of uveitis: A review,2021.
29. Mohapatra D, Yang E, Corson TW. Emulsion and Emulgel-Based ophthalmic drug delivery

systems. Pharmaceutics. 2025 Nov 21;17(12):1504.
30. Agarwal B, Jagdale S, Kanakdande T, Shinde R, Mitra SJ. Nepafenac Loaded Emulgel for Controlled Ocular Delivery: in vitro and ex vivo Characterization. INDIAN JOURNAL OF PHARMACEUTICAL EDUCATION AND RESEARCH. 2025 Jul 1;59(3):s849-62.
31. Nicolaescu OE, Belu I, Mocanu AG, Manda VC, Rău G, Pîrvu AS, Ionescu C, Ciulu-Costinescu F, Popescu M, Ciocîlteu MV. Cyclodextrins: Enhancing drug delivery, solubility and bioavailability for modern therapeutics. Pharmaceutics. 2025 Feb 22;17(3):288.
32. Carneiro SB, Costa Duarte FI, Heimfarth L, Siqueira Quintans JD, Quintans-Júnior LJ, Veiga Júnior VF, Neves de Lima AA. Cyclodextrin–drug inclusion complexes: In vivo and in vitro approaches. International journal of molecular sciences. 2019 Feb 2;20(3):642.
33. Grecu M, Minea B, Foia LG, Bostanaru-Iliescu AC, Miron L, Nastasa V, Mares M. Short review on the biological activity of cyclodextrin-drug inclusion complexes applicable in veterinary therapy. Molecules. 2023 Jul 21;28(14):5565.
34. Boczar D, Michalska K. Cyclodextrin inclusion complexes with antibiotics and antibacterial agents as drug-delivery systems—A pharmaceutical perspective. Pharmaceutics. 2022 Jun 30;14(7):1389.
35. Spiridon I, Anghel N. Cyclodextrins as multifunctional platforms in drug delivery and beyond: structural features, functional applications, and future trends. Molecules. 2025 Jul 20;30(14):3044.
36. Sarabia-Vallejo Á, Caja MD, Olives AI, Martín MA, Menéndez JC. Cyclodextrin inclusion complexes for improved drug bioavailability and activity: synthetic and analytical aspects. Pharmaceutics. 2023 Sep 19;15(9):2345.
37. Tekade AR, Yadav JN. A review on solid dispersion and carriers used therein for solubility enhancement of poorly water soluble drugs. Advanced pharmaceutical bulletin. 2020 May 11;10(3):359.
38. Rusdin A, Mohd Gazzali A, Ain Thomas N, Megantara S, Aulifa DL, Budiman A, Muchtaridi M. Advancing drug delivery paradigms: Polyvinyl pyrolidone (PVP)-based amorphous solid dispersion for enhanced physicochemical properties and therapeutic efficacy. Polymers. 2024 Jan 20;16(2):286.
39. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, Taylor LS, Kumar S, Zhou QT. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharmaceutica Sinica B. 2021 Aug 1;11(8):2505-36.
40. Nair AR, Lakshman YD, Anand VS, Sree KN, Bhat K, Dengale SJ. Overview of extensively employed polymeric carriers in solid dispersion technology. AAPS PharmSciTech. 2020 Nov 8;21(8):309.
41. Chang TL, Zhan H, Liang D, Liang JF. Nanocrystal technology for drug formulation and delivery. Frontiers of Chemical Science and Engineering. 2015 Mar;9(1):1-4.
42. Pirincci Tok Y, Mesut B, Güngör S, Sarıkaya AO, Aldeniz EE, Dude U, Özsoy Y. Systematic screening study for the selection of proper stabilizers to produce physically stable canagliflozin nanosuspension by wet milling method. Bioengineering. 2023 Aug 4;10(8):927.
43. Jadhav SP, Singh SK, Chawra HS. Review on nanosuspension as a novel method for solubility and bioavailability enhancement of poorly soluble drugs. Adv Pharmacol Pharm. 2023;11(2):117-30.

44. Bonhoeffer B, Kordikowski A, John E, Juhnke M. Numerical modeling of the dissolution of drug nanocrystals and its application to industrial product development1. ADMET and DMPK. 2022 Dec 6;10(4):253-87.
45. Ahmed LM, Mohamed FA, Elfaham TH. Nanocrystals as a promising approach for enhancing solubility and dissolution of etoricoxib using Box–Behnken design. Scientific reports. 2025 Aug 11;15(1):29347.
46. Pescina S, Grolli Lucca L, Govoni P, Padula C, Del Favero E, Cantù L, Santi P, Nicoli S. Ex vivo conjunctival retention and transconjunctival transport of poorly soluble drugs using polymeric micelles. Pharmaceutics. 2019 Sep 14;11(9):476.
47. Owen SC, Chan DP, Shoichet MS. Polymeric micelle stability. Nano today. 2012 Feb 1;7(1):53-65.
48. Grimaudo MA, Pescina S, Padula C, Santi P, Concheiro A, Alvarez-Lorenzo C, Nicoli S. Topical application of polymeric nanomicelles in ophthalmology: a review on research efforts for the noninvasive delivery of ocular therapeutics. Expert Opinion on Drug Delivery. 2019 Apr 3;16(4):397-413.
49. Noh G, Keum T, Seo JE, Choi J, Rakesh B, Shrawani L, Park B, Choi YW, Lee S. Development and evaluation of a water soluble fluorometholone eye drop formulation employing polymeric micelle. Pharmaceutics. 2018 Oct 28;10(4):208.
50. Hwang D, Ramsey JD, Kabanov AV. Polymeric micelles for the delivery of poorly soluble drugs: From nanoformulation to clinical approval. Advanced drug delivery reviews. 2020 Jan 1;156:80-118.
51. Waghule T, Dabholkar N, Gorantla S, Rapalli VK, Saha RN, Singhvi G. Quality by design (QbD) in the formulation and optimization of liquid crystalline nanoparticles (LCNPs): A risk based industrial approach. Biomedicine & Pharmacotherapy. 2021 Sep 1;141:111940.
52. Sharma S, Soni ML, Pathan HK, Sharma R. Quality by design in ophthalmic product development. InOphthalmic Drug Delivery 2026 Jan 1 (pp. 193-218).
53. Serafimovska T, Darkovska-Serafimovska M, Mitevska M, Stefkov G, Tonic Ribarska J. Development and validation of LC/MS/MS method for determination of mycotoxin, 2022.
54. Jeong JH, Yoon TH, Ryu SW, Kim MG, Kim GH, Oh YJ, Lee SJ, Kwak NW, Bang KH, Kim KS. Quality by Design (QbD)-Based Development of a Self-Nanoemulsifying Drug Delivery System for the Ocular Delivery of Flurbiprofen. Pharmaceutics. 2025 May 9;17(5):629.
55. Reddy A, Rahman SN, Kamdi IR, Gulbake A. Role of Quality by Design (QbD) in Ophthalmic Products. InComplex Ophthalmic Dosage Forms: Advances in Biomedical Applications and Future Perspectives 2025 Jun 10 (pp. 239-267).
56. Modi SS, Lehmann RP, Walters TR, Fong R, Christie WC, Roel L, Nethery D, Sager D, Tsorbatzoglou A, Philipson B, Traverso CE. Once-daily nepafenac ophthalmic suspension 0.3% to prevent and treat ocular inflammation and pain after cataract surgery: phase 3 study. Journal of Cataract & Refractive Surgery. 2014 Feb 1;40(2):203-11.
57. Singh RP, Lehmann R, Martel J, Jong K, Pollack A, Tsorbatzoglou A, Staurenghi G, Cervantes GC, Alpern L, Modi S, Svoboda L. Nepafenac 0.3% after cataract surgery in patients with diabetic retinopathy: results of 2 randomized phase 3 studies. Ophthalmology. 2017 Jun 1;124(6):776-85.
58. Singh R, Alpern L, Jaffe GJ, Lehmann RP, Lim J, Reiser HJ, Sall K, Walters T, Sager D. Evaluation of nepafenac in prevention of macular edema following cataract surgery in

patients with diabetic retinopathy. Clinical Ophthalmology. 2012 Aug 3:1259-69.
59. Singh RP, Staurenghi G, Pollack A, Adewale A, Walker TM, Sager D, Lehmann R. Efficacy of nepafenac ophthalmic suspension 0.1% in improving clinical outcomes following cataract surgery in patients with diabetes: an analysis of two randomized studies. Clinical Ophthalmology. 2017 May 29:1021-9.
60. Yüksel B, Karti Ö, Kusbeci T. Topical nepafenac for prevention of post-cataract surgery macular edema in diabetic patients: patient selection and perspectives. Clinical Ophthalmology. 2017 Dec 11:2183-90.
61. Bottós JM, Farah ME, Höfling-Lima AL, Aggio FB. Pharmacology, clinical efficacy and safety of nepafenac ophthalmic suspension. Expert Review of Ophthalmology. 2008 Apr 1;3(2):131-8.
62. Gaynes BI, Onyekwuluje A. Topical ophthalmic NSAIDs: a discussion with focus on nepafenac ophthalmic suspension. Clinical ophthalmology. 2008 Jun 1;2(2):355-68.
63. Abbas A, Shafqat SS, Nazar MF, Khan HU, Mukhtar A, Tayyab M, Syed A, Zafar MN, Masood SA, Kamran K. Molecular interaction of nonsteroidal anti-inflammatory prodrug nepafenac with ionic surfactants. International Journal of Chemical Kinetics. 2024 Jul;56(7):417-31.
64. Sharo C, Zhang J, Zhai T, Bao J, Garcia-Epelboim A, Mamourian E, Shen L, Huang Z. Repurposing FDA-approved drugs against potential drug targets involved in brain inflammation contributing to Alzheimer's disease. Targets. 2024 Dec 4;2(4):446-69.
65. Baig MS, Karade SK, Ahmad A, Khan MA, Haque A, Webster TJ, Faiyazuddin M, Al-Qahtani NH. Lipid-based nanoparticles: innovations in ocular drug delivery. Frontiers in Molecular Biosciences. 2024 Sep 17;11:1421959.
66. Viegas C, Patrício AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid lipid nanoparticles vs. nanostructured lipid carriers: a comparative review. Pharmaceutics. 2023 May 25;15(6):1593.
67. Gugleva V, Andonova V. Recent progress of solid lipid nanoparticles and nanostructured lipid carriers as ocular drug delivery platforms. Pharmaceuticals. 2023 Mar 22;16(3):474.

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