Integral BioSystems

Ophthalmic Drug Delivery
A Review

Shikha P. Barman, Ph.D.
Founder, President and CEO, Integral BioSystems

1 Executive Summary

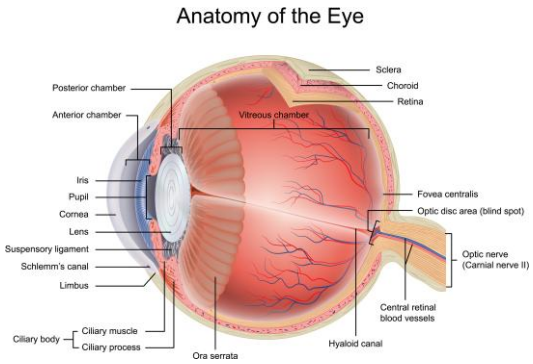
Ophthalmic drug delivery is not a single formulation problem. It is a system-design problem created by the eye's layered anatomy, rapid clearance mechanisms, small dosing volumes, stringent sterility expectations, and low tolerance for irritation or visual disturbance. A platform that improves solubility but fails on comfort, dose reproducibility, or manufacturability has not solved the product problem. Topical drops remain the least invasive and most familiar route, but precorneal loss and epithelial barriers constrain exposure, particularly beyond the anterior segment. Local injections and implants provide direct or sustained exposure but add procedural burden and route-specific safety risks. Nanocarriers, in situ gels, inserts, microneedles, depots, and device-enabled systems can widen the design space; none eliminates the need for a target-product-profile-first strategy.

- Define the anatomical target, pharmacologic concentration, onset, and duration before selecting a carrier.
- Use the simplest platform capable of meeting the exposure requirement; added complexity must earn its place through measurable product benefit.
- Treat comfort, sterility assurance, container–closure performance, particulate control, and dose delivery as core quality attributes—not late-stage checks.
- Build an orthogonal translation chain linking physicochemical attributes to release, tissue exposure, pharmacodynamics, and clinically meaningful outcomes.
- Lock scalable unit operations and stability-indicating controls early enough that nonclinical and clinical lots represent the intended commercial product.

Strategic implication: Platform selection should be an explicit, data-based trade study. The objective is not maximum ocular penetration; it is sufficient, reproducible exposure at the intended site with acceptable safety, usability, and product robustness.

2 Ocular Delivery: Key Factors

2.1 Anatomy Creates Route-Dependent Barriers



The ocular surface is protected by the tear film, blinking, nasolacrimal drainage, epithelial tight junctions, metabolic enzymes, and efflux transporters. These defenses rapidly remove foreign material and limit transcorneal passage. The corneal epithelium favors lipophilic permeants, whereas the hydrophilic stroma resists highly lipophilic molecules; a successful transcorneal candidate therefore needs balanced properties or a delivery system that changes the effective transport behavior. The conjunctiva offers a larger and more permeable surface but is highly vascularized, which can divert drug into systemic circulation. Reaching the posterior segment from a topical dose requires overcoming long diffusion distances, scleral/choroidal clearance, and the blood–retinal barrier. Direct intraocular routes bypass several barriers but impose procedure, safety, and device requirements.

Barrier or constraint	Development consequence	Useful engineering levers
Tear dilution and turnover	Short, variable contact time; low recovered dose	Mucoadhesion, viscosity, in situ gelling, controlled drop volume
Corneal epithelium	Restricts hydrophilic and large molecules	Prodrug design, permeation enhancement, nanocarrier interaction, iontophoresis
Corneal stroma	Restricts highly lipophilic molecules	Balanced logD, cyclodextrins, micelles, supersaturation control
Conjunctival vasculature	Local loss and systemic exposure	Residence control, depot placement, dose minimization
Blood–aqueous / blood–retinal barriers	Limits systemic-to-eye distribution	Local injection, implant, targeted biologic or gene delivery
Small tolerated dose volume	High concentration and delivery accuracy needed	Potent molecule, solubilization, device optimization

2.2 Bioavailability is a product-level outcome

Reported ocular bioavailability varies with molecule, formulation, species, sampling compartment, and endpoint. Consequently, a universal percentage is less useful than a mass-balance mindset: administered dose → retained dose → permeated dose → tissue exposure → target engagement → response. Each transition should have a fit-for-purpose assay and predefined uncertainty.

2.3 Routes of administration

Route	Best-suited targets	Principal advantages	Principal limitations
Topical	Tear film, conjunctiva, cornea, anterior chamber	Noninvasive; familiar; scalable	Rapid clearance; adherence; limited posterior exposure
Subconjunctival / periocular	Anterior and periocular tissues; selected posterior targets	Local depot; avoids epithelial barrier	Injection burden; clearance; tissue tolerability
Intracameral	Anterior chamber, iris/ciliary body	Direct, controlled anterior exposure	Procedure; endothelial and pressure risks
Intravitreal	Vitreous, retina, choroid	Direct posterior exposure; established pathway	Injection burden; endophthalmitis, inflammation, pressure and retinal risks
Suprachoroidal	Choroid and retina	Compartmentalized posterior delivery	Specialized device; variable anatomy; procedural training
Systemic	Bilateral or multisystem disease	Conventional dosing and distribution	Blood–ocular barriers; systemic dose and toxicity

Route rule: Choose the least invasive route that can reliably meet the tissue-exposure requirement. If a topical program claims posterior-segment delivery, require quantitative tissue PK, spatial localization, systemic-exposure controls, and mechanism-consistent PD.

3 Formulation and delivery platforms

3.1 Conventional dosage forms

Aqueous solutions offer simple manufacture, rapid release, and relatively straightforward characterization, but require adequate solubility and chemical stability. Suspensions can accommodate poorly soluble drugs and provide a dissolution-controlled input, while creating particle-size, redispersibility, dose-uniformity, irritation, and device-clogging risks. Emulsions and ointments improve loading of lipophilic drugs and residence time but can blur vision or reduce acceptability.

3.2 Residence-enhancing systems

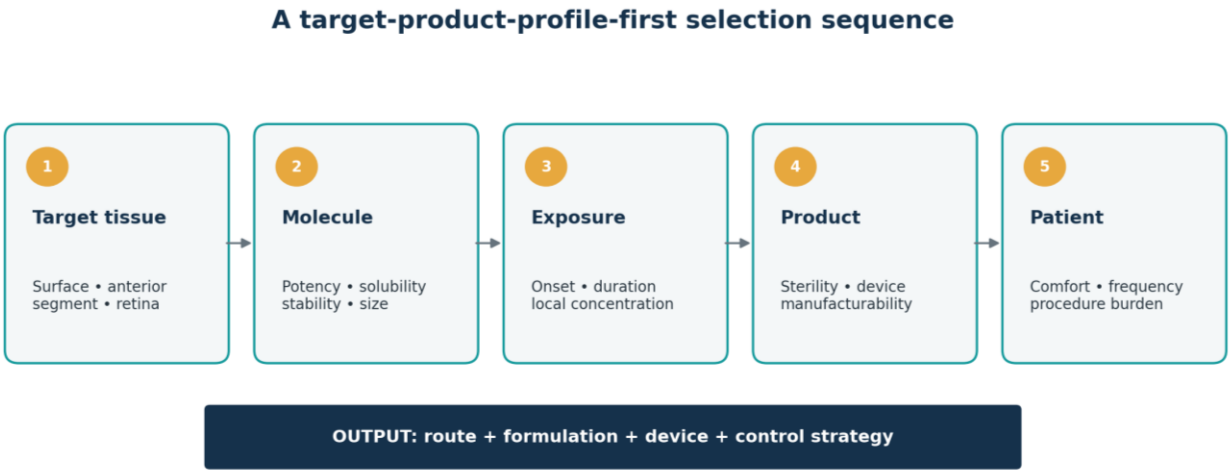
Viscosity modifiers, mucoadhesive polymers, and stimuli-responsive gels aim to retain drug at the surface without making dispensing or vision unacceptable. The useful design window is narrow: rheology at rest, shear thinning during blinking, drop formation, gelation kinetics, optical clarity, and preservative performance interact. Inserts and drug-eluting contact lenses may extend exposure further, but placement, comfort, retention, dose dumping, and combination-product considerations become prominent.

3.3 Colloidal and nanoscale systems

Liposomes, lipid nanoparticles, nanoemulsions, polymeric nanoparticles, nanomicelles, and nanosuspensions can improve apparent solubility, protect labile payloads, alter release, and enhance surface interaction. For oligonucleotides, proteins, and other biologics, carriers may also protect against degradation and facilitate cell uptake. These benefits must be demonstrated against a simpler control, because colloidal systems introduce composition, particle-size distribution, morphology, free-versus-associated drug, release, sterilization, aggregation, and long-term stability questions.

Platform	Primary value	Critical attributes	Frequent failure mode
Solution	Simplicity and immediate availability	pH, osmolality, assay, degradants, preservative	Insufficient solubility or rapid clearance
Suspension / nanosuspension	High loading of poorly soluble drug	PSD, polymorph, sedimentation, redispersion, dissolution	Growth/agglomeration and dose variability
Emulsion / nanoemulsion	Solubilization of lipophilic payload	Droplet size, phase behavior, free drug, osmolality	Physical instability or irritation
Liposome / lipid nanoparticle	Encapsulation, protection, controlled interaction	Size/PDI, morphology, lipid purity, encapsulation, release	Leakage, oxidation, aggregation, sterilization damage
Polymeric nanoparticle	Tunable release and surface chemistry	Molecular weight, residual solvent, size, release	Burst release or inflammatory response
Micelle / cyclodextrin	Apparent solubility with clear product potential	CMC, free drug, dilution stability, complexation	Precipitation after dosing or dilution
In situ gel	Longer residence with drop administration	Viscosity, gel trigger, clarity, dose delivery	Poor comfort or unreliable gelation
Implant / depot	Months-scale local exposure	Content uniformity, release, geometry, degradation	Dose dumping, migration, difficult reversibility

4 Platform selection: start with the target product profile



The selection sequence should be run before formulation optimization and revisited when new PK, tolerability, manufacturing, or human-factor data emerge. It converts "interesting technology" into a falsifiable product hypothesis.

TPP question	Decision enabled	Example acceptance concept
Which tissue and cell type must be exposed?	Route and localization strategy	Quantifiable exposure above a justified threshold
What concentration–time profile drives effect?	Immediate vs sustained release	Cmax/AUC/trough or duration above ECx
What dosing burden is acceptable?	Dosage form and device	Frequency and procedure interval compatible with use
What safety margin is required?	Dose, excipients, release and reversibility	Local and systemic NOAEL margin; recoverability
What commercial presentation is intended?	Sterilization, container and process	Stable, deliverable unit dose over shelf life

5 Formulation design and characterization

5.1 Preformulation and excipient strategy

Preformulation should map intrinsic solubility, pKa, logD, solid form, hygroscopicity, light/oxygen sensitivity, interfacial behavior, and degradation pathways across physiologically and pharmaceutically relevant conditions. Excipient selection must consider ocular exposure, concentration, route, frequency, impurity profile, and prior use; compendial status alone does not establish ocular tolerability.

5.2 Critical quality attributes

- Identity, assay, potency, related substances, elemental impurities where relevant, and mass balance under stress.
- pH, osmolality, viscosity/rheology, surface tension, appearance, optical clarity, and delivered drop or dose volume.
- Sterility, bacterial endotoxins where applicable, antimicrobial effectiveness for multidose products, and container–closure integrity.

- Visible and subvisible particulate matter, particle or droplet size distribution, morphology, charge, aggregation, and redispersibility.
- Encapsulation or association efficiency, free drug, in vitro release/dissolution, leakage, and dilution robustness.
- Device functionality, extractables/leachables, adsorption, dose accuracy, residual volume, and performance through shelf life.

5.3 Sterilization is a Design Input

Terminal sterilization is generally preferred when product and container can tolerate it. Otherwise, sterile filtration and aseptic processing require a formulation that passes the filter without unacceptable loss or size change and a process designed for contamination control. Nanoparticles, suspensions, viscous systems, biologics, and implants may be incompatible with conventional filtration or heat; the chosen method must be justified by product and process data.

> **Common inflection point:** A formulation should not advance because its fresh laboratory sample performs well. It should advance when the intended composition, manufacturing process, sterilization strategy, container–closure system, and stability profile jointly support the clinical use case.

6 Translational Evaluation Strategy

6.1 Data-Driven Decision Points

Stage	Question	Representative methods	Go/no-go signal
Bench	Is the product stable and deliverable?	Stress stability, rheology, release, device testing	CQAs remain within target under use conditions
Barrier model	Does drug cross or reside where intended?	Corneal cells, reconstructed tissue, diffusion cells	Improvement vs vehicle and mechanistic control
Ex vivo	Is transport preserved in intact tissue?	Excised cornea/sclera; imaging; tissue integrity	Flux/depot with acceptable barrier integrity
In vivo PK	Is target tissue exposed reproducibly?	Tear and tissue PK; systemic PK; spatial imaging	Exposure meets model-predicted threshold
In vivo PD	Does exposure drive biology?	Disease-relevant biomarkers and functional endpoints	Dose/exposure–response with coherent timing
Clinical	Is benefit meaningful and usable?	Symptoms, signs, imaging, function, adherence	Prespecified efficacy plus acceptable tolerability

An apparent exposure gain can be misleading if caused by residual formulation on tissue surfaces, vascular contamination, assay cross-reactivity, or barrier damage. Tissue collection, washing, perfusion, matrix effects, recovery, lower limits of quantitation, and distinction between intact payload and label should be validated. Imaging is strongest when paired with quantitative bioanalysis and functional PD.

6.2 Models Should Address Specific Risks

Species differ in blinking, tear volume, corneal thickness, ocular size, melanin, immune response, vitreous composition, and device fit. Rabbits are useful for topical tolerability and anterior-segment work but may not predict human residence or posterior distribution directly. Rodents enable disease biology and genetic tools; larger eyes can better support devices, injections, imaging, and surgical procedures. Model selection should follow the unanswered product risk, not convention alone.

6.3 Safety and Tolerability

Assessment should integrate slit-lamp examination, fluorescein staining, corneal thickness and endothelium when relevant, intraocular pressure, retinal imaging/function for posterior routes, histopathology, inflammation, immunogenicity for biologics, systemic exposure, and reversibility. Preservatives, surfactants, cationic materials, penetration enhancers, impurities, aggregates, and degradation products require particular scrutiny.

7 CMC and Regulatory Development

FDA's December 2023 draft guidance on topical ophthalmic drug products highlights microbiological quality, visible particulate matter, extractables and leachables, impurities and degradation products, optional in vitro release/dissolution approaches for certain dosage forms, container–closure design and dispensing, and stability. Development teams should confirm the current status of applicable guidance and align route- and modality-specific expectations with the relevant agency.

Workstream	Early development priority	Late-stage expectation
Process	Identify scale-sensitive mixing, size reduction, filtration and filling steps	Validated, controlled process with representative commercial equipment
Analytical	Stability-indicating methods and orthogonal particle/release assays	Qualified/validated methods with justified specifications
Microbiology	Sterilization/aseptic strategy and preservative rationale	Sterility assurance, integrity and in-use performance
Container/device	Material compatibility and delivered-dose characterization	Human factors, dose accuracy, extractables/leachables, shelf-life performance
Comparability	Link attributes to performance before major changes	Risk-based bridging after site, scale, process or device changes
Stability	Mechanistic stress studies in intended presentation	Long-term/accelerated data supporting shelf life and in-use period

Complex ocular products benefit from early regulatory interaction because the acceptable control strategy and clinical bridge may depend on how formulation microstructure, device performance, and in vitro release relate to local exposure. For gene, cell, biologic, implant, or combination products, product classification and lead-center coordination should be addressed early.

8 Emerging Directions

- Sustained and refillable delivery systems designed to reduce frequent intravitreal injections.
- Suprachoroidal and microneedle-enabled delivery that targets ocular compartments with smaller or more localized doses.
- RNA, gene-editing, and viral/nonviral gene-delivery systems requiring protection, cellular uptake, and durable expression control.
- Stimuli-responsive and bioadhesive materials that adapt release or residence to ocular conditions.
- Image-guided and biomarker-led development linking spatial distribution to target engagement.
- Model-informed development using ocular PBPK, population PK/PD, and quantitative systems pharmacology to integrate sparse tissue data.

The central translational challenge remains unchanged: a novel platform is valuable only when it produces a clinically relevant improvement that survives scale-up, sterilization, storage, administration, and real-world use.

9 Recommended development roadmap

Phase	Key activities	Decision gate
1. Product hypothesis	TPP, tissue target, exposure requirement, route trade study	One preferred route/platform and one fallback
2. Feasibility	Prototype screen; stress stability; release; barrier model; early tolerability	Reproducible benefit over simple control
3. Candidate selection	Scalable process; intended device; tissue PK/PD; preliminary safety	Candidate meets exposure, quality and safety thresholds
4. IND-enabling	GLP toxicology; GMP clinical process; specifications; stability; regulatory interaction	Evidence package supports first-in-human dosing
5. Clinical translation	Dose escalation; ocular/systemic PK where feasible; PD; usability	Dose and regimen supported by benefit–risk data
6. Registration readiness	Commercial process/device; validation; pivotal endpoints; lifecycle plan	Consistent product and clinically meaningful benefit

Portfolio recommendation: Maintain a written "platform value hypothesis" with a quantitative comparator. Retire complexity that does not improve exposure, duration, safety, usability, or manufacturability enough to change the product profile.

10 Conclusions

Ophthalmic drug delivery rewards disciplined integration. The eye's barriers make local exposure difficult, but the most important choice is not between conventional and advanced technologies. It is between an evidence-led product architecture and a technology-led formulation search.

A high-quality program defines the target tissue and exposure requirement, selects the least burdensome viable route, uses the simplest platform that meets the need, and constructs a translation chain from critical quality attributes through tissue PK and PD to clinical benefit. Sterility, device performance, comfort, manufacturability, and stability belong in that chain from the outset. When these elements are co-designed, advanced delivery technologies can convert potent molecules into differentiated, usable ophthalmic medicines.

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12 Abbreviations

Term	Definition	Term	Definition
CMC	Chemistry, manufacturing, and controls	CQA	Critical quality attribute
ECx	Concentration producing x% effect	GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice	IND	Investigational New Drug
LNP	Lipid nanoparticle	NOAEL	No-observed-adverse-effect level
PBPK	Physiologically based pharmacokinetic	PD	Pharmacodynamics
PK	Pharmacokinetics	PDI	Polydispersity index
PSD	Particle-size distribution	TPP	Target product profile