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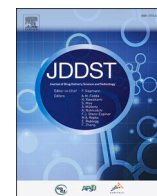
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3D-printed alginate implants for sustained-release of Faricimab; fabrication and characterisation

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ABSTRACT

Age-related macular degeneration (AMD) remains a leading cause of irreversible vision loss, with neovascular forms requiring frequent intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. While Faricimab, a bispecific antibody targeting VEGF-A and Angiopoietin-2, enables extended dosing intervals compared with earlier agents, frequent administration is still necessary due to rapid ocular clearance and limited bioavailability of biologics. Sustained-release ocular implants have demonstrated clinical utility for small-molecule drugs; however, limited established platforms exist for the controlled delivery of antibody therapeutics in AMD management. This study presents development and in-vitro evaluation of 3D-printed alginate-based micro-implants designed for prolonged release of Faricimab. Alginate was selected as the primary biomaterial for its biocompatibility, biodegradability, and mild ionic crosslinking supporting protein stability. To enhance mechanical integrity and modulate release kinetics, composite formulations including in-situ polymerized collagen and hyaluronic acid methacrylate were incorporated. 3D bioprinting enabled the production of micro size implants with dimensions of approximately 0.5–0.8 mm in diameter, a range that is within clinically approved ocular implants, release kinetics, structural stability, and degradation profiles were assessed using an ocular rig model replicating physiological aqueous humour turnover. The printed implants exhibited structural stability and enabled sustained release of Faricimab for more than 80 days. Importantly, the alginate matrix provided an enhanced protective microenvironment that preserved the structural integrity of the antibody. Stability studies showed that while Faricimab in solution rapidly aggregated and degraded within 24 h at 37°C, it maintained its stability in fabricated alginate scaffold. While it is necessary to conduct the long-term stability study, these findings highlight the dual role of the 3D-printed alginate implant as both a drug delivery platform and a protein-stabilising matrix. This work therefore establishes a novel strategy for fabricating injectable micro-scale ocular implants capable of delivering biologic therapeutics, offering a promising approach to reduce injection frequency and improve long-term treatment outcomes in patients with age-related macular degeneration.

1. Introduction

Age-related macular degeneration (AMD) is one of the leading causes of irreversible vision loss, particularly in individuals aged 60 and older. It is estimated to affect nearly 200 million people worldwide, with its prevalence continuing to rise due to increasing life expectancy [1]. This growing burden of AMD poses significant public health challenges, placing a strain on healthcare systems and necessitating the

development of efficient and long-lasting treatment strategies [2].

Intravitreal administration of vascular endothelial growth factor inhibitors (anti-VEGF) has become the standard treatment for this disease, as they inhibit VEGF activity, stabilise vascular integrity, and reduce fluid accumulation in the retina. Several anti-VEGF antibody-based medicines are already approved for clinical use, including Ranibizumab (Lucentis®), Aflibercept (Eylea®), Brolucizumab (Beovu®), Bevacizumab (Avastin®) and Faricimab. These biologics have

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demonstrated significant efficacy in improving visual acuity and halting disease progression [3–7].

Among these biologics, Faricimab has emerged as the most advanced biologic currently available for the treatment of AMD [8]. Unlike earlier biologics that exclusively target VEGF-A, Faricimab is a bispecific antibody that simultaneously inhibits VEGF-A and Angiopoietin-2 (Ang-2) [9]. This dual inhibition addresses additional pathways involved in vascular destabilisation and leakage, enabling improved vascular stability and prolonged suppression of disease activity [2,10].

Despite the therapeutic advancements introduced by Faricimab, several challenges persist, including the occurrence of vitreous floaters [11], severe intraocular inflammation [12], and infection risks following intravitreal injection [13]. These complications are partly linked to the frequency of injections and may also reflect limitations in long-term molecular stability and the potential formation of aggregates within the vitreous. Such issues remain a major obstacle in the long-term management of nAMD, underscoring the urgent need for innovative sustained-release delivery strategies with improved stability, the primary focus of this study.

Ocular implants have emerged as a promising approach, capable of maintaining therapeutic concentrations over extended periods, reducing injection frequency, and improving adherence [14]. By delivering drugs directly to the posterior segment in a controlled manner, these systems can address challenges of poor bioavailability and rapid clearance [10]. Existing implants, such as Ozurdex® (dexamethasone), Iluvien® (fluocinolone acetonide), and Durysta™ (bimatoprost), demonstrate the clinical potential of sustained-release devices, particularly for chronic ocular conditions [14,15]. These platforms, typically fabricated from biodegradable or non-biodegradable polymers, provide site-specific release over weeks to months, minimising systemic exposure and reducing treatment burden (Table 1). In the context of AMD, sustained intraocular delivery is particularly attractive because current anti-VEGF/anti-Ang-2 therapies require repeated intravitreal injections to maintain disease control [16].

Despite this progress, sustained-release implants have been successfully applied only to small-molecule agents, which are chemically stable and compatible with conventional polymer matrices. Antibody-based biologics such as Faricimab present unique challenges due to their high molecular weight, structural complexity, and sensitivity to pH, temperature, and enzymatic degradation [10]. Consequently, no clinically approved implant platform currently exists for the long-term delivery.

To address this unmet need, this study explores the development of a 3D-printed alginate-based micro implant designed at clinically relevant ocular dimensions (approximately 0.6–0.7 mm in diameter and 1–6 mm in length), allowing administration through intravitreal injections procedures, similar to approved implants such as Ozurdex, Iluvien and Durysta. The aim is to create a minimally invasive delivery platform capable of both sustained therapeutic release and maintaining the protein stability of biologics within a physiological environment. We

hypothesised that incorporation of Faricimab within the injectable ocular size implant would extend intraocular residence time while protecting Faricimab from degradation and aggregation overcoming key limitations of current treatments.

The selection of biomaterials plays a pivotal role in the development of these ocular implants for sustained drug delivery applications [23]. An ideal material ensures biocompatibility with the capacity to enable prolonged and controlled drug release while maintaining structural stability within the dynamic and sensitive ocular environment [24]. Over the past decades, both natural and synthetic polymers, such as alginate, chitosan, hyaluronic acid, collagen, gelatin, PLGA, Polycaprolactone (PCL), and PVA, have been extensively investigated for ocular applications owing to their biodegradability, mucoadhesive properties, and tunable mechanical profiles [25,26]. A number of these materials are already used in clinically approved implants (Table 1), underscoring their translational potential. Table 2 summarises their key physicochemical features and applications in ocular drug delivery.

Among these candidates, alginate (ALG) was selected as the principal biomaterial in this study due to its well-documented advantages [38]. ALG is a naturally derived, FDA-approved polysaccharide with excellent biocompatibility and low immunogenicity, both essential for intraocular applications. Its shear-thinning rheology enables precise extrusion during 3D bioprinting, while rapid ionic crosslinking with calcium ions

Table 2
Biomaterials commonly used for ocular drug delivery (ODD).

Biomaterial	Properties	Application in ODD	Reference
Alginate	Biodegradable, Mucoadhesive, Biocompatible	Sustained drug release, hydrogels, nanoparticles	[27]
Chitosan	Biodegradable, Mucoadhesive, Enhances corneal permeability	Nanoparticles, gels, contact lenses	[28]
Hyaluronic Acid	Biocompatible, Viscoelastic, promotes wound healing	Artificial tears, Hydrogels, Nanoparticles	[29]
Collagen	Biocompatible, supports cell adhesion	Corneal shields, drug-loaded films	[30]
Gelatin	Biodegradable, Cross-linkable, Bio adhesive	Nanoparticles, micelles, hydrogels	[31]
PLGA	Biodegradable, Tunable degradation, FDA-approved	Microparticles, Nanoparticles, Implants	[32]
PCL	Biodegradable, slow degradation	Implants, nanofibers	[33]
Pluronic	Thermosensitive, surfactant properties	Micelles, gels	[34]
PVA	Biocompatible, mucoadhesive	Contact lenses, hydrogels, micelles	[35]
Polyethylene Glycol (PEG)	Hydrophilic, reduces protein adsorption	Hydrogels, micelles, drug conjugates	[36]
Silk Fibroin	Biocompatible, mechanically strong	Films, hydrogels, nanoparticles	[37]

Table 1
Current small drug implants for ocular drug delivery.

Implants	Shape	Size (Approx.)	Placement	Non-biologic Drugs	Biomaterial	Medical Application	Ref.
Ozurdex	Rod-shaped (Cylindrical)	0.2–0.6 mm (diameter), 1–6 mm (length)	Intravitreal	Dexamethasone	poly(lactic-co-glycolic acid) (PLGA)	Uveitis, Diabetic Macular Edema, Retinal Vein Occlusion (RVO)	[17]
Iluvien				Fluocinolone	non-erodible polyimide	Diabetic Macular Edema	[18]
Durysta				Bimatoprost	PLGA	Glaucoma/Ocular Hypertension	[19]
Surolux	Disc or Tablet-Shaped	2–4 mm (diameter), 0.5–1.5 mm (thickness)	Subconjunctival, Intravitreal	Dexamethasone	PLGA with hydroxypropyl methylcellulose (HPMC)	Post-cataract surgery inflammation	[20]
Vitrasert				Ganciclovir	Polyvinyl Alcohol (PVA) and ethylene vinyl acetate (EVA)	CMV retinitis	[21]
Ocusert	Ring/Flexible Insert	Thin, (exact size varies by type)	Conjunctival sac	Pilocarpine	EVA and/or polydimethylsiloxane (PDMS)	Glaucoma	[22]

supports hydrogel formation under mild, aqueous conditions compatible with fragile biologics such as monoclonal antibodies. In addition, its intrinsic porosity and tunable degradation kinetics provide a favourable platform for sustained, diffusion-driven drug release. Additionally, optical transparency of ocular biomaterials is an important consideration, as materials placed within or near the visual pathway should minimise light scattering and visual disturbance. Alginate-based hydrogels have been proved to offer transparency, making them suitable for using in the ocular media [39,40].

To further improve mechanical performance and modulate release profiles, alginate can be combined with other biopolymers. In-situ polymerized pepsin-soluble Collagen (IPC) was incorporated for its bioactivity and extracellular matrix, mimicking properties, while Methacrylate Hyaluronic Acid (HAMA) were explored to improve structural stability and fine-tune release kinetics [30]. Together, these composite hydrogels more closely replicate the native ocular microenvironment, leveraging their bioactivity, mechanical stability, and capacity to modulate release kinetics [30], and thereby supporting both implant stability and drug preservation.

Implants were fabricated using 3D bioprinting, enabling precise control of geometry, architecture, and drug loading [41]. The implants were designed with dimensions and a cylindrical shape comparable to clinically approved devices, such as Ozurdex, to ensure clinical relevance. To replicate the ocular environment, a rig ocular model simulating aqueous humour turnover and intraocular clearance was employed, allowing evaluation of drug release kinetics, implant degradation, and structural integrity over time.

This work aims to establish a proof-of-concept for a novel sustained-release platform for antibody-based biologics in AMD, paving the way for next-generation ocular implants that reduce treatment burden, improve patient outcomes, and extend the clinical utility of Faricimab.

2. Materials and methods

2.1. Materials

Alginic acid powder (cat no. A17582.36), purchased from Thermo Fisher Scientific, Hyaluronic acid sodium salt (Low molecular weight 40-50 kDa, cat no. FH01773) were purchased from Biosynth. Pepsin-Soluble Collagen (6 mg mL⁻¹) in 0.01 M HCl 100 mL (cat no. FS22005), purchased from Collagen solutions. Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate (cat no. ED2SS), D-mannitol (cat no. M9546, MW: 182.17), Sodium bicarbonate (NaHCO₃, cat no. 13418), Calcium chloride (dried, powder, 97%, cat no. L13191.0I), Sucrose (cat no. S7903), Sodium hydroxide (NaOH, 1 M, cat no. L1980), MES monohydrate (≥99.0%, cat no. 69893), Sodium chloride (NaCl, ≥99.5%, cat no. S9888), 2-aminoethyl methacrylate hydrochloride (AEMA, 90%, cat no. 516155), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (97%, cat no. 348960050), Ru-Tris(2,2'-bipyridyl) dichloro-ruthenium (II) hexahydrate (cat no. 224758), Sodium persulfate (SPS) (cat no. 216232), Dulbecco's phosphate buffered saline (DPBS) (cat no. D8537). Spectrum™ Labs Spectra/Por™ 2 Dry Dialysis Kits (12-14 kDa MWCO) (cat no. 15390762), Micro BCA™ Protein Assay Kit (cat no. 23235) and Vabysmo™ Faricimab-svoa 120 mg mL⁻¹ (NDC 50242-096-01) donated from Moorfields eye hospital.

2.2. Bioink preparation

In this study, ALG was used as the main material for the bioink. Three different bioink formulations were prepared: (i) 5% (w/v) ALG, (ii) 5% (w/v) ALG mixed with 3% (w/v) HAMA, and (iii) a 1:1 (v/v) mixture of 5% (w/v) ALG and IPC. The 5% ALG concentration maintains a suitable viscosity to be used as bioink; neither too viscous to behave like a solid, which would hinder extrusion, nor too fluid, which would make it difficult to maintain the printed shape. All formulations were prepared

using sterile deionised water under aseptic conditions.

For the ALG bioink (i), sodium alginate powder was dissolved in deionised water at a 5% (w/v) concentration (50 mg in 1 mL) and stirred overnight at room temperature until a clear and homogeneous solution was obtained. The ALG-HAMA bioink (ii) was prepared by dissolving HAMA at 3% (w/v) in deionised water (30 mg in 1 mL), followed by adding 50 mg of sodium alginate powder and stirred overnight at room temperature until a clear and homogeneous solution was obtained. Also, HAMA was synthesized in-house via carboxyl group functionalisation of hyaluronic acid using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as a coupling agent [42]. Briefly, an active ester is first formed through aromatic substitution of the triazine by a carboxylic acid, followed by nucleophilic attack on the carboxylic carbon by an amine [43,44]. HA (MW: 30-40KDA, 1% w/v) was dissolved in MES buffer (pH 5.5, 5 mL, 100 mM). 69 mg of DMTMM powder (1:2 M ratio HA:DMTMM) was then added to the solution. After being stirred for 10 min, AEMA dissolved in MES buffer (21 mL, 100 mM) was added dropwise to the solution and stirred at room temperature. After 24 h, NaCl solution (8% of total solution volume, 2 mL) was added for enrichment. The resulting solutions were subjected to a series of washes (3 times) each with 96% cold ethanol (76 mL), each followed by precipitation through centrifugation at 4000 RPM for 10 min. The final product was then dried under a vacuum evaporator overnight and became as a dried compressed substance.

For the ALG-IPC formulation, a 5% (w/v) ALG solution was mixed in a 1:1 vol ratio with In-situ polymerized collagen (IPC). IPC was synthesized following a protocol described in a patent [45] and further optimised in this study. Briefly, in a falcon tube pepsin soluble collagen (15.0 mL, 6 mg mL⁻¹) was precipitated with NaCl (35.0 mL, 0.8 M). The tube was gently shaken to flocculate the collagen in the solution before being centrifuged at high speed (4600 RPM) for 30 min at 4°C. The white precipitated collagen collected at the bottom of the tube was carefully removed, and the excess supernatant was slowly removed. The collected collagen was inserted into the washed dialysed membrane (MWCO: 12-14 kDa), and both ends of the membrane were tied by dialysis tubing closures. The solution was then dialysed against 0.1M acetic acid to remove residual salts for 24 h. Following the initial dialysis, the collagen solution was then subjected to a second dialysis against 35 mM EDTA at a starting pH of 5.0 ± 0.2 for 24 h. The pH of the collagen solution was gradually increased from pH 5.0 to pH 7.0, during stepwise dialysis over 5 days. During the last step of the dialysis, the collagen solution was dialysed with 35 mM EDTA, 100 mM sucrose and 3.5% of D-mannitol.

2.3. Biomaterial characteristics

2.3.1. FTIR

FTIR analysis was conducted to assess the chemical composition and functional group interactions and the synthesis confirmation within the materials. Dried samples from each formulation were scanned using an FTIR spectrometer in the range of 4000–600 cm⁻¹. Spectra were compared across formulations to confirm successful incorporation of HAMA and IPC, as well as to detect any potential chemical interactions or structural changes post-crosslinking.

2.3.2. Rheological analysis

The rheological properties of the bioink formulations were evaluated using a rotational rheometer (e.g., Anton Paar MCR series) equipped with a parallel plate geometry (25 mm diameter). Viscosity was measured across a range of shear rates (0.1 to 100 s⁻¹) at 25°C to assess shear-thinning behaviour.

2.3.3. Degradation study

(i) Implant degradation on exposure in different ionic media

In this study, degradation rates of alginate-based implants were

investigated at two DPBS concentrations (0.02x DPBS, and 1x DPBS) to evaluate the effect of ionic strength on implant degradation. Alginate-based 3D printed scaffolds, including ALG, ALG-HAMA, and ALG-IPC formulations, were placed into well plates containing either 1x DPBS or 0.02x DPBS to compare their behaviour under high- and low-ionic-strength environments. This experiment was performed to identify the more stable bioink formulations for subsequent experimental stages. From each formulation, two scaffolds were incubated in 1x DPBS and two in 0.02x DPBS ($n = 2$ per condition). Samples were periodically monitored to evaluate their degradation within the solution, and implants remaining intact at the end of the 80-day observation period were recorded as right-censored (>80 days). No drug was used in this experiment.

(ii) Implant degradation on exposure in different drug amount

Degradation was also studied by incorporating different amounts of Faricimab (0.1, 0.5, and 1 mg) into individual alginate scaffolds to observe effects of high vs low Faricimab concentrations on the scaffold stability and find a balance between the scaffold stability and drug amount. To achieve final drug contents of 0.1, 0.5, and 1 mg per scaffold, Faricimab was diluted using sterile deionised water and incorporated directly into the biomaterial. Two scaffolds from each formulation were incubated in 0.02x DPBS at 37°C ($n = 2$ per condition). Samples were periodically monitored to evaluate their degradation within the solution.

2.4. 3D bioprinting design

The bioink formulations were printed using an extrusion-based 3D bioprinter (BIO X, CELLINK, Sweden). To obtain a more precise outcome, a syringe pump printhead was used to print a rod-shaped implant design with a diameter of 0.3 mm and a length of 10 mm per layer, each implant contains 3 layers. The rationale behind choosing this shape was to create an implant for the ocular environment and was created using computer-aided design (CAD) software (Autodesk Fusion) [46]. The implants were printed in a horizontal orientation to improve dimensional control and stability during extrusion.

2.5. Bioprinting, bioink and drug loading

Before printing, the bioinks and drugs were loaded into a 3 mL syringe. Faricimab was supplied as a solution and was incorporated into the bioink via direct mixing to achieve a final drug concentration of 50 mg mL⁻¹, resulting in 0.5 mg of the drug per implant. This concentration was chosen based on the outcomes of prior degradation experiment. Homogeneous distribution was achieved using a syringe-to-syringe mixing method with a Luer-lock connector, ensuring gentle and uniformity of all components. Additionally for ALG-HAMA bioink, sodium persulfate (SPS) (10 mM, 10 μ L) and tris(2,2-bipyridyl) dichlororuthenium (II) hexahydrate (Ru) (1 mM, 10 μ L) was then added as photo-initiators and mixed using the same method until the material was homogenous to ensure smooth printing.

The 3 mL syringes were fitted with 27-gauge printing nozzle. The extrusion parameters, including extrusion rate, nozzle size, and print speed, were optimised for each formulation to ensure consistent filament deposition and structural integrity. All prints were performed under ambient conditions on a Petri dish glass substrate. The extrusion rate range was set to be between 0.7 and 1 μ L s⁻¹, and the speed was 2 to 3 mm s⁻¹. Triplicate implants were evaluated for every printing condition, and the subsequent length and diameter measurements are expressed as the mean $\pm$ standard deviation. Infill density parameter was set to 85% percent for all the implants. Several trials and errors are performed to understand the impact of each parameter in the final printed shape ultimately leading to finding the shape which is the closest to the CAD design with the minimal error. The alginate-based

biomaterials were crosslinked using calcium chloride (CaCl₂) to stabilise the structures. A 300 mM CaCl₂ solution was freshly prepared in sterile deionised water. Immediately after printing, 3 to 5 drops of CaCl₂ were carefully added on top of the printed constructs so that they were immersed into the crosslinking agent, followed by an incubation for 10 min at room temperature to ensure sufficient ionic gelation of the ALG component. Additionally, for ALG-HAMA, the Petri dish containing the implants was placed under UV light for 10 min. After crosslinking, the constructs were then placed in the Rig well along with 0.02x DPBS for the initiation of the drug release study.

2.6. Drug release study

Following the printing and crosslinking, each implant was placed individually into a designated rig chamber connected to a peristaltic pump to simulate physiological aqueous humour flow (Fig. 1). The chamber's diameter and volume were 11 mm and 200 μ L, respectively, and a continuous flow of DPBS at a constant rate of around 2 μ L min⁻¹ was maintained into the chamber, mimicking the natural flow rate within the human eye [47]. The entire setup was maintained at 37°C. Samples released from the implant were collected at predefined time-points: 1 h, 3 h, 24 h, 48 h, Day 3, Day 7, and subsequently at regular intervals up to 85 days. Following the outcomes of the degradation test, each implant contained an initial Faricimab loading of 0.5 mg, and the gradual release profile were obtained by collecting the samples. The drug release was calculated by quantifying the amount of Faricimab released from the implant at different time intervals using the micro-BCA protein assay, allowing for precise cumulative calculation through the study period. This assay was selected due to its sensitivity and linear working range of 2–40 μ g mL⁻¹, which was suitable for the expected Faricimab concentrations in the release samples.

2.7. Protein stability

To explore the stability of Faricimab within the implant, SDS-PAGE and Dynamic Light Scattering (DLS) analysis were performed. SDS-PAGE was employed to assess the integrity and degradation of the protein. Complementarily, DLS measurements were performed in sterile cuvettes using a Malvern Zetasizer Advance Ultra (ZSU3305) to monitor hydrodynamic diameter and particle size distribution. These parameters serve as critical indicators of protein homogeneity and aggregation as well as conformational alterations that impact long-term drug stability [48]. Prior to DLS analysis, released samples were filtered using a 0.2 μ m syringe filter to reduce the presence of large alginate fragments and particulate material originating from the implant matrix. Empty ALG implant samples incubated under identical conditions were analysed as controls to distinguish alginate derived particle from Faricimab associated signals. DLS results were interpreted together with SDS-PAGE analysis to evaluate Faricimab stability after release from the implant.

3. Results and discussion

3.1. Characterisation

3.1.1. FTIR

FTIR spectroscopy was performed to identify functional groups and verify chemical interactions within the hydrogel systems (Fig. S1), to evaluate the formation of ALG-HAMA and ALG-IPC hydrogels. At first look, it largely overlaps, indicating the alginate backbone is retained. The ALG-HAMA blend exhibits minor broadening around 1600–1650 cm⁻¹ (overlap of vinyl C=C with alginate COO⁻) and a slightly elevated 1000–1150 cm⁻¹ region (C–O–C of HA/methacrylate), while the alginate 1415 cm⁻¹ symmetric COO⁻ band is maintained. Compared with neat alginate, the ALG-IPC trace shows a subtle increase in absorbance in the amide region ($\approx$ 1650 cm⁻¹, amide I; $\approx$ 1540 cm⁻¹, amide II) together with a slightly broader O–H/N–H envelope around

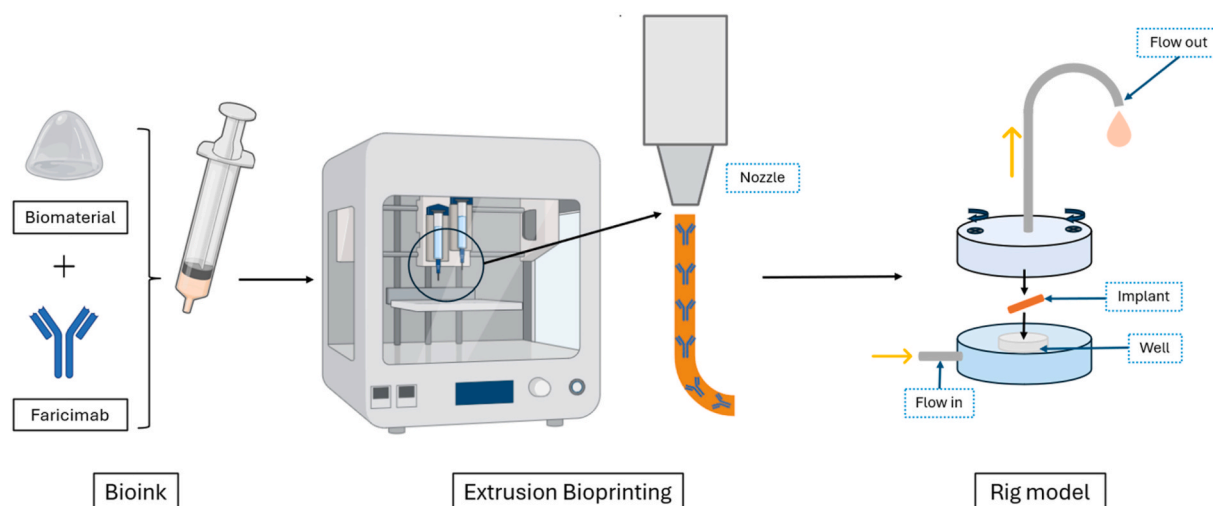


Fig. 1. Schematic view of the implant fabrication and ocular rig model.

3200–3500 cm^{-1} , which is consistent with the presence of collagen. These spectral features, although subtle, support incorporation of collagen and HAMA into the alginate matrix, without disruption of the alginate backbone.

3.1.2. Rheological properties

The rheological profiles of the three biomaterials, ALG, ALG-HAMA, and ALG-IPC, demonstrated characteristic shear-thinning behaviour (Fig. S2), a critical requirement for extrusion-based 3D bioprinting. All formulations showed decreasing viscosity with increasing shear rate, facilitating smooth extrusion through nozzles while ensuring structural integrity upon deposition. Among them, the ALG-IPC presented the

highest viscosity under low shear conditions ($0.1\text{--}10\text{ S}^{-1}$). This suggests stronger internal network interactions and higher resistance to flow under static or near-static conditions. As shear rate increases, the viscosity of ALG-IPC decreases more steeply than the other bioinks. This suggests that under high shear ($100\text{--}1000\text{ S}^{-1}$, as during extrusion through the nozzle), the polymer entanglements and physical crosslinks in ALG-IPC are disrupted to an extent that the resistance to flow becomes comparable to ALG and ALG-HAMA.

3.1.3. Degradation behaviour

(i) Implant degradation under different ionic strength conditions:

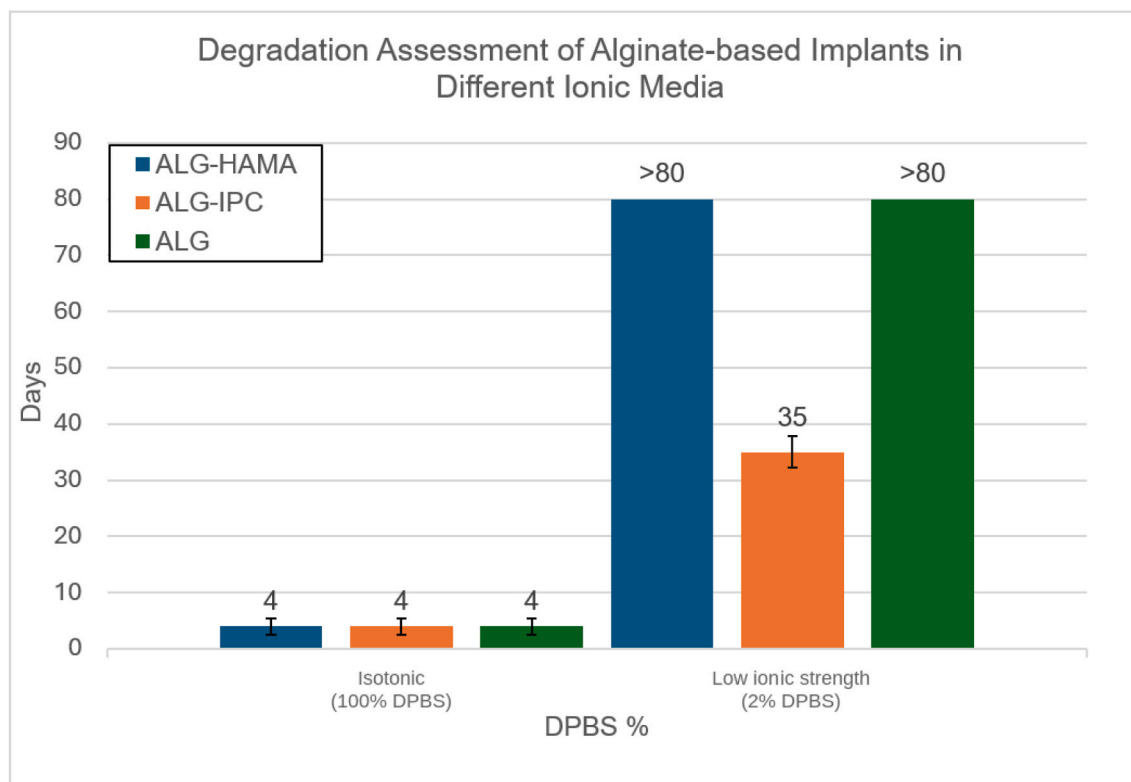


Fig. 2. Degradation profiles of 3D-printed alginate-based implants incubated in isotonic (1x DPBS) and low ionic strength (0.02x DPBS) media over time. Bars represent the duration (in days) until complete implant degradation for each formulation: ALG-HAMA (blue), ALG-IPC (orange), and ALG (green). No drug was incorporated in the scaffolds. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2 illustrates the degradation behaviour of the three alginate-based formulations incubated in either isotonic (1x DPBS) or low ionic strength (0.02x DPBS) conditions. Under the high ionic environment (1x DPBS), all implants exhibited rapid degradation, fully dissolving within 4 days, regardless of composition. This rapid erosion is consistent with the propensity of calcium-crosslinked alginate hydrogels to undergo accelerated ion exchange and depolymerisation when exposed to high concentrations of monovalent ions, such as sodium and phosphate ions present in standard buffer solutions [49,50].

In contrast, when the same implants were incubated in 0.02x DPBS, a diluted ionic environment intended to approximate the relatively low free ion concentration of the vitreous humour, marked stability improvements were observed.

ALG implant maintained structural integrity for more than 80 days, indicating that reducing ionic strength substantially retards the diffusion-driven exchange of calcium ions with monovalent cations and delays hydrogel disintegration. The ALG–HAMA composite also demonstrated prolonged degradation in 0.02x DPBS, persisting for more than 80 days, which suggests that the incorporation of methacrylated hyaluronic acid and UV-mediated secondary crosslinking has no discernible impact on the network's degradation through ionic exchange. By contrast, the ALG–IPC (1:1) formulation exhibited somewhat faster degradation under the same conditions, dissolving by day 35. This relatively reduced stability may be attributed to the presence of collagen, which does not participate in ionic or covalent crosslinking with alginate and may introduce microstructural heterogeneities that facilitate fluid infiltration and erosion over time.

Collectively, these findings highlight that ionic strength is a dominant factor controlling alginate degradation rates. Moreover, the results indicate that composite formulations differ in their resistance to hydrolytic and ion-driven degradation, with ALG and ALG–HAMA offering the highest stability due to ionic and covalent crosslinking, whereas ALG–IPC showed somewhat less durability. From an application perspective, this behaviour underscores the importance of carefully considering the ionic composition of the local ocular environment when designing degradable hydrogel-based implants. Furthermore, these

results validate the feasibility of tuning implant longevity both by formulation strategy, such as HAMA incorporation, and by anticipating the physiological media in which the device will reside.

(ii) Implant degradation under different drug loading amount:

The degradation studies highlighted the critical influence of drug loading and implant length on the stability of the implants (Fig. 3). Implants containing 1 mg Faricimab degraded within a few days, suggesting that high protein content accelerated breakdown of the alginate matrix. This phenomenon is likely attributed to the excessive protein concentration disrupting ionic interactions and thereby impeding the structural development of the alginate network.

Reducing the Faricimab to 0.5 mg improved implant stability, especially in larger implants (0.3 mm × 10 mm), which remained intact for more than 80 days in 0.02x DPBS. This observation can be partly explained by the reduced drug-induced osmotic imbalance and the decreased surface area-to-volume ratio in longer implants. The latter results in slower diffusion of ions and water molecules into the core of the implant, thus prolonging structural integrity. These findings are consistent with prior work demonstrating that the size of polymeric ocular implants can strongly modulate degradation rates and, consequently, drug release kinetics.

Furthermore, at the lowest tested drug amount (0.1 mg), both 5 mm and 10 mm implants exhibited nearly identical degradation profiles, with negligible erosion over 30 days. This suggests that below a critical threshold of incorporated drug, degradation becomes primarily governed by polymer hydrolysis and ionic exchange rather than geometric parameters. This insight is significant because it implies that implant design can be rationally tuned by balancing drug concentration and geometry to optimise both stability and release duration.

Collectively, these results indicate that for sustained ocular delivery of Faricimab, implants incorporating 0.5 mg of drug with higher length offer a promising compromise between sufficient drug loading and prolonged structural persistence in vitro. Based on these findings, incorporating 0.5 mg of Faricimab into alginate-based implants D0.3

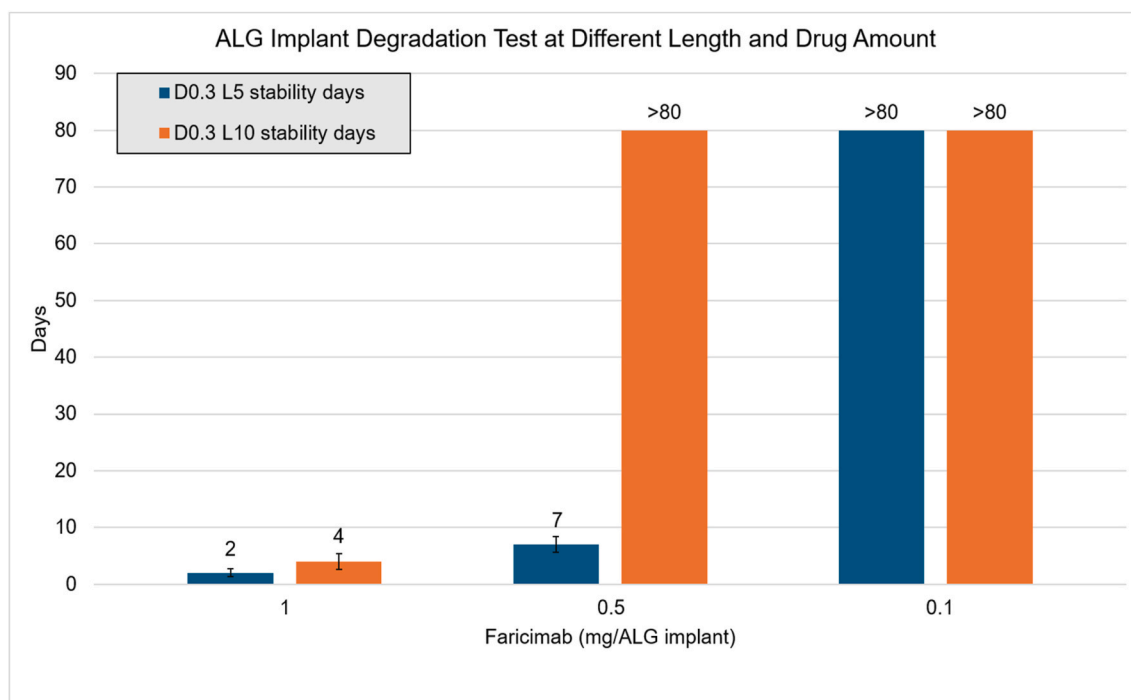


Fig. 3. Degradation of ALG implants at two length designs (D0.3 L5 and D0.3 L10), and three Faricimab loading amounts (1 mg, 0.5 mg 0.1 mg per implant) in 0.02x DPBS at 37°C. Values are independently printed implants per condition (n = 2).

L10 was selected for subsequent experiments evaluating implants of the same dimensions prepared from different biomaterials. Furthermore, minor variations in implant diameter (± 0.3 mm) did not significantly affect stability.

3.2. Printing parameters and shape assessment

The dimensions of the implant were designed to be small enough to permit intravitreal injection. However, the final size and geometry were influenced by multiple printing parameters, which affected the fidelity of the fabricated constructs relative to the CAD design. In particular, bioink viscosity during extrusion played a critical role in determining the precision of the printed shape. Because of the viscous nature of the bioinks, not all printing settings resulted in a successfully formed structure. When the extrusion rate was too low, insufficient material was deposited, leading to discontinuities or incomplete layers. Similarly, when the printing speed was too fast, the extruded filament could not keep up with the nozzle movement, causing irregularities and deformation in the printed pattern. Consequently, some combinations of printing parameters were not even printable, as the interaction between viscosity, extrusion rate, and printing speed prevented the consistent formation of a stable implant geometry.

Given the fragile, gel-based nature of the implants and the need for accurate dimensional characterisation, image analysis was employed to assess their size and morphology. For each printing condition, three independently printed implants were analysed. The resulting length and diameter values are reported as mean $\pm$ standard deviation in Tables 3 and 4.

Tables 3 and 4 summarise the effect of printing parameters on implant diameter. As shown in Table 3, reducing the extrusion rate at a constant nozzle speed decreased the implant diameter, indicating that less bioink was deposited per unit length. Similarly, as shown in Table 4, increasing the nozzle speed while maintaining a constant extrusion rate resulted in a decrease in implant diameter, reflecting the reduced volume of bioink deposited during printing. Based on these results, a balance between extrusion rate and nozzle speed was required to obtain implants with the desired geometry and consistent morphology. Therefore, for subsequent experiments, the printing parameters were set to an extrusion rate of $0.8 \mu\text{L s}^{-1}$ and a nozzle speed of 2 mm s^{-1} , as these conditions produced implants with dimensions closest to the target geometry and acceptable reproducibility. These settings were used for all following experiments to ensure consistency across characterisation and degradation analyses.

3.3. Drug release study

The cumulative release of Faricimab from the alginate-based implants was monitored over 80 days in 0.02x DPBS. As can be seen in Fig. 4, the release profiles exhibited an initial burst phase within the first 24 h, reaching approximately 15–20%, followed by a gradual and sustained release phase over the subsequent weeks, approaching complete release by day 85. In comparison, to observe the impact of the implants on sustained and controlled release, free Faricimab without incorporating in the implant was also evaluated in the rig system. Within the first 24 h, almost 85% of the drug was collected, and almost all the Faricimab was cleared from the mimicked eye rig model within 7 days.

While 0.02x DPBS does not fully replicate the osmotic or biochemical environment of the vitreous humour, its lower ionic strength provides a simplified model for diffusion-controlled release under conditions that minimise alginate degradation. This enables assessment of drug diffusion behaviour and long-term release kinetics primarily governed by matrix porosity and crosslink density, rather than by ionic destabilisation of the hydrogel network.

As can be seen in Fig. 4, both implant formulations showed sustainable release profile of the incorporated 0.5 mg of Faricimab, over more than 80 days. While the ALG implant shows a slightly higher cumulative release, reaching approximately 90% by day 85, the ALG-HAMA formulation provided a more controlled release profile – approximately 80%. Notably, the sharp increases observed in certain regions of the release profiles stem from the onset of implant breakage, which facilitated a more rapid release of the drug at those points.

Interestingly, despite the better Rheological behaviour observed for the ALG-IPC bioink, this formulation exhibited the most rapid degradation (By 35 days) and drug release in vitro (7 days). This can be explained by the unique nature of collagen–alginate interactions. While IPC increases viscosity through physical entanglement prior to crosslinking, it does not form covalent or ionic crosslinks with the alginate network. As a result, the final implant structure is stabilized primarily by calcium-mediated ionic crosslinks between alginate chains, with collagen remaining loosely integrated within the matrix. Upon immersion in aqueous media, the collagen component is prone to partial leaching or rehydration, leading to increased porosity of the implant and more rapid erosion. Additionally, the pronounced shear-thinning behaviour of ALG-IPC suggests that under extrusion conditions, the entanglement network is readily disrupted, resulting in less cohesive structural integrity after printing. In contrast, the ALG-HAMA formulation benefits from dual crosslinking mechanisms: ionic crosslinking of

Table 3
Implant diameters and corresponding images under varying extrusion rates (p-value < 0.05 in length and diameter calculations).

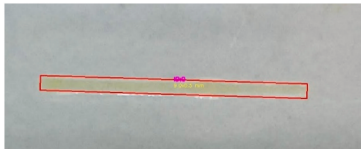
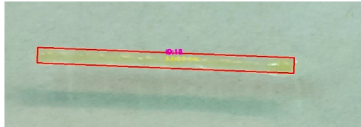
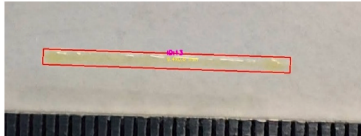
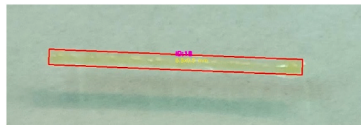
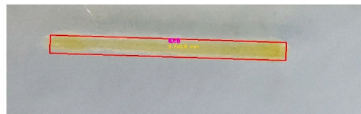
Extrusion rate ($\mu\text{L s}^{-1}$)	Speed (mm.s^{-1})	Length (mm)	Diameter (mm)	Image
0.8	2.0	9.87 ± 0.10	0.50 ± 0.02	
1.0	2.0	9.06 ± 0.26	0.64 ± 0.12	
1.2	2.0	9.00 ± 0.35	0.67 ± 0.07	

Table 4

Implant diameters and corresponding images under varying nozzle speeds (p-value < 0.05 in length and diameter calculations).

Extrusion rate ($\mu\text{L.s}^{-1}$)	Speed (mm.s^{-1})	Length (mm)	Diameter (mm)	Image
1.0	2.0	9.06 ± 0.26	0.64 ± 0.12	
1.0	1.3	9.06 ± 0.30	0.78 ± 0.02	

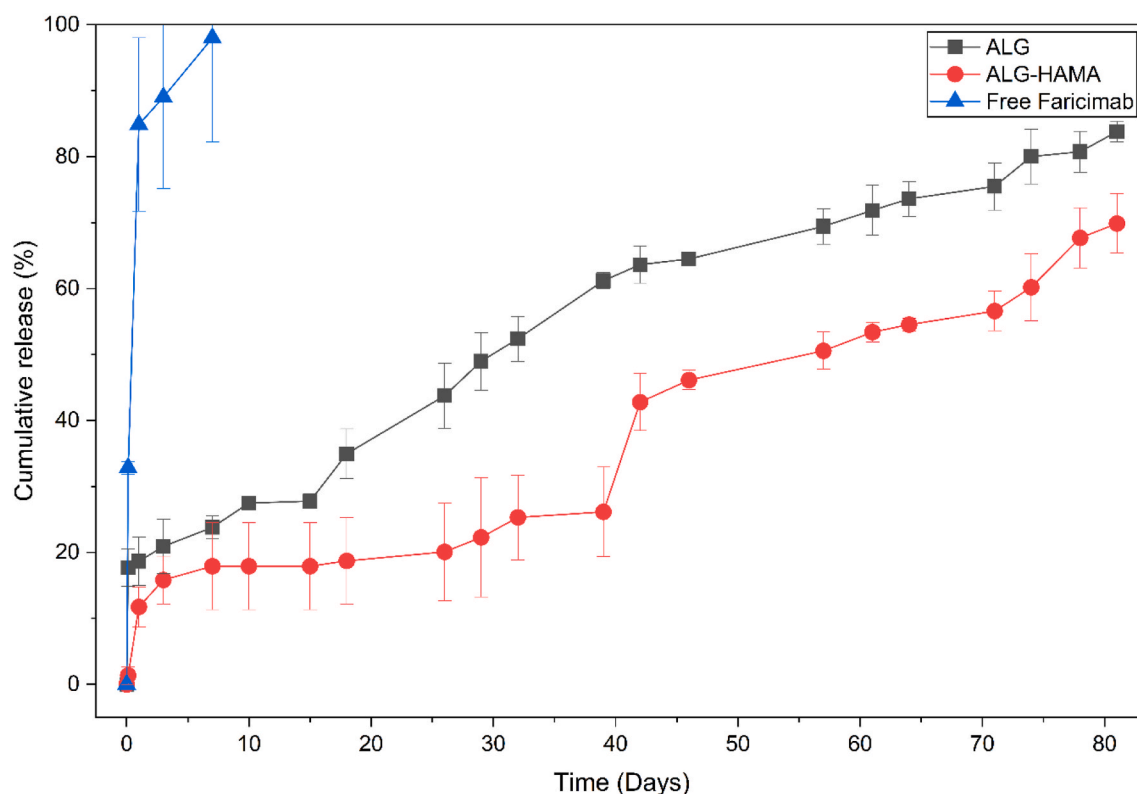


Fig. 4. Rig drug release study of 0.5 mg Faricimab from ocular implants: comparison of free Faricimab with release from ALG and ALG-HAMA implant formulations. Data are mean $\pm$ SD (ALG n = 2, ALG-HAMA n = 2, free Faricimab n = 4). Cumulative release from ALG was higher than from ALG-HAMA across the 19 shared sampling timepoints with median difference of 18.4 percentage points, ALG higher at all timepoints.

alginate, and UV-induced covalent crosslinking of methacrylated HA. This dual network significantly enhances the implant's resistance to swelling and degradation, translating into the more sustainable release profile. These results underscore the importance of distinguishing between rheological properties relevant for printability and the cross-linked microarchitecture that ultimately governs in situ performance.

The sustained drug release observed in Fig. 4 suggests the potential of the alginate-based implant system to prolong antibody delivery compared with frequent injection. This is relevant to neovascular AMD, where repeated intravitreal anti-VEGF injections are required to maintain therapeutic efficacy. However, the release profile observed in this study cannot yet be considered optimal for AMD treatment, as the optimal intraocular release rate would depend on the bioactivity after release, ocular clearance, and in vivo pharmacokinetics. Therefore, further optimisation and in vivo studies are required to determine whether the release kinetics are suitable for maintaining therapeutic Faricimab levels over clinically relevant timeframes.

3.4. Stability of Faricimab as solution and as implants

The stability of Faricimab was evaluated in solution across different time points and temperature conditions (Fig. 5). To assess structural integrity and aggregation behaviour, DLS and SDS-PAGE analyses were performed. These complementary techniques enabled monitoring of changes in hydrodynamic size distribution and protein binding patterns, providing insight into how storage environment and duration influence Faricimab protein stability.

In addition, the stability of Faricimab incorporated within the alginate implant was assessed and compared with that of the free drug in solution (Fig. 6). This analysis aimed to determine whether encapsulation within the alginate matrix offers enhanced protection against degradation, thereby improving the overall stability of Faricimab during storage and release.

DLS measurement at Day 0 showed a single peak at 11.2 nm, corresponding to a stable monomeric Faricimab protein (Fig. 5A). After

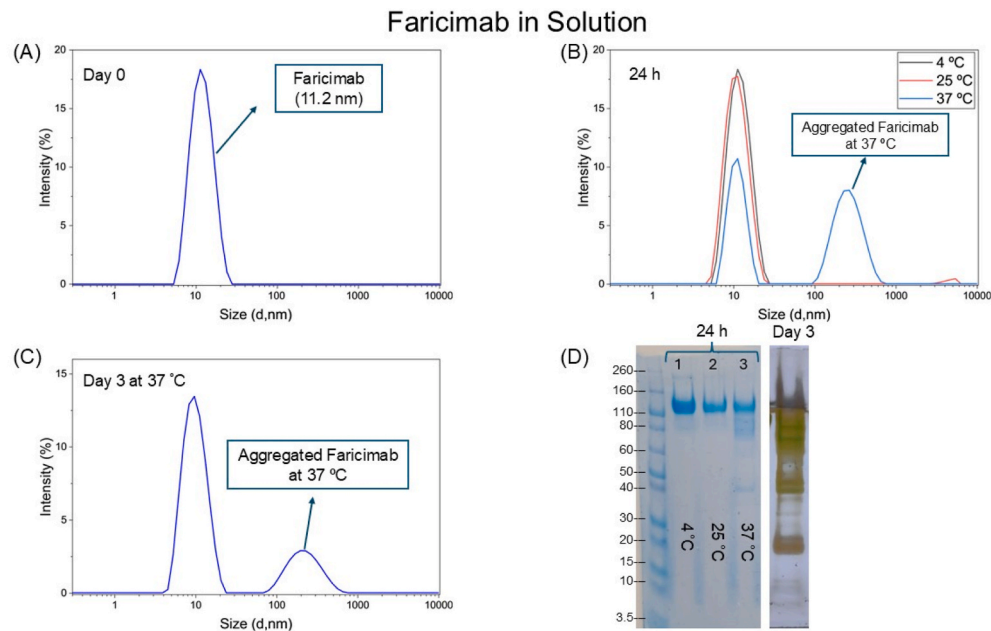


Fig. 5. Stability of Faricimab in solution at multiple temperatures and incubation times; (A) DLS analysis at Day 0, (B) DLS analysis at 4°C, 25°C and 37°C at 24 h, (C) DLS analysis at 37°C at Day 3, (D) SDS-PAGE analysis of Faricimab at 4°C, 25°C and 37°C at 24 h, and at 37°C at Day 3.

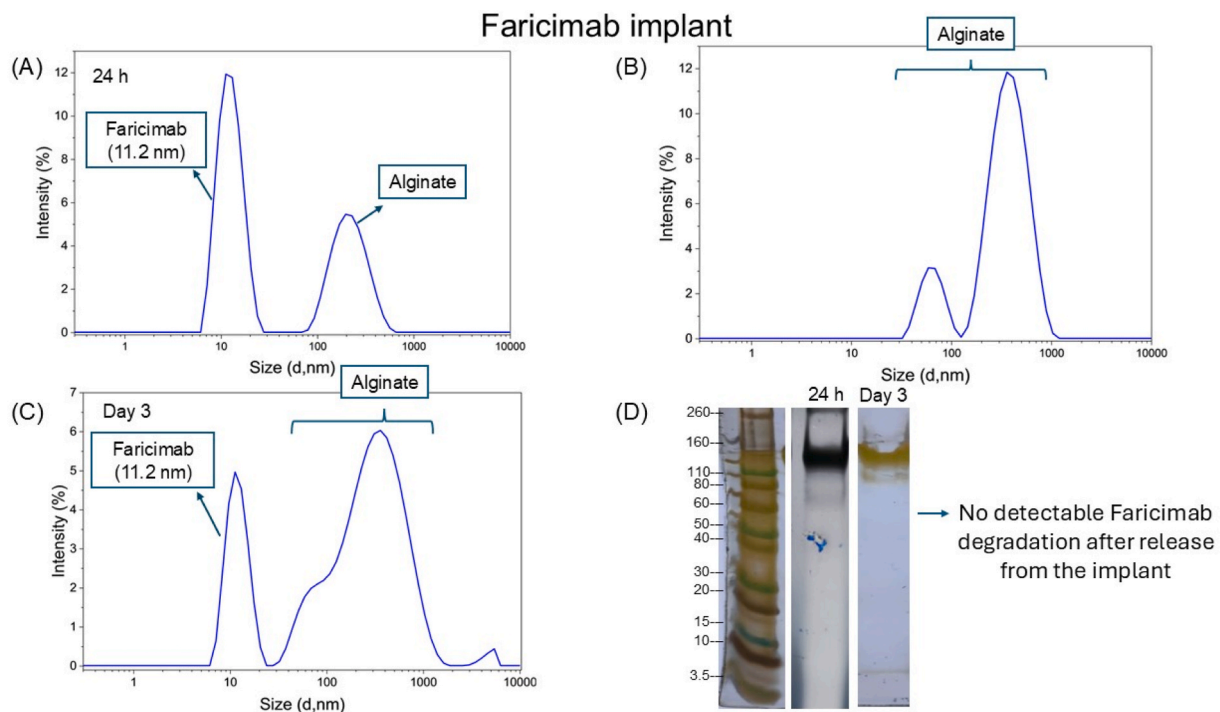


Fig. 6. Faricimab stability within a CaCl₂-crosslinked ALG implant incubated at 37°C. (A) DLS analysis of the implant after 24 h from printing, (B) DLS analysis of ALG implant control. (C) DLS analysis of the implant after 3 days of incubation, (D) SDS-PAGE analysis of the released Faricimab from the implant.

24 h, Faricimab remained stable at 4°C and 25°C, as confirmed by both DLS and SDS-PAGE. However, incubation at 37°C led to aggregation, as evidenced by DLS (Fig. 5B), and degradation, as shown by SDS-PAGE (Fig. 5D). After three days, both aggregation and degradation increased further, demonstrating that prolonged temperature exposure accelerates Faricimab degradation over time (Fig. 5C). Furthermore, SDS-PAGE analysis backs up the DLS results by showing distinct bands at 4°C and 25°C representing the stable protein, while incubation at 37°C resulted in multiple bands on the gel, indicating aggregation and

degradation of Faricimab, which could negatively affect its therapeutic efficacy.

As seen in Fig. 6A, the Faricimab-alginate implant showed two peaks at 11.2 nm and 197 nm, corresponding to Faricimab and the alginate associated particles, respectively. The control (Fig. 6B) was used to distinguish alginate-derived particle populations from Faricimab associated signals. This suggests that incorporation of the protein in the alginate, suggests improved stability of the drug at 37°C without immediate aggregation. At Day 3, the DLS analysis (Fig. 6C) showed both

the Faricimab and alginate peaks. Although samples were filtered prior to DLS analysis using a 0.2 μm syringe filter, residual alginate derived particles may still contribute to the detected size distribution. Nevertheless, minimal aggregation was observed, suggesting that after three days Faricimab remained relatively stable within the alginate matrix protective environment. In addition, the SDS-PAGE analysis (Fig. 6D) further supported the DLS results by showing no evident fragmentation or major degradation bands after 3 days of incubation at 37°C within the implant.

Following the DLS and SDS-PAGE results, a comparison can be made between Faricimab in solution (Fig. 5) and Faricimab implant (Fig. 6). While Faricimab in solution experienced instability within 24 h at 37°C caused by temperature-induced stress, with aggregation observed, its stability was ameliorated when incorporated into the implant. This can likely be due to the alginate matrix reducing the drug protein aggregation at 37°C [51].

4. Conclusion and future directions

This study demonstrated the fabrication and characterisation of 3D-printed alginate-based intravitreal implants for the sustained release of Faricimab. Using extrusion-based bioprinting, rod-shaped micro-implants with clinically compatible dimensions were produced with high precision and reproducibility. The optimised formulations, particularly ALG-HAMA composites, showed excellent printability, mechanical stability in low-ionic environments, and predictable degradation kinetics. Importantly, these implants enabled sustained Faricimab release over an extended period of up to 80 days under simulated ocular flow conditions, representing a significant advancement toward reducing the frequency of intravitreal injections in patients with neovascular AMD.

Rheological and FTIR analyses confirmed that the bioinks possessed the appropriate behaviour for extrusion printing, while maintaining the chemical integrity of incorporated biomolecules. Protein stability assays further demonstrated that encapsulation within the alginate matrix created an amended environment for Faricimab avoiding it from aggregation and thermal degradation for a longer period of time, supporting the biocompatibility and gentle processing conditions of this platform. Among the formulations tested, the ALG-HAMA composite with dual ionic-covalent crosslinking exhibited the most controlled drug release profile, potentially leading to a prolonged therapeutic delivery. A drug loading of 0.5 mg per implant was identified as an optimal configuration, balancing prolonged release with implant stability.

Together, these findings validate 3D-printed alginate composites as a promising class of biomaterials for long-acting biologic delivery to the posterior segment of the eye. The ability to tailor implant geometry, drug loading, and degradation rate provides a versatile framework for the design of next-generation ocular therapeutics.

Looking ahead, several directions will further strengthen the translational potential of this work. Although sustained Faricimab release was observed for more than 80 days, antibody stability was assessed only during the short-term stability study. Therefore, while the present results suggest that alginate encapsulation can reduce early instability, further studies are required to evaluate the long-term structural integrity, aggregation profile, and biological activity of Faricimab throughout the complete release period.

Future in-vivo investigations are also required to assess the pharmacokinetics, biocompatibility, and retinal safety of these implants in animal models. Such studies will also clarify how intraocular factors, such as enzymatic activity, pH variation, and aqueous humour turnover, influence drug release and biomaterials degradation. In parallel, the integration of patient-specific geometries derived from ocular imaging and the development of multi-drug or stimuli-responsive release systems (e.g., pH- or pressure-triggered) represent exciting future opportunities. Together, these advances could transform current treatment paradigms by enabling precisely engineered, long-acting biologic delivery platforms that enhance therapeutic efficacy, minimise injection burden, and

ultimately improve the quality of life for patients with chronic retinal diseases.

CRediT authorship contribution statement

Arian Farokh: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Camelia Lucia Bogdan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hamid Heidari Kashkooli:** Methodology, Investigation, Conceptualization. **Ali Horo:** Visualization, Data curation. **Massoud Zolgharni:** Supervision, Software, Resources, Project administration, Funding acquisition. **Hanieh Khalili:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jddst.2026.108899>.

Data availability

No data was used for the research described in the article.

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