Comparative Evaluation of Amino Acids and β-Cyclodextrin on the Release and Corneal Permeation of Rebamipide from Hydrogel Contact Lenses

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Abstract

Background: Rebamipide (REB), a mucin secretagogue clinically indicated for dry eye disease, has limited application due to its poor aqueous solubility and low ocular bioavailability. The current study hypothesized that hydrogel contact lenses (CLs) based on Poly (2-hydroxyethyl methacrylate)/ N-vinyl pyrrolidone (HEMA/NVP) could provide prolonged ocular delivery of REB, while amino acids (arginine, lysine, and taurine) and β-cyclodextrin (β-CD) would modulate solubility, release, and corneal permeation of REB.

Methods: REB-loaded contact lenses were obtained via soaking. Solubility was measured in phosphate buffer (pH 7.4). In vitro release and ex vivo corneal permeation (sheep cornea) were evaluated using a Franz diffusion cell. Steady-state Flux (Jss), apparent permeability coefficient (Papp), and cumulative permeation were calculated as permeation parameters. Statistical analyses were performed using linear mixed-effects models ($p < 0.05$).

Results: REB solubility was improved by β-CD and amino acids, with the greatest improvement observed with arginine (ARG), followed by lysine (LYS), whereas no effect was observed with taurine (TAU).-The highest release was observed for arginine-based formulations, followed by lysine, β-CD, and taurine. In permeation studies, β-CD (1:3) yielded the greatest permeability amongst all formulations, whereas taurine (1:2) exhibited slightly lower permeability than its corresponding formulation but provided a more controlled release profile. Formulations containing arginine and lysine had higher release but lower permeation.

Conclusion: Taurine (1:2) provided the best balance between release rate and corneal permeation. This system permits the delivery of ~400 μg REB per lens, highlighting its potential as a sustained ocular drug delivery device.
Keywords: Rebamipide; Hydrogel contact lenses; Ocular drug delivery; β-Cyclodextrin; Amino acids; Sustained release.

Introduction

Dry eye disease (DED) is a complex ocular surface disorder characterized by tear film instability, ocular discomfort, and damage to the ocular surface.[1,2] It is primarily associated with dysfunction of the lacrimal glands, Meibomian glands, cornea, and conjunctiva, which are responsible for regulating tear film composition and stability.[3]

Conventional ophthalmic formulations, particularly eye drops, exhibit low ocular bioavailability (generally <5%), mainly due to precorneal elimination mechanisms such as blinking, tear turnover, and nasolacrimal drainage.[4-6] These limitations necessitate multiple daily dosing and may adversely affect therapeutic efficacy and patient compliance. Rebamipide (REB), a mucin secretagogue with anti-inflammatory properties and a quinolinone derivative, was introduced in Japan in 2012 as a 2% ophthalmic suspension (Mucosta®) for the treatment of DED and corneal or conjunctival injuries.[7] However, its relatively high concentration and turbid appearance may cause ocular irritation and transient visual disturbances, thereby limiting patient acceptance.[8]

Various formulation approaches, including nanoparticles, liposomes, in situ gels, and cyclodextrin-based complexes, have been explored to enhance the ocular delivery of REB. While these approaches improve drug solubility, stability, and short-term retention, they remain limited by rapid ocular clearance mechanisms such as blinking and tear turnover. Additionally, both short- and long-term adverse effects, including blurred vision and ocular discomfort following administration, can further reduce patient compliance. In contrast, drug-eluting contact lenses provide continuous contact with the corneal surface, enabling sustained drug release, prolonged residence time, and improved therapeutic adherence. Therefore, hydrogel-based contact lenses represent a promising strategy to overcome the limitations of conventional REB delivery systems.[9-11]

REB is a weak acidic drug ($pK_a = 3.38$).[12] Due to its acidic nature, it can form ion pairs or salts with basic compounds such as arginine and lysine, thereby improving its solubility and dissolution

behavior.[13-15] In addition, taurine, as a sulfur-containing amino acid, was selected for analysis owing to its physiological relevance in ocular tissues. Its zwitterionic nature makes it a good choice for ocular formulations. Notably, taurine transporters (TauT, SLC6A6) are expressed in the corneal epithelium,[16] suggesting a potential role in transmembrane transportation processes. This indicates a potential role for taurine in modulating drug permeation and enhancing corneal permeation via engagement with endogenous transport pathways.[17,18] Moreover, cyclodextrins (CDs), cyclic oligosaccharides derived from starch, are one of the common excipients in ocular formulations.[19] They are capable of forming inclusion complexes by encapsulating hydrophobic drug molecules within their hydrophobic cavity while maintaining a hydrophilic outer surface[20-22,] thereby increasing drug solubility. Although various formulation strategies have been investigated to improve the ocular delivery of REB,[8,23,24] but relatively limited attention has been given to the comparative evaluation of multifunctional excipients in hydrogel contact lens systems. The novelty of this study is the direct comparison of two types of excipients, amino acids and β-CD, within the same HEMA/NVP hydrogel platform. These excipients act through different mechanisms to increase drug delivery and may differentially influence the balance between sustained release from polymer network and corneal permeation of REB. Therefore, this study provides insights in optimizing the sustained ocular delivery of REB.

In this study, REB-loaded HEMA/NVP hydrogel contact lenses were developed as a sustained ocular drug delivery platform with prolonged residence time, controlled drug release, and reduced dosing frequency.[25] Furthermore, the effects of selected amino acids (L-arginine, L-lysine, and L-taurine) and β-CD on drug release behavior and ex vivo corneal permeation were systematically investigated.[26,27]

Methods

Materials

Rebamipide (REB, ≥99% purity) was purchased from Aladdin Industrial Corporation Ltd. (Shanghai, China). 2-hydroxyethyl methacrylate (HEMA, ≥99% purity), N-vinyl pyrrolidone (NVP, ≥99% purity), poly (ethylene glycol) diacrylate (PEGDA, average Mn ~700), azobisisobutyronitrile (AIBN, ≥98% purity), taurine (≥99% purity), and sodium hydroxide (NaOH, analytical grade) were all obtained from Macklin Biochemical Co., Ltd. (Shanghai, China). HEMA and NVP were used as monomers, PEGDA as the crosslinking agent, and AIBN

as the thermal initiator. L-arginine (≥99% purity) and phosphate-buffered saline (PBS, pH 7.4) were supplied by HiMedia Laboratories Pvt. Ltd. (Maharashtra, India). L-lysine (≥98% purity) was purchased from Shanghai Haphong Biomedical Technology Co., Ltd. (Shanghai, China). β-Cyclodextrin (β-CD, ≥98% purity) was obtained from Baoji Guokang Bio-Technology Co. All chemicals were used without further purification.

Differential Scanning Calorimetry (DSC)

A Shimadzu DSC-50 differential scanning calorimeter (Kyoto, Japan) was used for thermal analysis. Approximately 3 mg of the sample was accurately placed in an aluminum pan, with an empty aluminum pan used as the reference. Samples were heated from 25 °C to 350 °C at a rate of 10 °C/min. The thermogram was recorded, and the melting point of REB was determined from the peak temperature of the endothermic transition.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra were recorded using a Shimadzu FTIR-8300 spectrophotometer (Kyoto, Japan) over a spectral range of 4000-400 cm^{-1}. Solid samples (pure REB, β-CD, and inclusion complexes) were analyzed using the KBr pellet method. For contact lens and solution-based samples, spectra were obtained using attenuated total reflectance (ATR) mode under identical spectral conditions. All spectra were recorded, and characteristic peaks were compared to evaluate possible interactions and structural integrity.

Evaluation of REB solubility

An excess amount of REB was added to 10 mL of distilled water and phosphate buffer solution PBS (pH 7.4) in tightly sealed containers. The suspensions were continuously agitated for 72 hours in a temperature-controlled water bath at 25°C. After equilibration, the samples were centrifuged at 4000 rpm for 10 min. The supernatant was filtered through a 0.45 μm membrane filter, and the concentration of REB was determined using a UV spectrophotometer Shimadzu UV-1650 PC spectrophotometer (Kyoto, Japan) at a wavelength of 227 nm. All experiments were performed in triplicate.

Scanning Electron Microscopy (SEM)

Surface morphology was examined using field-emission scanning electron microscopy (FESEM; Inspect F50, Thermo Fisher Scientific, USA). Samples were mounted on aluminum stubs, sputter-coated with a ~20 nm layer of gold, and imaged under high vacuum at an accelerating voltage of 10 kV.

Powder X-ray Diffraction (PXRD)

Crystallinity of samples was evaluated using a Malvern Panalytical Aeris diffractometer (Netherlands). Diffractograms were recorded over a 2θ range of 2°–60° using Cu Kα radiation (λ = 1.5406 Å) at 40 kV and 30 mA, with a step size of 0.05° and a scan rate of around ~5°/min.

Preparation of Contact Lenses

The hydrogel matrix was prepared by mixing HEMA and NVP, followed by the addition of PEGDA as the crosslinking agent and AIBN as the thermal initiator. Details of formulations containing different amounts of compounds were listed in Table 1. The mixture was stirred until a clear solution was obtained, cast into polypropylene molds, and polymerized at 50 °C for 3 h. The prepared lenses were washed with ethanol and distilled water, and subsequently equilibrated in PBS (pH 7.4).

Table 1. Composition of Hydrogel Contact Lens Formulations (F1–F5)

Formula	HEMA % v/v	NVP % v/v	PEGDA %v/v	AIBN %w/v
F1	97.51%	1.99%	0.50%	0.20%
F2	95.52%	3.98%	0.50%	0.20%
F3	93.53%	5.97%	0.50%	0.20%
F4	91.54%	7.96%	0.50%	0.20%
F5	89.55%	9.95%	0.50%	0.20%

Characterization of Contact Lenses (CLs)

Optical transparency and visual inspection

Optical transparency was evaluated as the percentage of light transmittance in the range of 400–700 nm using a UV-Vis spectrophotometer.

Folding endurance

Folding endurance was determined by repeatedly folding hydrated lenses until breakage or crack formation, up to a maximum of 250 folds. All lenses were soaked in distilled water for 7 days before testing.

Swelling ratio

Lenses were dried to a constant weight (W_0) at 70 °C and subsequently immersed in 5 mL of PBS (pH 7.4). At predefined time intervals, lenses were removed, blotted dry, and weighed (W_t). The swelling ratio (SR%) was calculated accordingly. [28]

$$\text{Swelling ratio } (\%) = \frac{\text{Ws} - \text{Wd}}{\text{Wd}} \times 100\%$$

where Ws is the swollen weight of the lens, and Wd is the dry weight of the lens.

Equilibrium water content and oxygen permeability

Oxygen permeability (Dk) was estimated from equilibrium water content (EWC) using the following relationship:[29]

$$\text{Dk} = 1.67\, e^{0.0397\ \text{EWC}}$$

Selection of optimal CL formulation

Physicochemical parameters, including equilibrium water content, swelling ratio, estimated oxygen permeability, optical transmittance, and mechanical properties, were used to select the optimal formulation for REB loading.

Calculation of dose

The target REB dose for the contact lens system was estimated by comparing the absorbed dose from conventional eye drop administration with the expected absorbed dose from the lens. Approximately 5% of the administered dose (200 µg/day from 4000 µg/day of 2% REB eye drops) is assumed to be systemically absorbed.[30-32] Assuming 50% bioavailability of the contact lens system, a loading dose of 400 µg was calculated to achieve a comparable systemic exposure.[33]

However, for practical standardization of the soaking procedure and to ensure sufficient drug uptake into the hydrogel matrix, soaking solutions containing REB equivalent to 1000 µg were used during lens loading.

Preparation of β-CD–REB Inclusion Complex

Inclusion complexes with molar ratios of 1:1, 1:2, and 1:3 (REB: β-CD) were prepared using the kneading method. REB and β-CD were initially mixed and wetted with a minimal amount of PBS buffer (pH 7.4) to form a homogeneous paste. The mixture was kneaded for 45 min, dried at 40 °C for 48 h, pulverized, and sieved through a 100-mesh screen before storage in sealed vials.[34] The prepared complexes were characterized by FTIR, DSC, SEM, and PXRD.

Preparation of Contact Lenses Loaded with β-CD–REB Complex

Solutions containing β-CD–REB complexes equivalent to 1000 µg REB were prepared in PBS (pH 7.4). Pre-formed F5 contact lenses were immersed in the solutions and incubated under static conditions for 12 h. The loaded lenses were subsequently used for in vitro release and ex vivo permeation studies.

Amino Acid–REB Formulations

REB was mixed with L-arginine, taurine, and L-lysine at mass ratios of 1:1, 1:2, and 1:3 (drug: amino acid, w/w) in PBS. The details are listed in Table 2. The pH was adjusted to 7.4. F5 contact lenses were immersed in the prepared solutions for 12 h and gently blotted to remove excess surface solution. Both solutions and drug-loaded lenses were subjected to FTIR analysis before in vitro release and ex vivo permeation studies.

Table 2. Composition of amino acid-based formulations

Formulation	**REB: Amino acid ratio (w/w)**
F5A1	1:1 (REB: Arginine)
F5A2	1:2 (REB: Arginine)
F5A3	1:3 (REB: Arginine)
F5L1	1:1 (REB: Lysine)
F5L2	1:2 (REB: Lysine)

F5L3	1:3 (REB: Lysine)
F5T1	1:1 (REB: Taurine)
F5T2	1:2 (REB: Taurine)
F5T3	1:3 (REB: Taurine)

In vitro release and ex vivo corneal permeation studies

In vitro release was evaluated using a Franz diffusion cell (15 mL, diffusion area ≈ 1.77 cm^2) equipped with a dialysis membrane (MWCO 8–10 kDa). PBS (pH 7.4) was used as the receptor medium and maintained at 35 ± 1 °C under stirring at 150 rpm. Samples were collected every 24 h and replaced with fresh medium. REB concentration was quantified spectrophotometrically at 227 nm (n = 3).

For ex vivo permeation studies, sheep corneas were mounted with the epithelial side facing the donor compartment. Experiments were performed under similar conditions at 36±0.5 °C. The steady state flux (Jss) was calculated from the linear portion of the permeation profile.[35]

$$Jss = (dM/dt)/A \ldots\ldots$$

Drug content evaluation in contact lenses

Drug loading was performed by soaking pre-formed F5 lenses in PBS (pH 7.4) containing REB equivalent to 1000 µg per lens for 12 h under static conditions. For drug content determination, REB was extracted from the lenses using fresh PBS. Samples were collected at 6, 12, and 24 h, with media replacement at each interval until no absorbance at 227 nm was detected. Total drug content per lens was calculated as the sum of all extracted amounts and expressed as µg/lens (mean ± SD, n = 3). This method ensured complete drug recovery prior to release and permeation studies.

Statistical analysis

Statistical analyses were performed using GraphPad Prism (version 10) and R (version 4.5.1). For time-dependent data, linear mixed-effects models were applied with fixed effects of time, excipient type, and ratio, and random effects of replicate. Release kinetics were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models based on adjusted R^2. The steady-state flux (Jss) was calculated from the linear portion of the permeation profile (6–12 h), and lag time was determined by extrapolation. Statistical significance was defined as $p < 0.05$.

Results

Characterization and Selection of Blank Contact Lenses

Visual inspection of prepared contact lenses

All formulations (F1–F5) were successfully prepared as uniform, circular, concave lenses. They were smooth, transparent, and showed no visible defects such as cracks or edge deformation. This indicates good mechanical integrity and successful polymerization.

Optical transparency and mechanical strength

All formulations exhibited high optical transparency (>93%) and excellent mechanical strength, sustaining up to 250 folding cycles without physical degeneration. The swelling rate was formulation dependent, with F5 showing the highest swelling ratio (more than 50%), which is likely due to its higher NVP content and increased hydrophilicity.

Equilibrium water content and oxygen permeability

An increase in NVP content resulted in a gradual rise in both EWC and Dk (Table 3). This indicates enhanced hydration and oxygen permeability of the hydrogel lenses.

Table 3. Equilibrium water content and oxygen permeability

Formulation	EWC%	Dk
F1	25.69 ± 0.27	4.630
F2	28.25 ± 0.28	5.126
F3	30.94 ± 0.25	5.703
F4	33.58 ± 0.15	6.334
F5	37.01 ± 0.28	7.258

EWC: equilibrium water content; Dk: oxygen permeability coefficient.

FTIR of monomers and hydrogel

FTIR analysis confirmed successful copolymerization of HEMA and NVP (Figure S1). The disappearance of the vinyl C=C peak (~1635 cm^{-1}) suggested completion of polymerization, while broadening of the O–H band suggested hydrogen bonding within the hydrogel network.

Selection of optimal formulation

As the NVP content increased from F1 to F5, the hydrophilicity of the hydrogel correspondingly improved, leading to higher swelling ratios and EWC, with F5 exhibiting the highest values. The increased hydration expanded the polymer network, facilitating drug absorption and diffusion, as drug transport in hydrogels largely depends on the water content and the degree of network porosity. Therefore, F5 was selected as the optimal formulation.

Characterization of β-CD-REB inclusion complex

FTIR analysis

The disappearance or reduction of characteristic REB peaks in the β-CD-REB inclusion complex indicates successful host-guest interaction, suppression of drug crystallization, and encapsulation of the drug within the β-CD cavity. Similar spectral features observed in loaded contact lenses suggest incorporation of the complex into the hydrogel polymer without any chemical interaction (Figure S2).

Differential Scanning Calorimetry

The thermogram of pure REB displayed a sharp endothermic peak at approximately 291 °C, corresponding to its crystalline melting point. β-CD exhibited a broad endothermic event around 102 °C, attributed to the loss of bound water, indicating a significant degree of hydration. In the physical mixture, the melting peak of REB remained unchanged and identical to that of pure REB, suggesting the absence of interaction between the components. In contrast, the DSC thermogram of the β-CD-REB inclusion complex showed the complete disappearance of the characteristic REB melting peak (Figure S3). Additionally, a broadened thermal event appeared around 220 °C, may suggest reduced crystallinity of REB and suggesting the successful formation of the inclusion complex.

XRPD analysis

Pure REB exhibited sharp diffraction peaks (10-30˚), confirming its crystalline structure. In comparison, the β-CD–REB inclusion complex showed peaks of markedly lower intensity along with partial peak broadening, signifying a reduction in crystallinity (Figure S4). This partial loss of structural order may indicate a successful complexation with β-CD, a process known to enhance the solubility and dissolution rate of crystalline drugs.

Field Emission Surface Electron Microscopy (FESEM) analysis

FESEM images of the β-CD-REB inclusion complex (A and B) revealed irregular sheet-like aggregates with a rough porous surface and nanoscale cavities (15-95 nm). These morphological features differ markedly from the smooth, well-defined crystalline particles observed in pure REB (C and D). Such structural alterations suggest the successful formation of the inclusion complex (Figure 1).

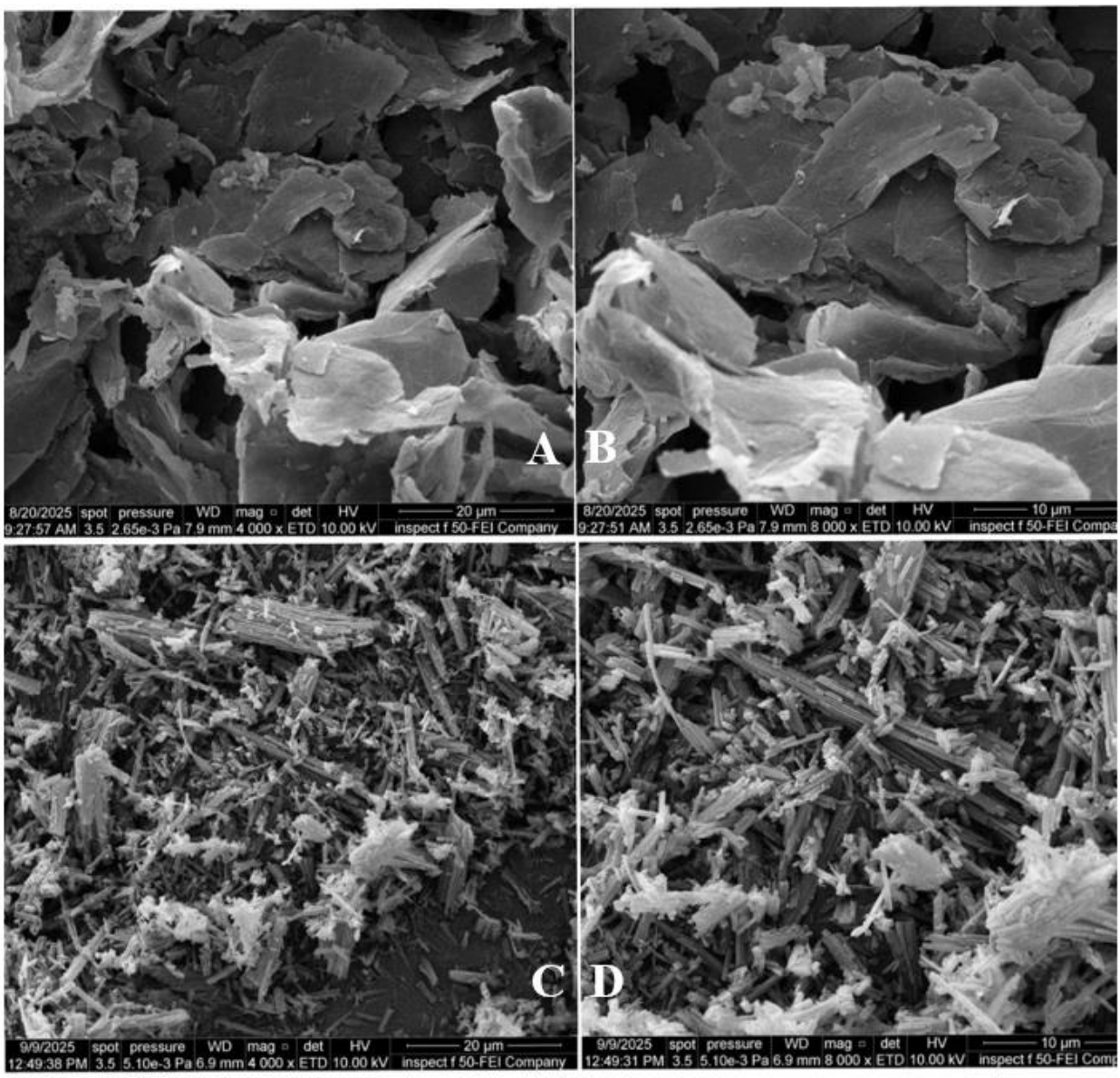


Figure 1. FESEM micrographs of the β-CD–REB inclusion complex (A and B) and pure REB (C and D), showing morphological differences and altered particle organization following complex preparation.

Solubility

Solubility studies of the REB-β-CD inclusion complexes in PBS (pH 7.4) demonstrated clear molar-ratio-dependent enhancements. At a 1:1 drug-to-β-CD ratio, solubility increased only slightly compared to pure REB, reaching 3.77 mg/mL. Increasing the complexation ratio to 1:2 produced a marked improvement, raising solubility to 4.91 mg/mL—a significant enhancement. A

further increase to a 1:3 ratio resulted in a solubility of 5.28 mg/mL, representing only a modest additional gain compared with the 1:2 ratio. Overall, these findings indicate that β-CD complexation substantially enhances REB solubility, with the 1:2 molar ratio providing the most pronounced improvement. Higher β-CD ratios appear to reach a plateau, likely due to saturation of the complexation capacity.

Evaluation of REB-Amino acid formulations

The various REB-amino acid formulations were prepared for incorporation into the F5 contact lens. Each formulation code corresponds to the specific amino acid used and the applied drug-to-amino acid ratio (Table 2).

FTIR of REB-Amino acids formulations

FTIR spectra of REB, arginine, REB-Arg solution, and REB-Arg-loaded contact lenses are illustrated in Figure S5. When REB was mixed with Arginine in solution, the FTIR spectrum exhibited a broad N–H/O–H stretching band in the 3300–3200 cm^{-1} region, along with the amide C=O stretching band near 1680–1650 cm^{-1}. Several characteristic aromatic C–H and C=C vibrational bands spanning 1500–700 cm^{-1} became noticeably attenuated. The amide and aromatic peaks between 1650–1500 cm^{-1} showed a loss of sharpness and peak intensity. These spectral changes are consistent with hydrogen-bonding interactions between the amide/carboxyl functional groups of REB and the guanidinium moiety of arginine. Importantly, no new absorption bands were observed, indicating that the interaction is purely physical and does not involve any chemical transformation (Figure S5).

In the solution spectra for REB–lysine, FTIR analysis demonstrated broadening and decreased intensity of characteristic peaks associated with REB. The latter results suggested possible intermolecular interactions between REB and lysine in this system. The REB-Lys system remained molecularly dispersed after loading into the hydrogel matrix, and no chemical bonding to the polymer network was observed. These findings indicate that the drug was incorporated through physical interaction, thereby preserving the structural integrity of both the drug and the hydrogel matrix (Figure S6).

FTIR analysis of REB-taurine formulations showed that taurine retained its characteristic SO_3^- peaks (1200–1250 and 1030–1080 cm^{-1}), while REB exhibited its main amide band around 1660 cm^{-1} and aromatic bands in the 1500–1600 cm^{-1} region. In the REB-Taurine lenses, these peaks appeared broadened or slightly shifted, suggesting weak hydrogen-bonding interactions without structural modification of the drug. In addition, the characteristic polymer peaks, including the O–H stretching band at 3450 cm^{-1} and the C=O stretching band near 1720 cm^{-1}, dominated the spectra of the loaded lenses. The absence of new absorption bands confirms that drug loading occurs through physical entrapment within the hydrogel matrix rather than chemical reactions (Figure S7).

Effects of amino acids on REB solubility

In phosphate buffer (pH 7.4), REB demonstrated a solubility of 3.78 mg/mL in the absence of amino acids. The addition of arginine significantly increased solubility to 8.69 mg/mL, while lysine produced a moderate enhancement, reaching 4.80 mg/mL. In contrast, taurine did not produce any significant effect, with REB solubility remaining comparable to that of the drug alone in buffer alone.

Drug content

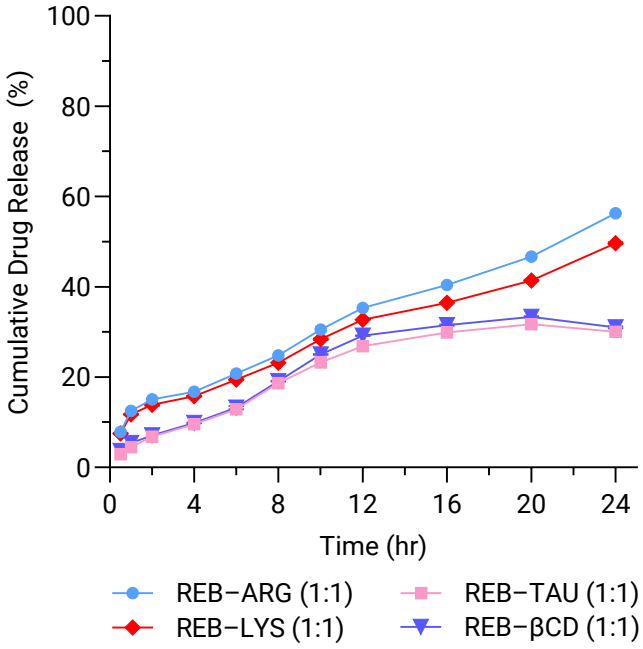
The drug content per lens was consistent across all the formulations, ranging from 728 ± 0.71 to 753 ± 0.49 µg (Table S1). The low standard deviation values (<1 µg) showed minimal variability and excellent reproducibility of the soaking method. These results confirm that all formulations possessed equivalent drug loads, regardless of excipient ratio or type. This uniformity is essential for ensuring that subsequent in vitro release and ex vivo permeation studies are not influenced by differences in initial drug loading. Although the theoretical target dose of 400 µg, soaking solutions containing ~1000 µg REB provided loading values between approximately 700–750 µ g/lens due to passive uptake and drug partitioning within the hydrogel network.

In vitro release

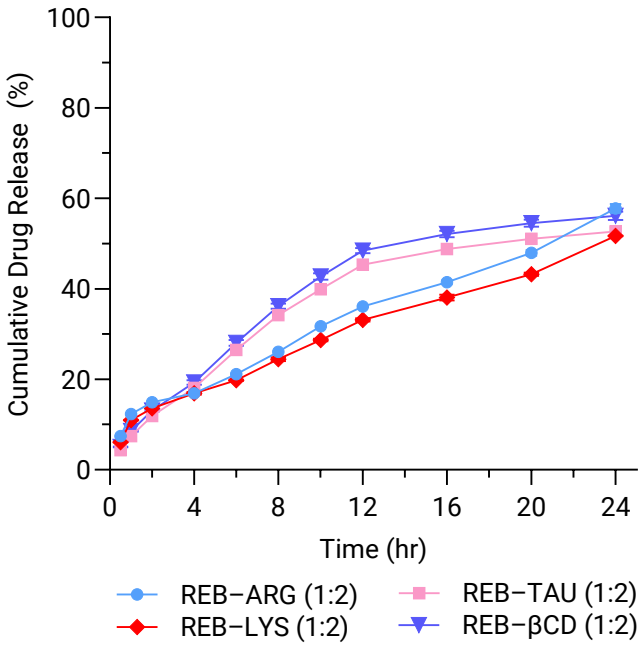
The in vitro release kinetics of REB from F5 contact lenses loaded with different amino acids and β-CD at varying drug-to-excipient ratios were evaluated over a 24-hour period. The corresponding release profiles are presented in Figure 2. Overall, all formulations demonstrated a time-dependent

increase in cumulative drug release. Among them, formulation F5A3 exhibited the highest cumulative drug release at the end of the study period.

Statistical analysis revealed that both the type of excipient and the drug-to-excipient ratio significantly influenced the cumulative release of REB ($p < 0.05$).



(a)



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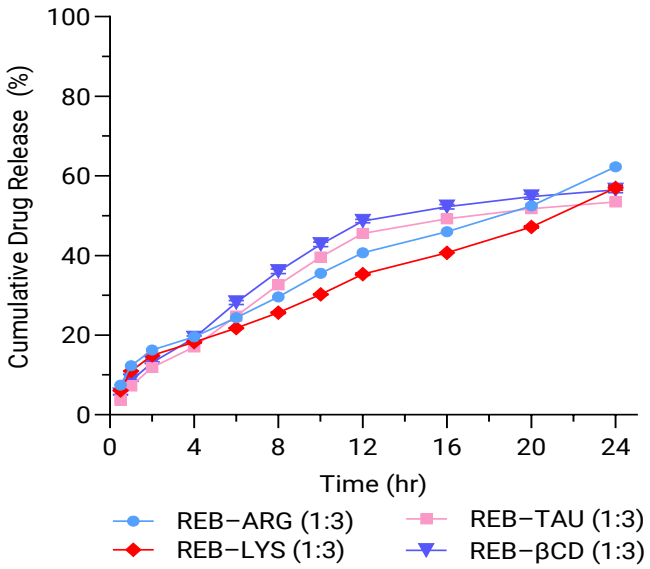


(c)

Figure 2. In vitro cumulative release profile of REB from hydrogel CLs containing different excipients at a drug-to-excipient ratio of (a) 1:1 (b) 1:2 and c (1:3) over 24 h. Data are presented as mean ± SD.

Release kinetics

Zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models were applied to evaluate the drug release behavior of the prepared contact lens formulations. Model selection was based on the highest adjusted coefficient of determination (R^2_{adj}). Arginine- and lysine-based formulations exhibited the best fit to the Korsmeyer–Peppas model, with diffusion exponent (n) values indicating non-Fickian (anomalous) transport. In contrast, formulations containing taurine and β-CD followed the Higuchi model, suggesting diffusion-controlled release (Table 4).

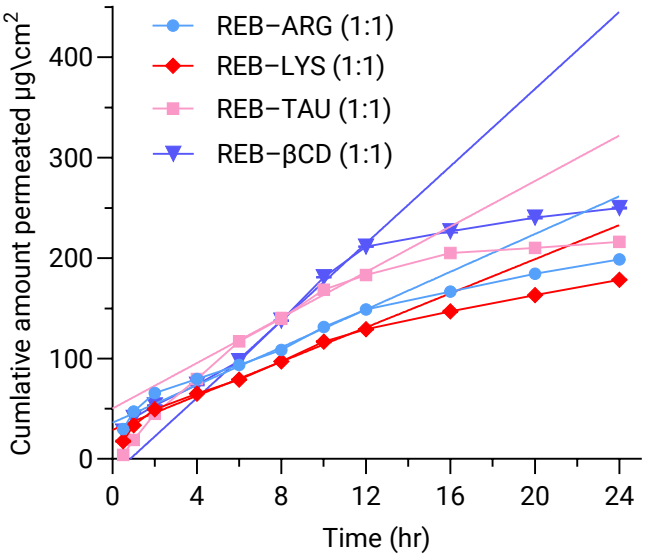
Table 4. Release kinetics parameters of the prepared CLs formulations

Formulation	Ratio	Zero-Order R^2_{adj}	First-Order R^2_{adj}	Higuchi R^2_{adj}	K-P R^2_{adj}	K-P Slope (n)	Best Fit Model	Predominant Mechanism
REB–ARG	1:1	0.9897	0.9862	0.9599	**0.9929**	0.6749	K-P	Anomalous Transport
	1:2	0.9888	0.9868	0.9652	**0.9943**	0.6802	K-P	Anomalous Transport
	1:3	0.9829	0.9905	0.9810	**0.9946**	0.6409	K-P	Anomalous Transport
REB–LYS	1:1	0.9847	0.9892	0.9689	**0.9912**	0.6350	K-P	Anomalous Transport
	1:2	0.9847	**0.9913**	0.9768	**0.9909**	0.6292	First-Order / K-P	Anomalous Transport
	1:3	0.9867	0.9871	0.9732	**0.9891**	0.6363	K-P	Anomalous Transport
REB–TAU	1:1	0.8815	0.8945	**0.9510**	0.9055		Higuchi	Fickian Matrix Diffusion
	1:2	0.8758	0.9173	**0.967**	0.9164		Higuchi	Fickian Matrix Diffusion
	1:3	0.8902	0.9291	**0.9700**	0.9240		Higuchi	Fickian Matrix Diffusion
REB–βCD	1:1	0.8656	0.8756	**0.9338**	0.8870		Higuchi	Fickian Matrix Diffusion
	1:2	0.8782	0.9222	**0.9668**	0.9165		Higuchi	Fickian Matrix Diffusion
	1:3	0.8808	0.9251	**0.9680**	0.9191		Higuchi	Fickian Matrix Diffusion

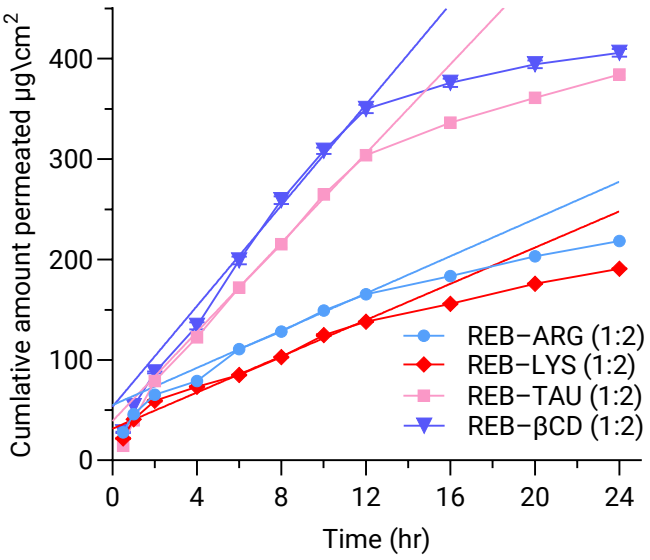
R^2adj, adjusted coefficient of determination; K-P, Korsmeyer–Peppas; n, release exponent indicating the drug release mechanism

Ex vivo permeation study of prepared formulations

The cumulative ex vivo permeation profiles of REB from F5 contact lenses loaded with different amino acids and β-CD at drug-to-excipient ratios of 1:1, 1:2, and 1:3 over a 24-hour period are presented in Figure 3. A statistically significant difference in drug permeation was observed among the formulations ($p < 0.05$). All tested formulations demonstrated a time-dependent increase in cumulative permeation. At the end of the study, formulations containing taurine and β-CD exhibited the highest cumulative permeation values.



(a)



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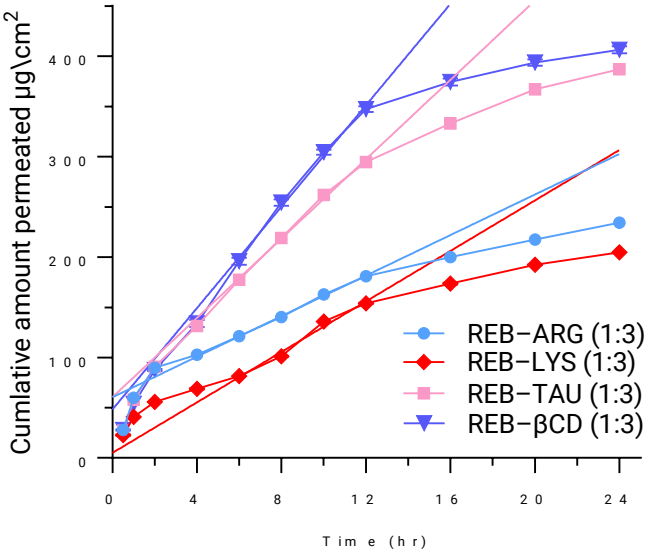

(C)

Figure 3. Ex vivo corneal permeation profile of REB from hydrogel contact lenses containing different excipients at a drug-to-excipient ratio of (a)1:1 (b) 1:2, and (c) 1:3 over 24 h. Data are presented as mean ± SD. The straight fitted lines represent the linear permeation region (6–12 h) used for steady-state flux determination.

Table 6. Permeation flux (μg/cm^2.min) calculated from the slope of the linear portion of the cumulative permeation profiles between 6 and 12 h, corresponding to the steady-state conditions. Lag time was determined from the x-axis intercept of the extrapolated linear region.

Formulation	Ratio	Permeation Rate (μg/ h)	Flux (μg/cm^2.min)	Lag Time (h)	R^2
REB–ARG	1:1	9.398	0.088	-	0.994
	1:2	9.270	0.087	-	0.998
	1:3	10.090	0.095	-	0.998
REB–LYS	1:1	8.498	0.080	-	0.991
	1:2	9.020	0.085	-	0.998
	1:3	12.570	0.118	-	0.985
REB–TAU	1:1	11.330	0.107	-	0.969
	1:2	22.220	0.209	-	0.994
	1:3	19.750	0.186	-	0.996
REB–βCD	1:1	19.230	0.181	0.841	0.995
	1:2	25.070	0.236	-	0.990
	1:3	25.250	0.238	-	0.993

Discussion

Statistical analysis demonstrated that permeation behavior was significantly influenced by time, excipient ratio, and their interactions ($p < 0.001$). These findings emphasize permeation as a discriminating parameter to differentiate between formulations.[36] Taurine-containing contact lenses showed the most controlled and desirable permeability profile, with the highest steady-state flux at the 1:2 ratio (0.209 μg/cm²·min). The zwitterionic nature of Taurine (having no net charge at physiological pH) facilitates weak, reversible interactions within the hydrogel matrix, promoting diffusion-driven transport rather than strong drug retention. Correspondingly, taurine formulations followed the Higuchi release model ($R^2 = 0.967$), indicating predominantly diffusion-controlled release. The strong correlation between release and permeation ($r = 0.998$, $p < 0.001$) suggests that the drug released from taurine-based lenses was effectively translated into corneal permeation. These results identify taurine as a promising excipient for achieving controlled and predictable REB permeation.[37,38]

The β-CD-REB inclusion complex showed a dense, fused, platelet-like morphology, distinct from the bright needle-shaped crystals of pure REB. This marked change in solid-state morphology confirmed successful complexation and reduced crystallinity, properties known to enhance wettability and dissolution.[39,40] However, despite higher absolute permeation values, the β-CD

formulations showed optical instability and loss of transparency over two days, limiting their practical use in contact lenses.

Arginine and lysine yielded the greatest enhancement in REB solubility, consistent with their ability to improve drug–water interactions and disrupt drug aggregation in aqueous media.[41] Arginine, in particular, is a well-known solubilizing agent due to its guanidinium group, which provides strong multipoint interactions.[42] Accordingly, the REB-Arg and REB-Lys formulations produced the highest drug release. However, despite enhanced solubility and release, these formulations did not improve corneal permeation. A likely explanation is that amino acid–mediated solubilization retains REB in a more hydrophilic, ion-associated, or complexed state, facilitating aqueous release but limiting partitioning into the lipophilic corneal epithelium. In contrast, the improved permeation seen with taurine and β-CD likely stems from superior interaction with epithelial barriers relative to the amount released.

Study limitations

The study was restricted to in vitro release and ex vivo corneal permeation models, which do not fully replicate the complex physiological conditions of the ocular surface, including tear turnover, blinking, and enzymatic activity. Additionally, long-term lens stability, optical clarity, and mechanical performance under extended wear conditions were not systematically evaluated. The study also lacked in vivo and clinical data to assess biocompatibility, ocular irritation, and safety. Furthermore, the limited range of excipient ratios and polymer compositions may restrict generalizability. Future studies should therefore include in vivo evaluation and clinical trials to validate chronic safety, therapeutic efficacy, and tolerability in patients.

Conclusion

This study demonstrated the possibility of using HEMA/NVP CLs lenses for sustained ocular delivery of REB, addressing limitations associated with conventional eye-drop formulations. The prepared lenses maintained suitable transparency, hydration, and structural stability while remaining compatible with REB and the investigated excipients. β-CD significantly enhanced REB solubility and contributed to sustained drug release, whereas arginine and lysine promoted enhanced release behavior through improved aqueous solubilization. Taurine, despite its minimal

effect on solubility, provided the most balanced release–permeation profile and produced the greatest enhancement in corneal permeation, highlighting its potential role in facilitating corneal transport. Overall, the developed REB-loaded CLs showed prolonged drug release and improved corneal permeation, suggesting their potential as an alternative strategy for dry eye disease management. Nevertheless, further in vivo studies, stability tests, and clinical studies are required to evaluate their long-term safety and therapeutic efficacy.

Authors' Contribution

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Competing Interests

None.

Ethical Approval

Not applicable.

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