Preparation and Formulation of Ocusert using Dipping and Solvent Casting Technique

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Abstract:

Background: One of the primary challenges in ocular drug delivery is maintaining therapeutic drug concentrations at the target site for a prolonged duration. This is particularly relevant for sulfacetamide sodium, a commonly used antibacterial agent in ophthalmic therapy.

Objective: This study aimed to develop a polymer-based ocular insert (Ocusert) for the extended release of sulfacetamide sodium over a 12-hour period.

Dipping and solvent casting method: Various formulations were developed using the dipping and solvent casting technique, with sodium alginate, polyvinylpyrrolidone K90 (PVP K90), and Eudragit RL PO. The inserts were evaluated for physical and functional properties, including folding endurance, thickness, drug content, swelling index, and in vitro drug release. The optimal formulations were further examined via *ex vivo* bioadhesion and *ex vivo* permeation studies using goat corneal tissue.

Results: All formulations demonstrated: pH (6.91–6.99), drug content (4.67 -5.26) mg, drug content percent (93.43%–105.26%), Thickness (0.11-0.53) mm, and weight variation (13.41-81.30) mg. Among them, formulation F14C—containing 1.5% sodium alginate, 7% PVP K90, and 15% Eudragit RL PO—exhibited controlled drug release for up to 12 hours, high folding endurance of over 300 times, swelling index of 242.96%, drug release kinetics of zero order, *ex vivo* bio-adhesive strength of 0.183 ± 0.016 g, a force of adhesion of 0.083 ± 0.016 N, a tensile strength of 3.116 ± 0.18 (N/mm²), a percent elongation of 358.87% ± 0.164, an SEM shows film thickness was in the range of 552.20 ± 5.30 µm, having a rate-controlling membrane of 616.6 ± 62.12 nm in thickness, and cumulative amount of drug permeated (0.398 mg) in *Ex vivo* drug permeation study.

Conclusions: The developed ocular insert offers a promising sustained-release platform for sulfacetamide sodium, potentially improving patient compliance and therapeutic outcomes in the management of bacterial ocular infections.

Keywords: Ocusert, ocular drug delivery, rate-controlling membrane, Sulfacetamide sodium, solvent casting, dipping method.

تحضير وصياغة اكيوسيرت باستخدام تقنية الغمس والصب بالمذيبات

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الخلاصة:

الخلفية: تُعد المحافظة على تركيزات علاجية مناسبة من الدواء في موقع التأثير لفترة ممتدة من أبرز التحديات في إيصال الأدوية عبر العين. ويُعد هذا الأمر بالغ الأهمية بالنسبة للسلفاسيتاميد الصوديوم، وهو عامل مضاد للبكتيريا يُستخدم على نطاق واسع في علاج التهابات العين.

الهدف: هدفت هذه الدراسة إلى تطوير أوكوسيرت تتيح إطلاقًا ممتدًا للسلفاسيتاميد الصوديوم لمدة تقارب 12 ساعة.

طريقة الغمس والصب بالمذيبات: تم تحضير اكيوسيرت بتقنية الغمس والصب بالمذيبات باستخدام مزيج من ألجينات الصوديوم، بولي فينيل بايروليدون**K90 (PVP K90)** ، ويودراجيت **RL PO** من خلال تقنيتي الغمر والصب بالمذيب. تم تقييم التركيبات من حيث التحمل للطي، السماكة، محتوى الدواء، معامل الانتفاخ، والإطلاق الدوائي في المختبر. كما خضعت التركيبات المثلى لتقييم الالتصاق الحيوي والانتقال عبر الأنسجة خارج الجسم باستخدام قرنية الماعز.

النتائج: أظهرت جميع التركيبات: الرقم الهيدروجيني (6.91-6.99)، ومحتوى الدواء (4.67 -5.26) مجم، ونسبة محتوى الدواء (93.43%-105.26%)، وسمك (0.11-0.53) ملم، وتباين الوزن (13.41-81.30) مجم. من بينها، أظهرت التركيبة **F14C** التي تحتوي على 1.5% ألجينات صوديوم و7 **% PVP K90** و15 **% Eudragit RL PO-**إطلاق دواء متحكم به لمدة تصل إلى 12 ساعة، وقدرة عالية على التحمل للطي أكثر من 300 مرة، ومؤشر انتفاخ بنسبة 242.96%، وحركية إطلاق الدواء من الدرجة صفر، وقوة التصاق حيوي خارج الجسم الحي بلغت 0.183 ± 0.016 جم، وقوة التصاق 0.083 ± 0.016 نيوتن وقوة شد تبلغ 3.116 ± 0.18 (نيوتن/مم²)، واستطالة مئوية تبلغ 358.87% ± 0.164%، ويظهر **SEM** أن سمك الغشاء كان في حدود 552.20 ± 5.30 مايكرومتر، مع وجود غشاء متحكم في المعدل يبلغ سمكه 616.6 ± 62.12 نانومتر، وكمية تراكمية من الدواء المتخلل (0.398 ملجم) في دراسة نفاذية الدواء خارج الجسم الحي

الخلاصة: توفر لاصقة العين المطورة التي تحتوي على سلفاسيتاميد الصوديوم نظامًا واعدًا لإيصال الدواء بإطلاق ممتد، ما يجعلها بديلاً محتملاً للقطرات العينية التقليدية، ويسهم في تحسين التزام المريض ونتائج العلاج في حالات التهابات العين البكتيرية.

الكلمات المفتاحية: أوكوسرت، توصيل الدواء للعين، غشاء متحكم بالإطلاق، سلفاسيتاميد الصوديوم، تقنية الغمس، الصب بالمذيبات.

Introduction:

It is abundantly evident that the eye is the most sensitive organ in the human anatomy. Although the eyeball is exposed to allergens, pathogens, and external injuries, it must preserve an intact and transparent surface to enable the retina's ability to detect light for optimum vision. (1). Under optimal physiological conditions, ocular barriers, including the lids and tear film, provide physical safeguarding to the eye, while a dynamic and intrinsic immune system, coupled with the normal flora, suppresses the proliferation of infectious agents (2). Disease may occur when these defensive processes are compromised by general illness, external impact, wearing contact, or diverse external factors. The ocular normal flora is the primary source of pathogens responsible for conjunctivitis, corneal inflammation, and endophthalmitis postoperatively (3).

Bacterial conjunctivitis (BC), referred to as "pink eye," occurs when the blepharal mucosa is inflamed and can be extended to the scleral surfaces and around the cornea due to a bacterial infection.(4). BC may disseminate and impact the entire cornea, ultimately leading to keratoconjunctivitis. BC is often reported as an ocular infection by health care providers worldwide. The primary reported bacterial isolates are *S. pneumoniae*, *S. aureus*, and *H. influenzae* (5). In general, BC incidences are estimated to be 135 in 10,000 in one study (6).

Sulfacetamide sodium (SAC) is chemically designated as sodium acetyl [(4-aminophenyl) sulfonyl] azanide. It is predominantly utilized in topically applied formulations as an antimicrobial agent. It can be employed in the treatment of

ulcerated cornea, conjunctival infection, and other minor infections (7).

Sulfacetamide is a synthetic equivalent and competitively antagonizes the bacterial para-aminobenzoic acid (PABA). It acts by disrupting the multiplication of bacteria by acting as a competitive antagonist with para-aminobenzoic acid, and this competitive antagonism translates into the inhibition of para-aminobenzoic conversion into folic acid, which is an essential metabolite for the production of bacterial nucleic acids (8, 9). In terms of physicochemical properties, it is a white or yellowish-white, crystalline powder with a melting point of 267 °C, freely soluble in water, sparingly soluble in ethanol, sparingly soluble in acetone, very slightly soluble in chloroform, slightly soluble in ether, soluble in mineral acids and alkali hydroxides. pKa 1.8, 5.4. Log P (octanol/water), -1.0. Its molecular weight is 255.25 g/mol (10, 11)

Topical medication delivery by conventional eye drops frequently results in low bioavailability, commonly around 5%, due to the elimination effects of blinking and tears, as well as poor patient compliance resulting from repeated dosing. Several initiatives have been committed to the development of controlled-release vehicles to address the drawbacks (12). Initiatives such as the addition of thickening agents and the formulation of hydrogels may substantially enhance medication bioavailability (13). However, these traditional methods might have a significant disadvantage, such as ocular discomfort, blurred vision, and might impact drug stability (14, 15).

The practical difficulties stated in the previous paragraph have significantly driven the advancement of innovative ocular medication delivery methods, such as the specialized hard or semi-hard wafers designed exclusively for ophthalmic applications that are referred to as ocular inserts (16).

Ocusert is a drug reservoir sandwiched between two microporous membrane sheets designed for insertion into the lower or upper fornix of the conjunctiva to deliver one or more active pharmaceutical ingredients to the ocular surface. In contrast to traditional ophthalmic formulations like eye drops, ocular inserts typically provide several benefits, including extended ocular retention of the medication, accurate dose, and reduced application number, leading to improved patient adherence (17). However, it may cause a slight discomfort at first, infrequent loss during sleeping or when rubbing the eyes, interfere with vision, and confuse placement (18).

Based on their solubility, inserts can be classified as soluble, insoluble, or biodegradable. Insoluble inserts or Ocusert, which is the primary focus in this research, must be retrieved from the eye after drug release. In contrast, soluble and bio-erodible inserts gradually dissolve and do not require removal. Drug release from ocular inserts occurs through the following pathways: osmotic, diffusional, and bio-erosion. Several preparation methods are wildly applied to produce Ocusert, like the solvent cast method, glass substrate techniques, hot-melt extrusion procedures, and accounting for its solid or semisolid nature (19, 20)The presently commercialized inserts are Lacrisert® and Dextenza® (21, 22).

Recent research employed a hot-melt extrusion method to formulate an SAC insert containing Sulfacetamide/prednisolone to manage both inflammatory and infectious ocular diseases through sustained and consistent release rates (23).

The current study is projected to efficiently fabricate an SAC Ocusert, which enables prolonged and regulated drug release.

Materials and Methods

Materials

Sulfacetamide Sodium (SAC) (TCI chemicals, Japan), polyvinyl pyrrolidine K90 (PVP K90), eudragit RLPO (Eu. RLPO) (Shanghai Macklin Biochemical co, China), dibutyl phthalate (DP)(Heowns, China), sodium alginate (Alg.) (Sigma-Aldrich, Germany), polyethylene glycol 400 (PEG), triethanolamine, sodium bicarbonate ($NaHCO_3$), sodium chloride (NaCl), calcium chloride ($CaCl_2$) (Loba Chemie, India) and marketed product (M.P) Locula (Sulfacetamide Sodium 10%) eye drops from local pharmacy. All other chemical reagents and solutions used were of laboratory quality.

Methods

The sulfacetamide sodium available dosage form was an ophthalmic solution of 10% (w/v) of SAC. The indicated dosing for the treatment of bacterial conjunctivitis and superficial ocular infection was two drops every 2-3 hours for one week, and the dose is tapered down following condition improvement (24).

A single drop volume was about 50 µL, so the single dose volume would be:

Volume of the drop × Number of drops = Total volume per dose

$$\boldsymbol{50\ \mu L \times 2 = 100\ \mu L/dose}$$

The total number of doses administered throughout the day would be:

24 hr. ÷ Dosing interval = Number of doses per day

$$\boldsymbol{24\ hr. \div 3\ hr.\ intervals = 8\ doses/day}$$

The total volume administered in a day would be:

Number of doses per day × Total volume per dose = The total volume administered in a day $\boldsymbol{8\ doses/day \times 100\ \mu L/dose = 800\ \mu L/day = 0.8 ml/day}$

Since the drug concentration (SAC) in the ophthalmic solution was 10% which would be equal to 10grams/100 ml or 100mg/1 ml, the total daily amount would be:

The total volume administered in a day × SAC concentration in the ophthalmic solution = The total daily amount of SAC

$$\boldsymbol{\frac{0.8ml}{day} \times \frac{100mg}{ml} = \frac{80mg}{day}}$$

It is worth mentioning that within 1.5 minutes post-application of conventional eye drops, there would be a 90% loss of the administered therapeutic agent (25). In general, Ocusert has inherited properties of an extended residence time and minimal drug washout, so one can safely formulate the desired Ocusert with the inclusion of only 10% of the total calculated daily dose that would otherwise be encountered with conventional eye drops. In conclusion, the total daily dose would be about 8 mg. Additionally, a 2 mg was also added to encounter precorneal clearance and systemic infective absorption.

So, the projected amount of drug content per Ocusert would be:

The total daily amount of SAC × 10% + predicted drug loss = The possible amount of SAC per Ocusert per day

$$\boldsymbol{\left(80\frac{mg}{day} \times \frac{10}{100}\right) + 2\ mg\ (drug\ loss)}$$

$$\boldsymbol{= 8\frac{mg}{day} + 2mg}$$

$$\boldsymbol{= 10\frac{mg}{day} = \frac{5mg}{12\ hr.}}$$

The possible amount of SAC per Ocusert per day ÷ 2 = The amount of SAC per Ocusert per 12 hr.

$$\boldsymbol{10\frac{mg}{day} + 2\ mg = \frac{5mg}{12\ hr.}}$$

Knowing the prepared formula was cast in a round plastic petri dish of 3 cm in radius, so the

$$\boldsymbol{area\ of\ the\ petri\ dish = area\ of\ the\ circle = \pi \times square\ of\ the\ radius = \pi \times (3cm)^2 = 28.27\ square\ cm}$$

Furthermore, the final film (insert) was cut into circles of 10 mm in diameter (0.1 cm in diameter or 0.05 cm in radius) with the aid of a sharp-edged steel borer from the

derided film within the petri dish (26). So, the area of the desired insert would be

$$\boldsymbol{area\ of\ the\ desired\ insert} = \boldsymbol{area\ of\ the\ circle} = \boldsymbol{\pi} \times \boldsymbol{square\ of\ the\ radius} = \boldsymbol{\pi} \times (\boldsymbol{0.05cm})^2 = \boldsymbol{0.7853\ square\ cm}$$

While the number of inserts that can be theoretically prepared per Petri dish would be:

$$\frac{\boldsymbol{area\ of\ the\ petri\ dish}}{\boldsymbol{area\ of\ the\ insert}} = \frac{\boldsymbol{28.27cm}}{\boldsymbol{0.7854cm}} \cong \boldsymbol{36\ inserts\ per\ petri\ dish}$$

From the upper calculations, it's estimated that the amount of SAC per insert would be about 5 mg/insert, so the total amount of SAC per petri dish would be:

The amount of SAC per Ocusert per 12 hr × The number of inserts that can be theoretically prepared per petri dish = The total amount of SAC per petri dish

$$\boldsymbol{5}\frac{\boldsymbol{mg}}{\boldsymbol{insert}} \times \boldsymbol{36}\frac{\boldsymbol{inserts}}{\boldsymbol{petri\ dish}} = \boldsymbol{180}\frac{\boldsymbol{mg}}{\boldsymbol{petri\ dish}}$$

So, it's advisable to prepare and cast 18 ml of formulation containing 180 mg of SAC or to prepare 20 ml containing 200 mg of SAC to simplify the calculation and account for any loss during casting.

Therefore, to further simplify the data presentation, the concentration of the SAC in each formula would be:

$$\frac{\boldsymbol{200mg}}{\boldsymbol{20ml}} = \boldsymbol{10}\frac{\boldsymbol{mg}}{\boldsymbol{ml}} = \frac{\boldsymbol{100mg}}{\boldsymbol{10ml}} = \frac{\boldsymbol{1grams}}{\boldsymbol{100ml}} = \boldsymbol{1\%(w/v)}$$

SAC inserts preparation (core layer)

The solvent-casting method was employed to produce the desired inserts, and it was started by the addition of 20 mL deionized water (D.W) into a glass beaker, then heated to 60 °C with the aid of a hot plate magnetic stirrer (Four E's Scientific, China). The SAC-polymer physical mixture, as detailed in Table 1, was incorporated and stirred at 1400 rpm for 30 minutes, after which a 30% w/w PEG 400 (plasticizer) was added to the previous solution, and the stirring was continued for an additional 30 minutes.

Table (1): CORE LAYER FORMING FORMULAS (W/V%).

Code	Carbopol 934	HPMC K15 M	HPMC K100 M	Ethyl cellulose L. V	Sodium Alg.	PVP K30	PVP K90
F1	0.5	0.5					
F2	0.5	1					
F3	0.5	1.5					
F4	0.5		0.5				
F5	0.5		0.75				
F6	0.5		1				
F7				2		1	
F8				2		1.5	
F9				2		3	
F10		0.75				1.5	1.5
F11		1				3	3
F12		1				4	7
F13					1.5		3
F14					1.5		7
F15					1.5		8

The percent weight of PEG 400 is estimated based on the total polymer weight employed in each formula mentioned in the earlier table. After the total stirring time of one hour, the hot plate magnetic stirrer is turned off, and the resulting hydrogel is allowed to

equilibrate with room temperature for about 4 hours, after which it is stored at a controlled temperature of 2-4 °C in the refrigerator for 24 hours to facilitate optimal polymer swelling and hydration. For Carbopol-containing formulations, 125 µL of triethanolamine has been included to neutralize their pH. In the case of formulas containing ethyl cellulose, the 20 mL of deionized water was replaced with 20 mL of methanol as the solvent, and the exact steps were followed without the heating step. After refrigeration at 2-4 °C, the 20 mL sample is equilibrated at room temperature for 4 hours. Subsequently, only 18 mL of the prepared liquid dispersion is transferred to a round plastic petri dish measuring 1 cm in height and 6 cm in diameter. The sample is then allowed to air dry at 25 °C for 72 hours to ensure complete solvent evaporation. The dried film is subsequently cut to a final diameter of 10 mm, containing 5 mg of SAC, using a sharp-edged steel borer of 10 mm in diameter (27).

The formulas were subjected to general evaluations and drug release tests to choose the best film-forming formula to be used in dual-layer preparation.

Preparation of the dual-layered inserts (rate-controlling layer)

The selected SAC-containing core layer was immersed for 5 seconds in an ethanolic solution of a variable strength of Eud. RLPO (Table 2), and this solution also contains 10% w/w of dibutyl phthalate (DP) as a plasticizer, which was calculated according to Eu. RLPO weight. Post dipping, the Ocusert was set aside to dry for one day at room temperature and then kept in a glass desiccator containing silica gel for additional evaluation. The final insert comprised a thin, flexible polymeric film that included a matrix layer enveloped by a rate-controlling layer(28).

Table (2): Rate Controlling Layer Dipping Solution (W/V%).

Dipping solution code	Eu. RL PO
A	5
B	10
C	15

Physical appearance:

The assessment of the produced core and dual-layer Ocusert was performed visually, emphasizing surface roughness, shape, size, and color.

Thickness:

A digital vernier caliper (Shanghai, China) was used to measure the thickness of ten films at three points (two at the opposing edges and the center), and then the mean and deviations from the average were determined(29).

Weight variation:

With the help of an analytical balance, 10 round films, each having an inner diameter of one centimeter, were selected at random and weighed separately. A test for the variations of weight was carried out with the assistance of an electronic balance (Kern ALS 220-4N-Germany)(30).

Surface pH:

The inserts that had been made were immersed in 1 mL of distilled water to ensure a proper pH reading for 15 minutes. Through the utilization of a pH meter (HANNA, USA), the surface pH of every insert was evaluated, and the resulting values were recorded. The technique was performed on three randomly selected inserts from each batch (31).

Folding endurance:
The folding endurance was evaluated by repeatedly folding the film 300 times within the index and thumb, following the center line of the film. The results of this evaluation provide crucial details regarding the fragility and adaptability of the insert after insertion. Having a folding endurance value of over 300 times without showing any signs of cracks or breakage indicates that the insert is of high quality (32).

Drug content:
For each prepared batch, ten randomly selected inserts were utilized for the SAC content study. Each insert was immersed in 100 mL of tear-simulated fluid (TSF) (pH 6.8) consisting of 670 mg NaCl, 200 mg $NaHCO_3$, 80 mg $CaCl_2$, and distilled water to a volume of 100 mL at 37°C for 24 hours with constant stirring. A solution sample was filtered using a 0.45 µm Whitman filter and measured at 257 nm with a UV-VIS spectrophotometer (Shimadzu-Japan), from which the average drug content for each batch was determined (33).

Swelling index percent (SI%):
Every ocular insert was placed on a plastic threaded mesh and submerged in 15 mL tear-simulated fluid (TSF) at 37°C to determine the percentage of swelling that it exhibited. Following the wipe-off of excess moisture with filter paper, the inserts were weighed at predetermined intervals of 0.16, 0.5, 1, 5, 10, 20, 30, 40, 50, 60, 120, 180, 240, 300, 360 min. A calculation was made to determine the swelling, where Wt is the weight that was measured at time t and W_0 is the weight of the inserts when they were first implemented(34):

$$SI\ \% = \frac{Wt - W_0}{W_0} \times 100$$

***In vitro* release study:**
To evaluate the SAC release from the prepared inserts and compare it against a marketed product (MP) , a study used a Franz diffusion cell (Figure 1.)

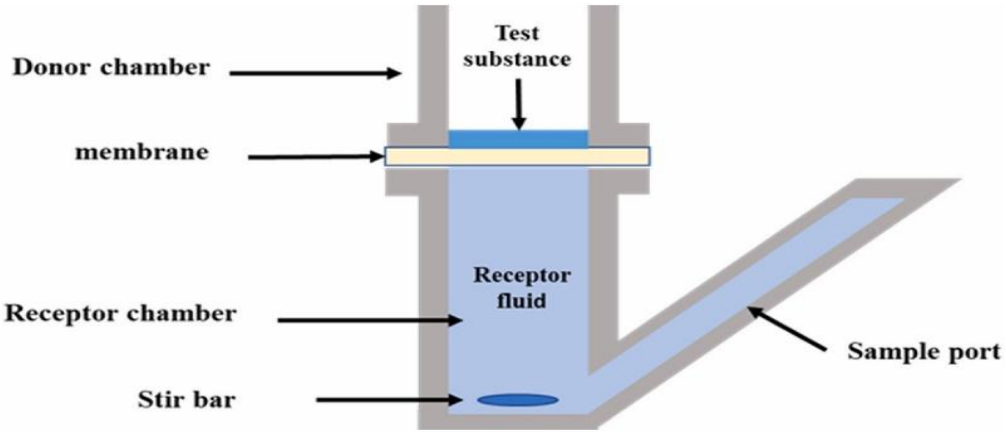


Figure (1): Franz diffusion cell

With a 22 mL receptor compartment and a 5 mL donor compartment separated by a dialysis membrane with a molecular weight cut-off of 12,000 to 14,000 Da. The dialysis membrane was submerged in TSF for a whole day before application(35, 36). The insert was positioned within the donor compartment, which contained 100 µl of TSF. At the same time, the space inside the receptor was filled with TSF and maintained at a temperature of 37°C ± 0.5°C. An amount of 1 mL of solution was

removed from a sampling port located within the receptor compartment, and at the same time, 1 mL of TSF was inserted into the sample port. This was carried out on an hourly basis for a total of 12 hours(37). The collected samples were examined for SAC concentration using a UV-VIS spectrophotometer at 257 nm after filtering them through a 0.24-micrometer syringe filter (38).

Drug release kinetics study:

Using the DD Solver® program, the data for the SAC release from the created formulations were analyzed kinetically against a variety of mathematical models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models(39).

***Ex vivo* bio adhesion:**

The bio-adhesive property has been evaluated using goat conjunctival tissue. This tissue was collected from a local slaughterhouse in a cold box while being submerged in a plastic bag containing normal saline solution 0.9%. A square section of tissue was removed and affixed using cyanoacrylate adhesive to the surfaces of the two plastic tissue holders. The film was placed between both of the tissue surfaces and maintained in touch with consistent, gentle pressure from the fingers for one minute to facilitate adhesion. The upper tissue holder was mounted to an iron stand employing a thin plastic thread, which was connected with a hook on the rear of the tissue holder. A pre-weighed light polyethylene bag was secured to the other end of the thread. After a one-minute pre-load interval, water was administered to the polyethylene bag through an intravenous drip set at a rate of two drops/second till the upper tissue holder became dislodged due to the considerable weight of the supplied water

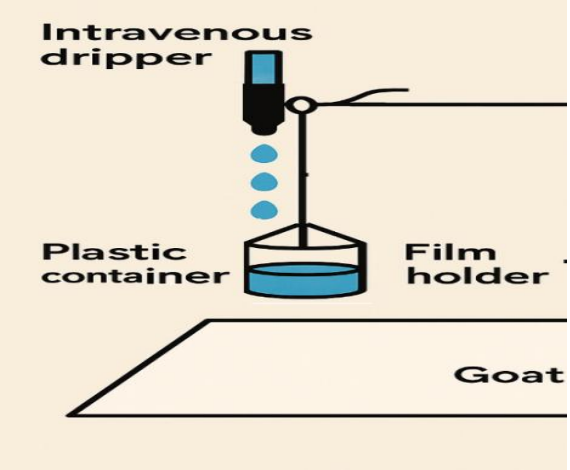


Figure (1): Ex vivo bio adhesion test illustration.

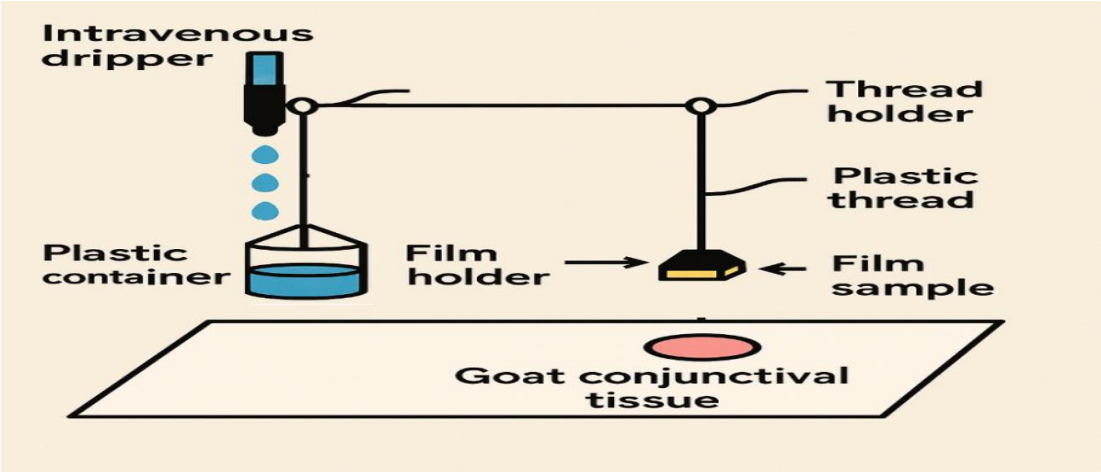


Figure (1): Ex vivo bio adhesion test illustration

The water accumulated in the bag was measured and expressed as the weight (gram force) required for separation, employing the following equation(40):

Force of adhesion (N) =
(Bioadhesive strength (g.) ×
9.81 gravity acceleration)/1000

Bond strength (N m^{-2}) = Force of adhesion/film surface area

***Ex vivo* drug permeation study:**

The eyes of the goat were procured from a local butcher, and the cornea was carefully dissected with the aid of surgical scissors, then washed with saline, and kept in freshly prepared TSF. The methods employed in the *in vitro* release study were implemented, substituting the dialysis membrane with goat corneal tissue. A goat corneal tissue having a surface area of 0.66 square centimeters was removed and placed between the donor and receptor compartments, clamped via a stainless-steel clamp, and capped with parafilm to avert loss of moisture, with the surface of the cornea oriented towards the donor compartment of the Franz cell Error! R eference source not found..

Figure (1): Franz diffusion cell

The operating temperature was regularly maintained at 37 ± 0.5 °C, and the stirring pace was sustained at 50 revolutions per minute during the course of the experiment. 1 mL of the specimen was withdrawn from the recipient chamber at

specified periods, with an equivalent volume of fresh TSF added simultaneously(41).

A graph based on cumulative drug release over time was generated from the *ex vivo* permeation data, and multiple variables were calculated as follows(42):

1. Steady-state drug flux (Jss) is the slope of the fitted linear curve.
2. Lag time (T_{lag}) is determined by extrapolating the fitted linear curve to the x-axis.

Mechanical characteristics:

Rectangular specimens measuring 40 x 20 mm were positioned between the texture analyzer (Tinius Olsen UK) holding grips and secured with clamps **Figure (**2**.**

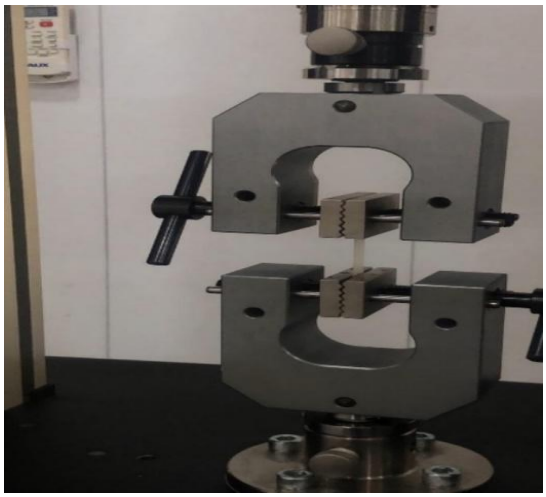


Figure (2): Texture analyzer

Subsequently, the sample was subjected to an upward pull by the upper movable grasp at a uniform rate of one mm/min until the film breakpoint was reached. The highest possible resistive strain and percent of elongation at the breakpoint have been determined in three separate experiments, and the average of each value was documented(43).

Drug-excipient compatibility study:

FTIR spectroscopy was performed separately on the drug, polymers, and the optimized insert. Specimens were dehydrated in a desiccator at $25C^0$ and relative humidity levels of 43%, combined with potassium bromide powder, then crushed via a manually operated pneumatic press. A Shimadzu FT-IR spectrometer was used to get the FT-IR spectra, which were scanned at a wavenumber between 400 and 4000 cm^{-1}(44).

The thermodynamic properties of the SAC, polymer compounds, and Ocusert have been investigated using differential scanning calorimetry (DSC). Samples weighing between 2 and 3 mg of every component were measured and placed in a temperature-regulated DSC cell. The container was then closed with an airtight lid. A reference cell devoid of a sample was employed. The specimens were subjected to heating at 275 °C at a rate of ten degrees Celsius per minute(45).

Statistical analysis:

All of the data that is shown is based on the average of three observations, and standard errors are provided. For statistical analysis, a one-way analysis of variance (ANOVA) was carried out. The level of significance was established at $p < 0.05$, which implies a statistically significant difference.

Results and Discussion

Core layer general evaluation:

All the formulated core layers were evaluated for thickness, folding endurance, pH, drug content, weight variation, and percentage of drug content **(Table 3).**

Table (3): Core Layer General Evaluation

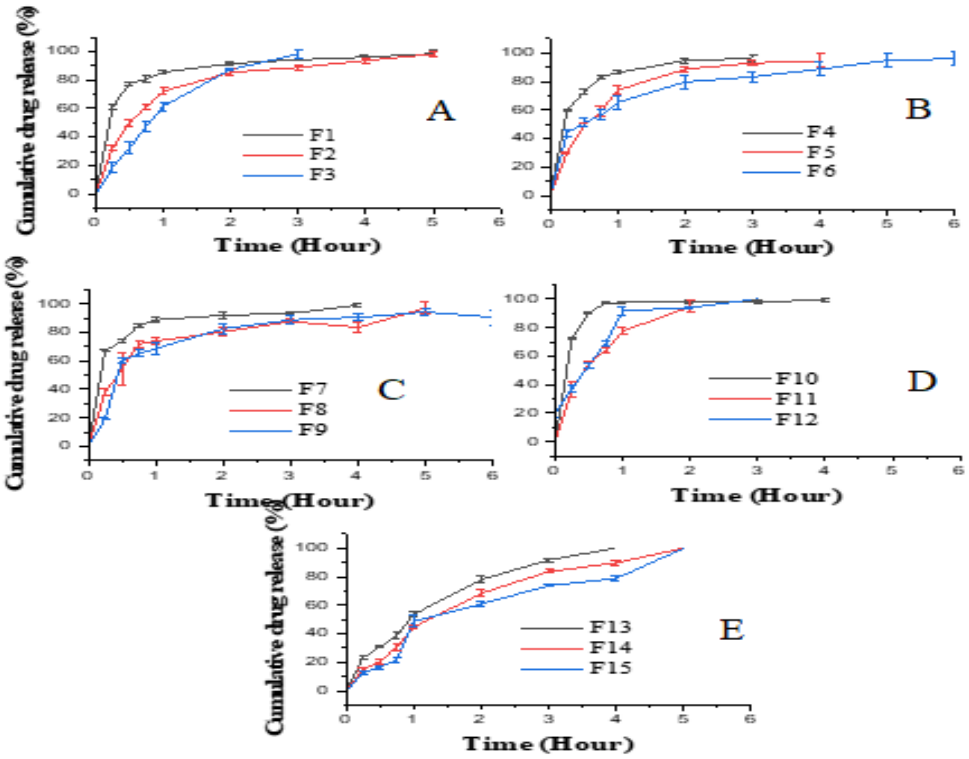
Formula	Folding endurance (number of times)	pH	Weight variation (mg)	Thickness (mm)	drug content(mg)	content percentage (%)
1	Over 300	6.95 ±0.01	13.41 ±0.72	0.11 ±0.02	5.26 ±0.41	105.26 ±8.15
2	Over 300	6.94 ±0.03	15.96 ±0.55	0.12 ±0.02	4.70 ±0.32	94.01 ±6.42
3	Over 300	6.91 ±0.01	19.59 ±0.77	0.17 ±0.03	5.07 ±0.37	101.30 ±7.32
4	Over 300	6.91 ±0.02	13.47 ±0.60	0.11 ±0.02	5.20 ±0.27	103.94 ±5.42
5	Over 300	6.92 ±0.02	14.71 ±0.71	0.12 ±0.02	5.22 ±0.34	104.30 ±6.70
6	Over 300	6.91 ±0.03	17.09 ±0.88	0.14 ±0.03	5.08 ±0.17	101.62 ±3.46
7	Over 300	6.95 ±0.04	26.12 ±0.97	0.20 ±0.02	4.73 ±0.28	94.56 ±5.59
8	Over 300	6.98 ±0.01	29.36 ±1.28	0.19 ±0.03	4.89 ±0.27	97.75 ±5.30
9	Over 300	6.98 ±0.02	38.10 ±0.48	0.23 ±0.03	5.21 ±0.22	104.26 ±4.38
10	Over 300	6.96 ±0.05	22.91 ±0.76	0.17 ±0.02	5.14 ±0.28	102.72 ±5.56
11	Over 300	6.99 ±0.03	37.34 ±1.23	0.22 ±0.03	5.07 ±0.34	101.38 ±6.89
12	Over 300	6.97 ±0.05	39.08 ±0.41	0.23 ±0.04	4.92 ±0.20	98.33 ±3.90
13	Over 300	6.97 ±0.02	34.26 ±1.64	0.22 ±0.03	4.79 ±0.22	95.81 ±4.47
14	Over 300	6.94 ±0.01	63.41 ±1.01	0.44 ±0.08	4.67 ±0.32	93.43 ±6.50
15	124± 14.06	6.97 ±0.02	67.44 ±0.63	0.45 ±0.05	4.82 ±0.31	96.41 ±6.39

The core layers exhibited a slightly yellowish coloration and a circular shape, measuring 10 mm in diameter. The core layer thickness was in the range 0.11-0.45 mm, which is still suitable for ocular inserts since the maximum thickness allowed is 10 mm [46]. The surface pH of all formulations tested ranged from 6.91 to 6.99, which falls in the acceptable range of 6.5-7.5 for ocular delivery, so one can safely propose that no ocular irritation can be expected (47, 48). The weight variation among the prepared core layers was in the range of 13.41- 67.41. A reduced standard deviation signifies enhanced consistency in film weights(49). All formulations exhibit adequate folding endurance, exceeding 300 cycles, except for F15, owing to its high PVP K90 content

(50). SAC content ranged from 4.67 to 5.26 mg, with a percentage content of 93.43% to 105.26% (51, 52).

Core layer *in vitro* drug release study:

Figure(3 Illustrates a plot of the cumulative percentile amount of drug released over time for the formulated film-forming compositions discussed in the previous section. This process was undertaken to enhance the understanding of the drug release profile among different formulation variables and assist in selecting a suitable candidate for further optimization.



Figure(3):Drug release profile for the core layer

Fig5.A and Fig.5B formulation carried by fixing the concentration of Carbopol 943 while altering the concentration of HPMC K15 M and HPMC K100 M, respectively.
Fig.5C, a fixed concentration of Ethyl cellulose L.V with a variable concentration of PVP K30.
Fig.5D, a fixed concentration of HPMC K15 M with a variable concentration of PVP K30.

The *in vitro* drug release patterns of the developed ocular films revealed substantial burst release during the initial 60 minutes across all tested formulations, regardless of the polymer type or concentration utilized. This pattern was particularly apparent in formulations including hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) and sodium alginate, which have been highlighted for their fast swelling upon hydration and their capacity to boost drug diffusion(53).

The formulation concept was altered to regulate the burst release while developing a more controlled delivery profile suitable for ocular administration. A rate-controlling layer was implemented, borrowing insight from multilayer film methods for transdermal and ocular systems that have proven effectiveness in limiting release rates (54).

Therefore, of the assessed formulations, the one demonstrating the most gradual release rate was chosen for inclusion into a bilayer structure. The 60-minute interval was

selected as the primary cutoff due to its correlation with the release profile and its coherence with reported ocular residence intervals, generally spanning from 30 minutes to 2 hours(55).

Figure 4 Demonstrates that, of the 15 formulations assessed, F14 displayed the least amount of cumulative drug release (SAC) throughout the initial hour.

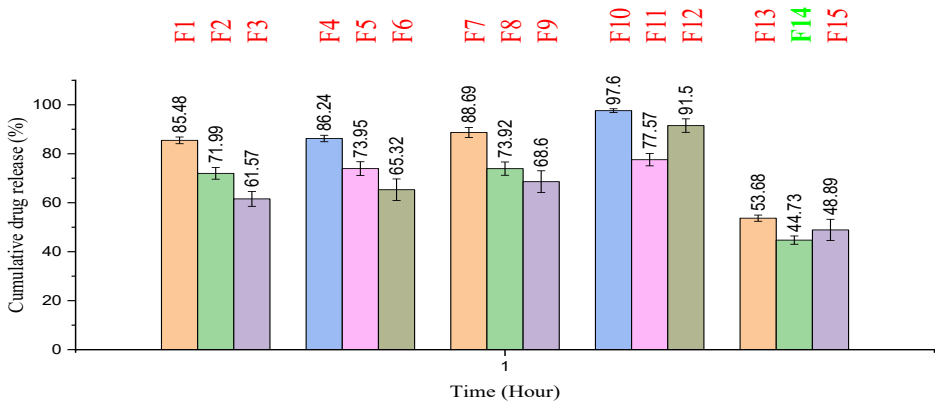


Figure 4: SAC release One hour core layer cut off

Statistical examination of F14 with F3, F6, F9, and F11—each indicating the slowest-releasing formulation in their categories—revealed a markedly reduced release rate for F14 ($p < 0.05$). The difference seen is statistically significant, highlighting the influence of formulation variables, including polymer type, concentration, and film shape, on drug release kinetics(56).

This suppression was attributable to the incorporation of PVP K90, which established a robust gel barrier that significantly impedes aqueous penetration and drug diffusion, thereby materially prolonging the release phase(57). Additionally, when sodium alginate interacts with divalent cations (e.g., Ca^{2+} present in tear fluid), it undergoes ionotropic gelation, yielding a dense hydrogel 'egg-box' network. This network effectively entraps the drug molecules and retards their migration, resulting in slower release kinetics(58).

These mechanistic interpretations are supported by existing evidence:

- The role of gel-forming polymers such as PVP K90 (often in combination with HEC) in creating thicker gel layers that decelerate drug release has been documented by Roy et al(59).
- PVP's capability to modulate drug-release profiles toward zero-order or bimodal behavior by structuring the hydrophilic matrix has been detailed in formulation patents(60).
- Sodium alginate's gelation in the presence of multivalent cations and its resulting controlled-release properties are well established in the literature(61)

Evaluations of the dual-layered Ocusert:

As indicated in the preceding section, F14 with 1.5% ALG and 7% PVP K90 is selected as the appropriate candidate owing to its slow-release profile and also shows a proper Folding endurance, pH, weight variation, thickness, drug content, and content percentage for further optimization. Utilizing the dipping method outlined in Table 2, three formulations were developed by varying the concentration of EUD. RLPO

The dual-layer Ocusert is assessed similarly to the core layer regarding folding

endurance, pH, weight variation, thickness, drug content, and content percentage. There were no statistical differences ($P > 0.05$) except in terms of weight variation and thickness ($P < 0.05$). The final findings are summarized in Table 4, with each parameter discussed in its respective section.

Table (4): Ocusert general evaluations

F	Folding endurance	pH	Weight variation (mg)	Thickness (mm)	Drug content(mg)	Content percentage (%)
A	Over 300	6.96 ±0.02	75.18 ±1.02	0.46 ±0.05	4.78 ±0.36	95.52 ±7.21
B	Over 300	6.96 ±0.01	78.09 ±1.01	0.49 ±0.04	4.73 ±0.28	94.63 ±5.66
C	Over 300	6.97 ±0.02	81.30 ±1.21	0.53 ±0.06	4.68 ±0.39	93.70 ±7.84

Visual inspection of inserts

The Ocusert exhibited a slightly yellowish hue and a circular morphology with a diameter of 10 mm (79 mm^2), conforming to the maximum allowable diameter of 10 mm(62). The prepared Ocusert exhibited a circular shape with a uniform appearance, a slight yellowish hue, and a smooth texture, devoid of surface imperfections, roughness, or phase separation between the matrix and the drug, indicating uniform drug distribution(63).

Thickness

The prepared insert exhibits a thickness range of 0.46-0.53 mm, which falls within the acceptable limits of 0.3-1 mm, and the low standard deviation value suggests a uniform composition of the insert(30, 46). The observed variation in film thickness is likely due to differences in polymeric composition and concentration; however, it remains within acceptable limits (64).

Weight variation

Ten films were selected (n=10) for each batch, and the results indicate a uniform weight among the formulated films, as evidenced by a low standard deviation(65)Consistency in weight also reflects good film uniformity and reproducibility in the casting or molding process(66).

Drug content and drug content percent

In multilayered inserts, drug loss or migration across layers during casting, drying, or storage may lead to uneven therapeutic efficacy(67). The drug content of all prepared Ocusert ranges from 93% to 95%, which is within the acceptable pharmacopeial limits for drug content uniformity (85%-115%). Additionally, the low standard deviation also conforms to acceptable limits(51, 52).

Surface pH

Since the addition of a second layer, usually intended as a rate-controlling or protective outer membrane, can significantly influence the microenvironmental pH (68). The formulated Ocusert exhibited pH values ranging from 6.96 to 6.97, which fall within the acceptable range of 6.5 to 7.5. Therefore, we can propose that there should be no ocular irritation (47, 48).

Folding endurance

This test indicates the material's resistance to deformation; all the prepared formulations exhibited a folding endurance of over 300 times, therefore, they can be

handled and inserted into the conjunctival sac without compromising their integrity(50)These findings are in agreement with previous reports, which suggest that a folding endurance value above 300 is considered acceptable for ocular films(69).
All SAC Ocusert, namely F14A, F14B, and F14C, have successfully passed the general evaluation tests and show no statistical significance ($P > 0.05$) among them, qualifying them for further investigation(70).

Swelling index percent (SI%):
The water absorption or swelling index, measured following the placement of an ocular insert in TSF, serves as a key indicator of the hydrophilic or hydrophobic nature of the polymeric composite(52). This parameter is critically important as it directly influences drug dissolution and release kinetics, and also correlates with the host's physiological acceptance of the insert. In particular, it helps predict whether the formulation will provoke a foreign body sensation upon administration. Conversely, excessive swelling or rapid surface erosion can compromise the mechanical integrity of the insert, hinder adhesion, and lead to increased leaching of polymeric particles, which may trigger ocular irritation or a foreign body sensation. Therefore, controlling the swelling index is not only crucial for maintaining drug release profiles but also for ensuring clinical acceptability and comfort(71).
As shown in **Error! Reference source not found.** Formulations F14A, F14B, and F14C exhibited maximum swelling indices of 270.39%, 233.47%, and 242.96%, respectively, within the first 120 minutes of immersion and were considered well within the range of less than 300% according to previous research (72).

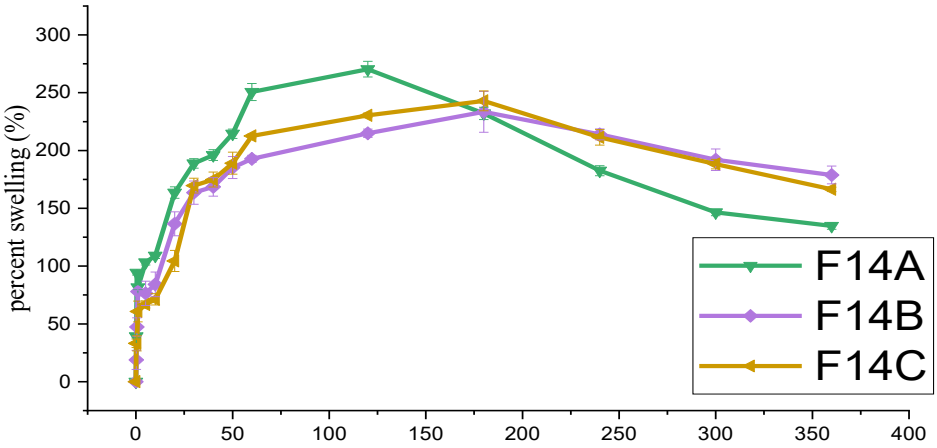


Figure (1): Franz diffusion cell

This peaked swelling of 270.39%, 233.47%, and 242.96% for F14A, F14B, and F14C, respectively, was followed by a gradual decline over time, suggesting minimal polymeric leaching and well-controlled hydration behavior(73). However, the difference in the swelling values was statistically non-significant ($P > 0.05$). The controlled swelling profile is likely attributed to the presence of Eudragit RLPO in the outer layer, which functions as an effective rate-controlling membrane(74). By regulating both water influx and efflux, Eudragit RLPO helps maintain structural integrity and prevents excessive fluid absorption or surface erosion, thereby enhancing the stability and performance of the inserts (75).

***In vitro* release study and Kinetics:**

All formulated dual-layer Ocusert underwent *in vitro* drug release testing to evaluate relevant variables and to compare the formula of interest with F14 and the marketed product Locula (M.P).

As mentioned earlier, the F14 core layer, formulated by combining 1.5% Alg and 7% PVP K90, is the sole formulation that achieved a satisfactory minimum drug release among all the formulated core layers within a one-hour cutoff and complete drug release within 5 hours.

However, the Ocusert design was modified by incorporating a rate control layer of Eud RLPO hydrophobic polymer to achieve a slower and prolonged release duration (76). Across F14A, F14B, and F14C, a stepwise increase in Eudragit® RL PO (rate-controlling layer) produced a statistically significant ($P < 0.05$) prolongation of the operational release time (≈6 h, 8 h, and 12 h, respectively). This trend is consistent with the diffusion-barrier mechanism of ERLPO films: greater polymer content/coating level increases film continuity and tortuosity, thereby reducing water influx and drug diffusivity across the membrane and extending release duration. The behavior aligns with prior reports that (i) Eud RL/Eud ERS copolymers govern pH-independent, diffusion-controlled release, and (ii) increased Eud RL PO content or coating level yields stronger release retardation by lengthening the diffusional path and decreasing porosity(73, 77-80). Furthermore, these formulations displayed an acceptable swelling profile while preserving their structural integrity after 12 hours, owing to their EU. RL PO content **Error! Reference source not found.**(75).

In summary, it's worth noting the factors that contributed to the rapid drug release and the formulation variables employed to address this issue. Notably, SAC exhibits high water solubility, which leads to its rapid solubilization and expulsion from a polymeric matrix composed exclusively of hydrophilic polymers, such as PVP K90 and Alg. The results indicate the essential requirement for a hydrophobic polymer, such as EU. RL PO, in conjunction with a high polymer to SAC ratio, provides a strong hydrophobic barrier that hampers solubilization and diffusion of SAC out of the Ocusert, thus prolonging the drug release (81).

The conventional eye drops of SAC demonstrated only a 30-minute *in vitro* drug release, highlighting the significant advantage of the formulated F14C in reducing the frequency of administration from 8–12 times to 2 times per day, and thus being chosen as an optimal formula for further investigations **Error! Reference source not found.** (82) .

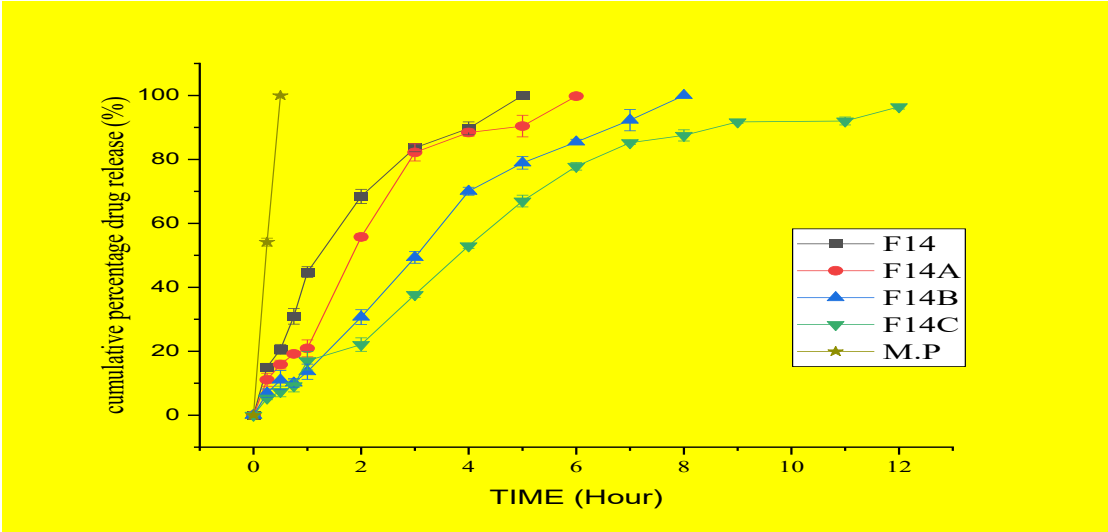


Figure (1): Franz diffusion cell

Now, concerning drug release kinetics modeling, the data included represent 60% of the release data for Higuchi and Korsmeyer-Peppas and 100% of the release data for the Zero-order and First-order, and were conducted comparatively between the core layer formula F14 and the final optimal formula F14C to highlight the drug release mechanism difference upon formulation modification presented in Table 5.

Table (5): Kinetic analysis

Optimum formula	kinetics constants	F14	F14C
Zero-order	k0	23.778	13.583
	Rsqr	0.7727	0.974
First-order	K1	0.573	0.188
	Rsqr	0.9904	0.9385
Higuchi	KH	44.744	24.266
	Rsqr	0.9608	0.8170
Korsmeyer-Peppas	Kkp	40.951	14.524
	N	0.583	0.919
	Rsqr	0.9745	0.9542

Table 5. presents that F14 exhibited a square regression nearest to unity, aligning with the first-order mathematical model. This release model indicates that the drug release from the core layer, established in the initial formulation phase, is directly proportional to the drug quantity within the polymeric matrix(83). Conversely, F14C exhibited distinct drug release kinetics, as anticipated from the linearity of the drug release profile. This was substantiated by the regression value approaching one, indicating a correlation with zero-order release kinetics. The significant transition from concentration-dependent drug release observed in F14 to a more controlled, time-dependent release can be ascribed to multiple factors. The pores of the polymeric composite forming the rate-controlling layer surrounding the core layer containing SAC are sized to match the drug molecules, facilitating a slow and controlled inflow of the TSF, followed by the solubilization and gradual outflow of SAC-containing media(84). Objectively, the insert may experience a complex interwinding event that begins with slow surface-level degradation, followed by water-induced swelling and relaxation. Subsequently, water reaches the core layer, solubilizing the drug and creating an osmotic gradient. Consequently, drug release is regulated osmotically in a consistent and controlled manner via the surface pores created by swelling and degradation(71).

This zero-order kinetic drug release behavior ensures a stable drug release without daily fluctuations, thereby minimizing adverse effects.

***Ex vivo* Bio adhesion:**

Discussion and evaluations will focus on the F14C, as it demonstrated an extended drug release of approximately 12 hours.

F14C provided an *ex vivo* bio-adhesive strength of 0.183 ± 0.016 g and a force of adhesion of 0.083 ± 0.016 N. The bioadhesive properties of the insert are attributed to the cationic charge imparted in the Eudragit RLPO of protonated amino NH_4^+ that interacts with the counter-anionic charge of the mucin layer covering the conjunctiva(85). This bio-adhesion property is desired to enable the insert to withstand the force of the eye movement or blinking(86).

***Ex vivo* drug permeation study**

The 12-hour *ex vivo* drug permeation test was carried out between F14C and M.P. to signify the impact of bioadhesion on the drug permeation throughout the corneal tissue.

F14C provided a significant ($P < 0.05$) difference in the cumulative amount of drug permeated (0.398 mg) when compared to M.P. (0.240 mg). The steady-state drug flux (Jss) values for M.P. and F14C were 0.015 mg/cm²/h and 0.032 mg/cm²/h, respectively (Figure (5).

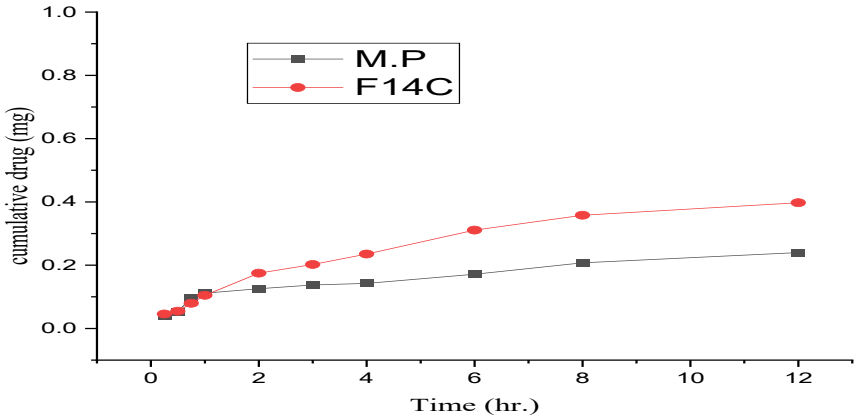


Figure (5): Cumulative permeation of optimized F14C in comparison with M.P

The steady-state data also demonstrate significant ($P < 0.05$) enhancement in terms of drug flux through the corneal tissue. Moreover, the topic of the percentage of drug permeation is presented in Figure (6, and F14C demonstrated an enhancement of approximately twofold in comparison to M.P.

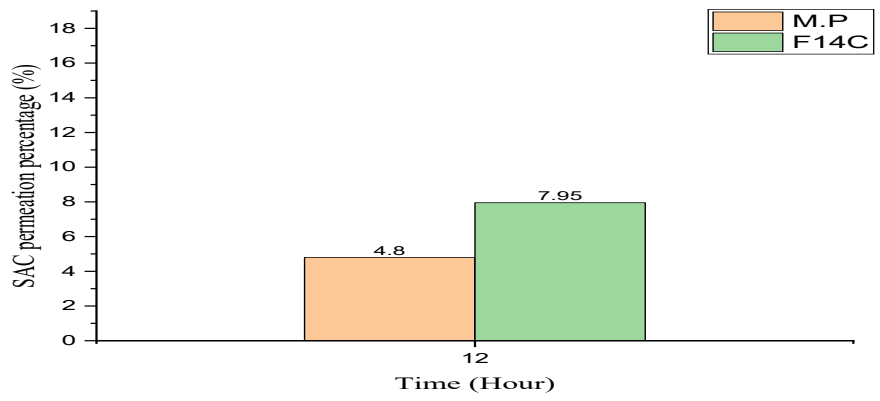


Figure (6): SAC permeation percentage

Further examination reveals that the increased corneal drug permeation of F14C is likely attributable to the intrinsic characteristics of the weak bio-adhesion of EU. RL PO independently thins the mucin layer covering the cornea and expands the tight junctions that impede drug influx **(87)**. The drug permeation latency time (T lag) for F14C and M.P. was 4.7 and 4.5 minutes, respectively, indicating no significant enhancement among the tested entities ($P > 0.05$).

Mechanical characteristics:

The tensile properties, including tensile strength and percentage elongation at break, are utilized to evaluate the mechanical characteristics of the formulated films. The significance of these parameters is further demonstrated by the mild stress experienced by the produced inserts due to the eye's blinking action, and during their handling and placement in the eye(88).

F14C exhibited a tensile strength of 3.116 ± 0.18 (N/mm²) and a percent elongation of 358.87% ± 0.164, properties that are advantageous for enduring mild stress associated with the blinking action of the eye and during handling and placement (89, 90).

Visualization of inserts by scanning electron microscopy (SEM):

By the application of different powers of magnification, the film thickness was in the range of 552.20 ± 5.30 µm, having a rate-controlling membrane of 616.6 ± 62.12 nm in thickness. Figure 11. While the surface morphology results of the optimal formula under SEM were a further reassurance of surface smoothness, thickness acceptability, and no signs of cracks or fractures, the drug was uniformly distributed(91).

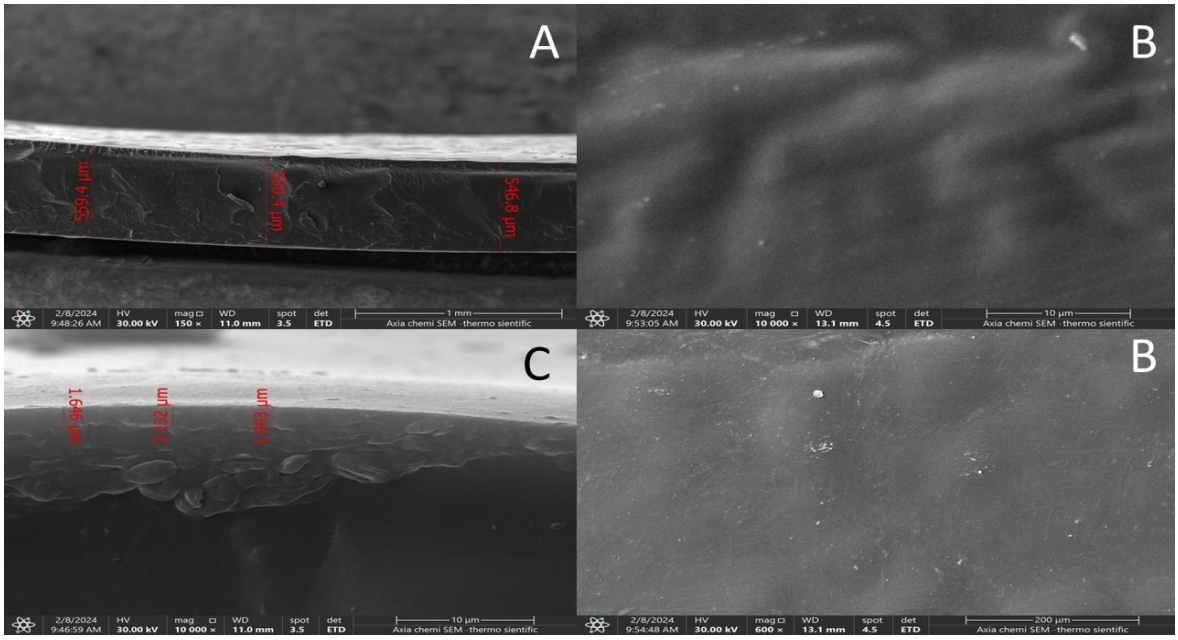


Figure (11): SEM. A)Cross sectional veiw. B)Surface view. C)Rate controlling membrane

DSC Drug-Excipients Compatibility Study

DSC is considered a sensitive and reliable technique for the detection of drug polymorphism, melting behavior, and drug-polymer interactions. The comprehensive data presented earlier, in conjunction with (F14C) DSC data, indicated the disappearance of the distinctive SAC peak, which signifies the absence of SAC crystallinity and confirms the transition to an amorphous state (92) Figure 12.

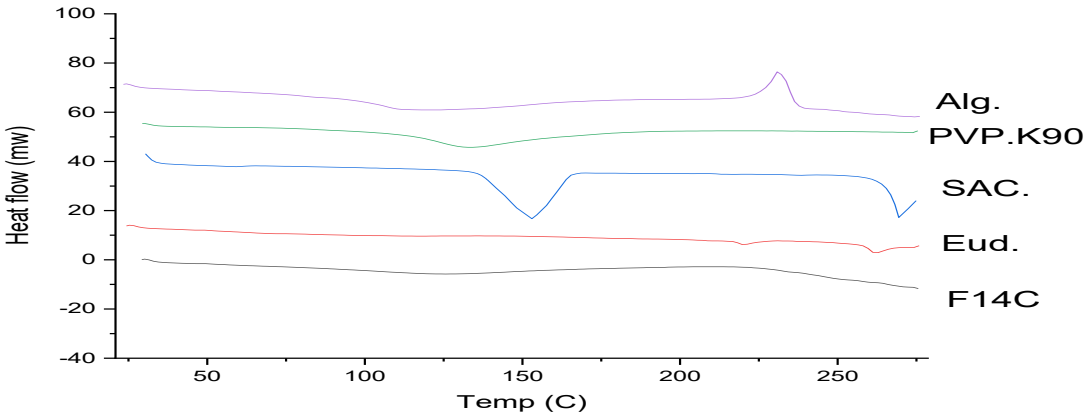


Figure (12): DSC analysis of Ocusert component

FTIR Drug-Excipients Compatibility Study

F14C displays increased intensity and a shift from 1678 to 1660 in the carbonyl region, as well as red shifting and peak enhancement in the O-H stretch region (3000-3700), which strongly suggests the establishment of hydrogen bonds between the SAC amide carbonyl and the alginate hydroxyl groups (93, 94) (Figure 13).

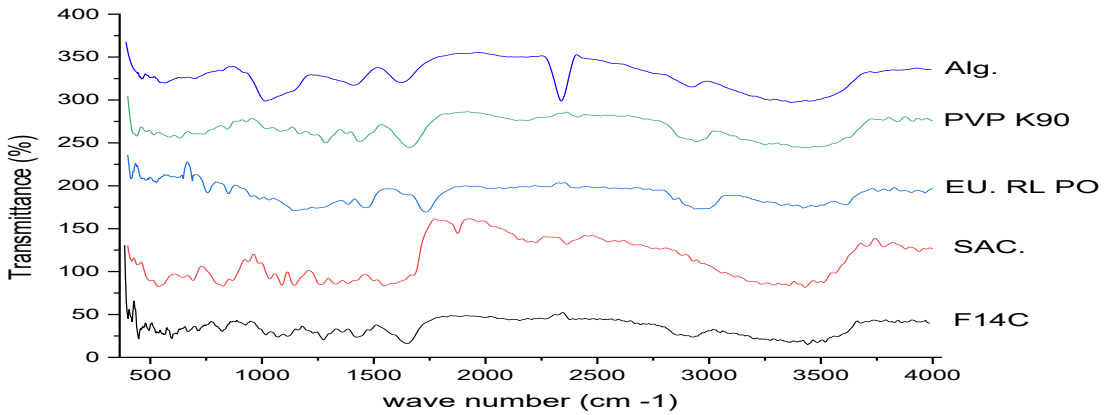


Figure (13): FTIR analysis of insert component

The FTIR analysis indicated no chemical interaction or incompatibility.

Conclusion

The SAC Ocusert was produced employing a core layer consisting of 1.5% (w/v) alginate and 7% (w/v) PVP K90, which had been coated with a rate-controlling layer composed of 15% (w/v) Eud. RL PO. This formulation demonstrated a sustained SAC release that lasted 12 hours, adhering to zero-order kinetics, and resulted in a twofold improvement in corneal permeation. These qualities reduce the routine of administering medication from 12 times, as seen with conventional eye drop solutions, to only twice daily, while ensuring a steady drug release. The data indicate that the SAC ocular Ocusert may improve patient compliance compared to traditional ocular preparations.

Ethics approval and consent to participate

The Institutional Ethical Committee-Department of Pharmacy, Al Mustansiriyah University, reviewed and approved the protocol.

Availability of data and materials

Supplementary data can be shared upon reasonable request

Author's contribution

Haider H. Kikawoos contributed to data gathering, analysis, and the practical and written parts of the study. Athmar DH. H. Al-Shohani: final approval and agreement for all aspects of the research, supervision, revision, and rearrangement.

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Conflicts of interest

The authors have no conflict of interest to declare.

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