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Aspirin–hydrogel ocular film for topical delivery and ophthalmic anti-inflammation

ASHIRBAD NANDA[1,2], SHUBHASHREE DAS[2], RUDRA N. SAHOO[1,2], SOUVIK NANDI[1], RAKESH SWAIN[1], SUNIL PATTANAIK[1], DEBAJYOTI DAS[1] and SUBRATA MALLICK[1]*

[1]*School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, 751003, India and* [2]*Centurion University of Technology and Management, Odisha, India*

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Abstract: Ocular drug delivery in hydrogel forming film form has several benefits over conventional dosage forms. An ophthalmic anti-inflammation study was undertaken using topically applied aspirin in a hydrogel film formulation. A hydroxypropyl methylcellulose (HPMC) matrix film formulation was prepared by the solvent casting and evaporation technique by taking triethanolamine (TEA) as a plasticizer. *Ex vivo* corneal permeation as well as anti-inflammatory potential of aspirin was studied on carrageenan induced rabbit eye model. Moisture uptake was found to be in the range of 17.1 and 19.1 % for all the film formulations. The film with the higher HPMC content exhibited both increased moisture uptake and amount of swelling. Among the formulations, the swelling order was found to increase with increasing amount of HPMC in the film. Presence of the hydrogel matrix forming polymer sustained the drug release and corneal permeation for more than 6 h and controlled the process by the diffusion mechanism. The signs of carrageenan induced acute inflammation was inhibited completely within just 2 h of placing the film in the rabbit eye whilst the positive control continued showing redness and increased tear secretion. Aspirin ocular film formulation could be utilized for ocular anti-inflammation for an extended period of time with better patient compliance.

Keywords: non-steroidal anti-inflammatory drug; ocular delivery; HPMC; swelling and erosion.

INTRODUCTION

Hydrogel-based formulations for ocular drug delivery have several benefits over conventional dosage forms, *i.e.*, enhanced probability of delivering drugs at a slow and uniform flow, improved ocular residence time and proper dosing.[1]

* Corresponding author. E-mail: profsmallick@gmail.com; subratamallick@soa.ac.in
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This will also ensure better patient compliance due to the reduced frequency of administration and lowering incidence of side-effects. This ocular film would be retained in the cul-de-sac of the eye for an extended period of time. Thus, a small piece of film will stay in the patient's eye without any kind of discomfort.[2] Acetylsalicylic acid (aspirin), a nonsteroidal anti-inflammatory drug (NSAID) is used as an anti-rheumatic, antipyretic, and anti-thrombotic drug.[3–5] Anti-inflammatory activity on the corneal surface may be possible due to aspirin or its metabolites secretion in the tear fluid in low dose aspirin users of cardiac patients.[4] Cardiac subjects taking 100 mg aspirin orally for antiaggregant purposes have faced less dry eye syndrome without interfering with the tear flow. Internal bleeding, gastrointestinal inflammation, and ulcer are the main dose-dependent adverse effects caused by oral administration of aspirin. The therapeutic drug levels may be obtained in the anterior and posterior segment of the eye by a topical film-type delivery system avoiding systemic distribution and related side effects.[6] Retinal bioavailability of aspirin may not be sufficient after oral administration due to blood eye and blood-retinal barriers.[7] Therefore, an option was developed for topically applied film formulation with increased ocular residence time.[8] Delivery of medication to the human eye is an integral part of medical treatment. Conventional ocular dosage forms, *i.e.*, eye drops and eye ointments, have certain disadvantages such as poor availability, repeated administration and irregular doses and drug loss due to nasolacrimal drainage.[9] Reducing the volume of dose could moderately develop some local action and diminish side effects. As a solid film formulation, this could be one improvement step for ophthalmic delivery of drugs.[10] Ocular bioavailability could be significantly improved by extending residence time in the cul-de-sac rather than losing most of the drug in nasolacrimal drainage. Currently, hydrophilic soft gels are attracting a lot of attention in ophthalmic drug delivery systems.[11] These provide a uniform store of the drug at the place of administration after being exposed to the watery biological fluid. The solid matrix hydrogel swells and produces a transparent viscous gel layer, facilitating distribution of drug in a controlled process.[12] *In situ* gel loaded with a hydrogel forming agent may be a potential tool for improving the bioavailability by extending the ocular residence time.[13] In ophthalmic drug delivery systems, mucoadhesive biodegradable polymer can adhere to the conjunctival mucosa for an extended period of time and the drug releases *via* erosion from the place of its administration.[14] HPMC is drawing considerable attention in the field of controlled release drug delivery systems for the formation of a hydrogel in the presence of water and is popularly employed in mucoadhesive ocular drug delivery.[15,16] The present work was undertaken for the development of ocular mucoadhesive hydrogel film by embedding the drug in an HPMC matrix. HPMC is reported to show cytoprotection against thimerosal induced DNA damage in Chang conjunctival cells.[17] Moreover, HPMC is able to provide protection to

aspirin from hydrolytic degradation.[18,19] Aspirin in the presence of HPMC K100 polymer has shown significant stability after 5 weeks of exposure to 40 °C and 75 % RH.[20] The ocular anti-inflammatory activity of aspirin has been investigated in the carrageenan induced rabbit eye model. Analytical characterizations were conducted in order to understand the drug excipient interaction and stability of the film formulation.

MATERIALS AND METHODS

Aspirin was obtained from Himedia Laboratory Pvt. Ltd., Nashik, India. Hydroxypropyl methylcellulose (HPMCK100M: 100,000 cPs) was locally purchased from Burgoyne and Co (Mumbai, India) and triethanolamine (TEA) was procured from Merck Pvt. Ltd. (Mumbai, India).

Animal

Male New Zealand rabbits of 1.5–2.0 kg and albino rats of 150–250 g were obtained from the institutional animal house for *in vivo* and histological study. All the animals and handling protocols were reviewed and approved by the animal ethical committee of the institute. The animals were approved by CPCSEA of SOADU (IAEC/SPS/SOA/04/2019) before starting the study.

Aspirin film formulation

Aspirin films (Table I) were prepared by the casting and solvent evaporation method. HPMC was weighed and sprinkled in about 40 ml of water contained in a 100 ml beaker. The beaker was then placed in the refrigerator below 10 °C for 2 days for complete swelling. Accurate amount of triethanolamine (plasticizer) was added to HPMC swelled gel with continuous stirring for 24 h at laboratory ambient condition.[21] Aspirin (200 mg) solution was prepared in another 100 ml beaker with a small amount of ethanol (10 ml), and HPMC swelled gel was added over it with continuous stirring for 12 h (Table I). The transparent polymeric mass was spread onto the petri dish uniformly (casting) and placed in the hot air oven at 40 °C until constant weight of prepared film was obtained. Prepared films were separated from the Petri dish and packed in the zip lock Tarson pouch and preserved in a wide mouth airtight plastic container until further studies.

TABLE I. Aspirin film formulations and physicochemical characteristics for ocular delivery

Film code	$m_{\text{HPMC 100K}}$[a] mg	Triethanolamine[b] mg	Thickness[c] µm	Moisture content[c] %	Moisture uptake[c], % *RH* / %			Surface pH	Assay value[c], %
					65	74	85		
AH1	900	135 (15 %)	210± 8.3	8.42± 0.92	14.5± 0.15	17.10± 1.61	18.3± 0.2	7.4	16.02± 0.24
AH2	1000	120 (12 %)	231± 5.5	10.97± 0.88	14.51± 0.08	17.47± 1.25	18.5± 0.15	7.5	14.98± 0.19
AH3	1100	100 (9 %)	244± 3.3	11.94± 1.13	16.8± 0.1	18.80± 1.29	19.7± 0.2	7.3	14.04± 0.28
AH4	1200	110 (9.17 %)	260± 5.1	11.99± 1.16	18.8± 0.05	19.14± 0.80	20.4± 0.2	7.6	12.75± 0.42

[a]Hydrogel forming agent; [b]plasticizer, aspirin was given 200 mg for each of the formulations, value in brackets represents the amount of triethanolamine based on the HPMC content; [c]mean±*SD*, $n = 3$

Physicochemical characteristics

The thickness measurement of the film formulations was realized utilizing a Mitutoyo digital micrometer (Japan). Random 10 cut portions of the film were measured and the average values were recorded.[18,22] Folding endurance of the film formulations was determined by continually folding a 2 cm×2 cm of the formulated film at a particular portion. This action was continued until the film broke at the point of folding. The number of times the film could be folded was considered as the folding endurance value.[23] For moisture content determination, a cut piece of the prepared film was weighed and put into an airtight desiccator containing activated silica gel. The film was then removed after 24 h or until it reached to constant weight. The difference between the initial and final weight gave the moisture content. For the determination of moisture uptake, a preweighed cut piece of film was placed under 65, 74 and 85 % relative humidity (*RH*) by using saturated solutions of KCl, NaCl and $AlCl_3$, respectively. The film was then placed in a desiccator containing activated silica gel and weighed after it achieved a constant dry weight. The difference between the initial and final weight gave the moisture uptake at various relative humidity conditions. A small piece of the film was allowed to swell up for 2 h in distilled water under ambient laboratory condition for the determination of the surface pH. The surface pH was measured using pH meter by dipping the electrode into the swollen mass of the film.[24] Three observations were recorded for each formulation to calculate the mean value. The assay of aspirin was performed by taking a preweighed cut piece of film and dissolving it in water by continuous stirring and gentle boiling with the addition of 1 M HCl.[25] After hydrolysis, salicylic acid was produced that forms violet-blue complexes with Fe^{3+}. The intensity of the colour depends on the salicylic acid concentration in a sample. Ferric nitrate (Fe^{3+}) was added for colour development and then the salicylic acid content was determined by UV–Vis spectroscopy, at 561 nm (Jasco, V-630 spectrophotometer).[26-29]

Swelling behaviour of the films

The swelling properties were estimated after determining the percent swelling and erosion of the film formulations. The swelling profile of the formulations (≈1 cm×1 cm) was evaluated by placing them in Petri dishes with approximately 40 ml of phosphate buffer (pH 6.8).[22] The excess water in the Petri dish was removed after careful swabbing with tissue paper without disturbing the swollen film and the weight gain by the film was measured at different time intervals.[30] The dry weight of the swollen film was determined after drying at 60 °C overnight in a hot air oven and preserved in a desecrator for a furtherr 24 h. The swelling rate (K_s) was determined from the slope of the initial linear region of percentage swelling *vs*. time plot:[31]

$$\text{Swelling}=100\frac{\text{Weight of swollen mass} - \text{Dry weight before swelling}}{\text{Dry weight of film before swelling}} \quad (1)$$

$$\text{Matrix erosion}=100\frac{\text{Dry weight of film} - \text{Dried weight after swelling}}{\text{Dry weight of film before swelling}} \quad (2)$$

Scanning electron microscopy (SEM)

SEM was performed to study the morphology of the film formulation. Pieces of the film formulations were examined at various magnifications to observe the surface morphology using a scanning electron microscope (JEOL, JSM-6510).

Fourier transform infrared (FTIR) spectroscopy

Powder sample of the drug and formulations were estimated with Bruker FTIR spectrophotometer. The samples were placed on the attenuated total reflectance (ATR) with ZnSe (zinc selenide) crystals and pressed using the integrated pressure application device.

X-Ray diffractometry

The of X-ray diffraction patterns of the crystalline aspirin, film formulations and a placebo film were measured using an X-ray diffractometer (Rigaku, Ultima IV) applying 40 kV voltage and 15 mA current. CuKα (radiation 1.5406 Å) was used as the source of X-rays anode material and the diffraction was measured at a scan speed of 1° per min for 2θ 5–70°.

Differential scanning calorimetry (DSC)

DSC data of aspirin, matrix films and placebo films was obtainrd using a differential scanning calorimeter (Mettler Toledo; DSC 1, Switzerland) in the temperature range from 30 to 300 °C to understand the drug excipient interaction. Aspirin and film sample were taken in aluminium crucible and examined under a dynamic nitrogen atmosphere (50 mL min^{-1}) at a heating rate of 10 °C min^{-1}.

In vitro *dissolution of the drug*

In vitro dissolution of aspirin from the films was performed in a USP type II dissolution apparatus (Electolab, TDT06L, India) utilizing 200 mL phosphate buffer (pH 6.8) as the dissolution medium at 34.0±0.2 °C and 50 rpm for 6 h.[18,31-33] A piece of film, weighing between 55–72 mg, was cut and attached to a glass slide using cyanoacrylate glue and carefully placed at the bottom of a vessel containing the dissolution medium. At different time intervals, 10 ml samples were withdrawn through a membrane filter (0.45 μm, syringe driven) and the same volume of fresh medium was placed in each vessel. The evaluation of the aspirin contents was then performed by UV–Vis spectroscopy at 561 nm following the above given method. Conversion factor of 1.3004 was used to estimate aspirin content from salicylic acid produced. The dissolution data of the film formulations were reported as the mean of minimum 3 determinations. The kinetics of drug release from the matrix film formulations were elucidated using different kinetic models such as the first order, Higuchi, Korsmeyer–Peppas and Peppas–Sahlin models.

The mathematical equations used for describing kinetics of drug release and corneal permeation were:[19]

First order:

$$\log C = \log C_0 + K_1 t/2.303 \quad (3)$$

Higuchi model:

$$C = K\sqrt{t} \quad (4)$$

where C_0 = initial drug content; C = cumulative amount of drug release/permeating per unit area of the film; K_1 = First order release rate constant; K = Higuchi release/permeation rate constant.

Korsmeyer–Peppas model (this power law model describes drug release from a polymeric matrix):

$$C_t/C_\infty = Ktn \quad (5)$$

where C_t/C_∞ = fraction of release/permeation of drug at time t; K = Peppas release/permeation rate constant; n = release/permeation exponent.

Peppas–Sahlin model:

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m} \quad (4)$$

were M_t/M_∞ = Fraction dissolved, %; k_1 = the constant related to the Fickian kinetics; k_2 = the constant related to Case II relaxation kinetics; m = the diffusional exponent.

Ex vivo *corneal permeation*

The *ex vivo* corneal permeation study was performed using fresh, undamaged whole goat eyes, collected from a local slaughterhouse within one hour after sacrifice.[34] The whole eyes were washed in distilled water followed by rinsing with phosphate buffer (pH 6.8). About 5 to 6 mm sclera of the cornea were removed from the whole eye. Pieces of films weight ranging from 42.8–72 mg were employed at the centre of the cornea on the modified Franz diffusion apparatus and the diffusion of drug testing was performed for 6 h at 34±0.2 °C and 50 rpm in triplicate. The epithelium of the cornea was facing vertically tonthe donor compartment with an effective area of 1.4 cm^2 and 200 ml of phosphate buffer (pH 6.8) medium as the diffusion media taken in the receptor chamber. Samples were withdrawn from the receptor chamber at regular intervals using syringe driven membrane filter (0.45 µm). Absorbance data at 561 nm were obtained using a UV–Vis spectrophotometer.[31] The steady state flux (*J*ss) of the drug was measured from the slope of the linear regression line of the cumulative amount of drug in the receptor chamber (Q_f) *vs*. time plot.[35]

Effect of aspirin on ocular inflammation

The effect of aspirin on ocular inflammation was studied in rabbits. Food and water were made accessible to the animals *ad libitum*. Acute conjunctival inflammation was induced in the rabbit eye by injecting (Dispo Van 30 G, India) carrageenan (100 µl, 3 %) to the upper palpebral region.[18,36] Proparacaine hydrochloride ophthalmic solution USP (0.5 %) was used for anesthetizing rabbit eye prior to the injection. Signs of inflammation and redness were recognized 1 h after the injection. A small piece of film (AH4) was placed in the cul-de-sac region after sterilizing it by UV exposure[18,22] at a distance of 25 cm from the UV light source for 10 min just before the anti-inflammatory study (UV wavelength at 277 nm using Phillips TUV 30w, India) under ambient laboratory condition. Images were captured and all the signs and symptoms were visualized.

RESULTS AND DISCUSSION

Physicochemical characteristics of film formulations

The mean thickness and the standard deviation of the films were determined. The thickness of all the film formulations was found to be in the range of 210.0±8.3 to 260.0±5.1 µm. A gradually increased content of HPMC in the formulation increased the thickness of the film. The films have exhibited good folding-endurance (more than 200) showing sufficient strength and flexibility but not fragility.[18,22] Under ambient laboratory conditions, the moisture content of the film formulations ranged from 8.42 (AH1) to 12 % (AH4). The film formulations remained stable without being fully dried and fragile due to the presence of moisture in the films. The significant increase in moisture content was observed owing to the increased content of HPMC ($P < 0.01$). Among the films tested, AH1 and AH4 showed the minimum and maximum moisture uptake, *i.e.*, 17.097 and 19.139 %, respectively, at *RH* 74 %. The maximum moisture uptake was found in the film containing the highest concentration of HPMC, which readily absorbs moisture when exposed to the atmosphere. The pH of the film surface

was found in the range as 7.4 to 7.6, which are assumed to give no irritation to the mucosal tissues. The film formulations and physical characteristics of aspirin film formulations are given in Table I.

Swelling and erosion study

Hydration and swelling behaviour followed by matrix erosion studies were performed for understanding drug residence time and drug release dynamics due to its great significance related to dose, dosage form and effect. When the hydrophilic polymeric (HPMC) matrix film comes in contact with water it begins to swell.[16] The erosion is accompanied with hydration and degradation of the hydrophilic matrix film. The hydration and swelling increased and the increase in hydration as the function of time was recognized from the swelling profile of the films (Fig. 1A). AH4 showed the highest percentage swelling (2216 %) than the other formulations owing to its high content of HPMC polymer. The order was: AH1 < AH2 < AH3 < AH4. In another report, the swelling of hydrogel transdermal films were found to be about 2000 % after 13 h.[37] All the film formulations were almost transparent and the writing background was clearly seen through the film (Fig. 1C). AH4 exhibited least erosion (13.7 %) among the film formulations owing to the presence of high content of polymer (Fig. 1B).

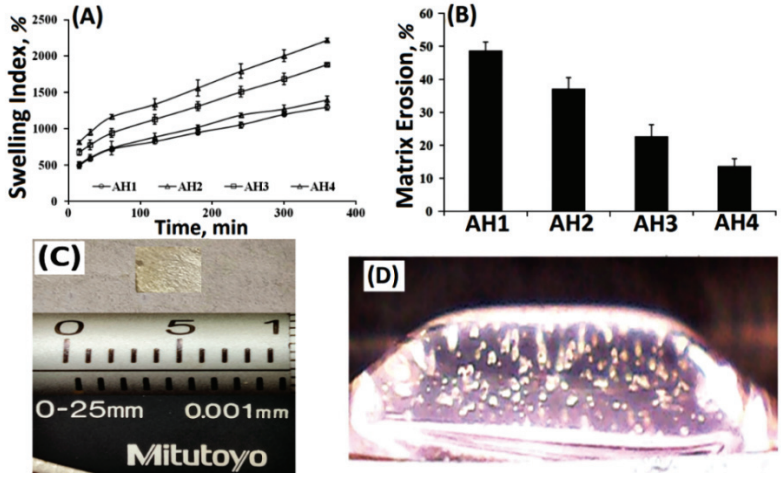

Fig. 1. A) Swelling behaviour of aspirin film formulation; B) matrix erosion of the film formulations after 6 h; C) digital image of films before swelling; D) after swelling.

Scanning electron microscopy

Scanning electron microscopy was used for examining crystal morphology of aspirin and the surface morphology of aspirin containing film formulations (Fig. 2). Distinctive geometric crystals (brick-shaped) with or without twinning was observed in the photomicrographs of pure aspirin (1000×).[38,39] On the other

hand, the crystal geometry disappeared in the photomicrographs of the films. The smooth and non-porous surface of the film formulations confirmed the almost homogenous mixing and uniform distribution of the drug. Uniform solubility of aspirin in the HPMC matrix of the films was probably due to the drug amorphization decreasing the crystalline intensity.

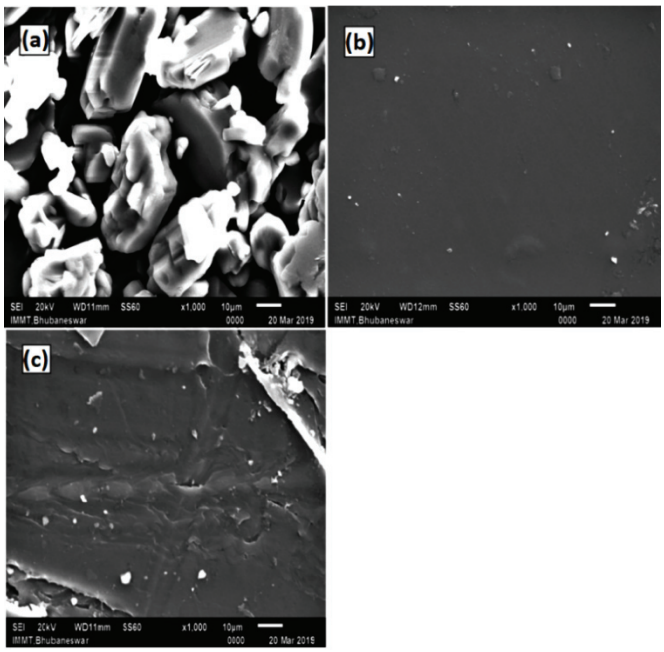

Fig. 2. Scanning electron micrographs of: a) crystalline aspirin; b) AH1; c) AH4.

Fourier transformation infrared spectroscopy

The Fourier transform infrared spectra of aspirin and the formulations are shown in Fig. 3A.

Aspirin exhibits characteristic peaks due to the presence of benzene ring, carboxylic acid and ester groups. The bands in between 2800 to 3000 cm^{-1} (narrow absorptions) represents the interactions with C–H bonds (O–H stretch from CO–OH vibration). The peak at 1678 cm^{-1} is due to stretching of carbonyl groups (C=O), C=O stretch at 1750 cm^{-1} indicates the presence of ester groups.[40] All formulations showed decreased intensity of the peak and a shifting of the broad band in the spectral region 4000–3000 cm^{-1} of O–H stretching vibrations was observed. This was again due to the intramolecular hydrogen bonding between the polymer and the drug, which confirms the drug is completely incorporated within the polymeric matrix.

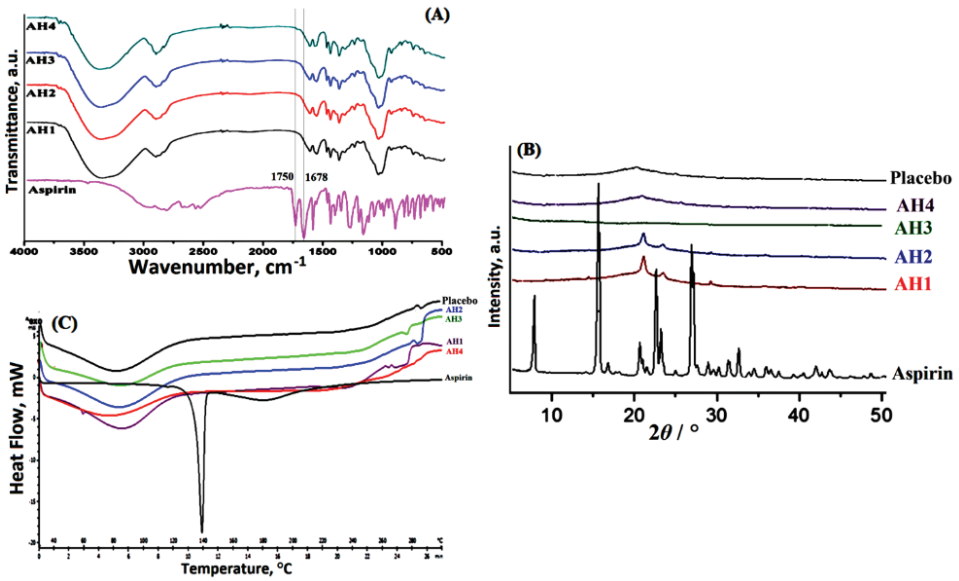

Fig. 3. A) FTIR spectra of aspirin and the film formulations; B) XRD patterns of aspirin and the film formulations; C) DSC thermograms of aspirin and the film formulations.

X-ray diffractometry

The powder X-ray diffraction patterns of pure aspirin and the films are presented in Fig. 3B. The diffractogram of aspirin showed a series of intense peaks at 2θ of 15, 20, 23 and 27° indicating its own crystalline pattern.[41] These characteristic peaks were not observed in the diffraction patterns of the AH1, AH2, AH3 and AH4 films. This result indicated the occurrence of a true drug–polymer solid solution and the amorphization of aspirin to a great extent in the films was confirmed. It is understood that a major part of the drug exists as a solid-solid solution in the HPMC matrix, and a minor part is probably present in the semi-crystalline or microcrystalline form. The HPMC polymers formed solid solutions with the drug by forming an amorphous polymeric network. HPMC film plasticized by triethanolamine also offered a considerable performance in the significant inhibition of drug crystal growth. HPMC as the matrix polymer inhibited crystal growth the drug in the film.[18,19] This is the very reason that greater HPMC amorphized the drug relatively more in the respective film formulation containing increased amount of HPMC. Accordingly, the XRD peaks are relatively more intense in AH1 and AH2 compared to AH3 and AH4.

Differential scanning calorimetry

The results of thermal analysis of pure aspirin and the formulations by DSC are shown in Fig. 3C. Aspirin showed a characteristic sharp melting endothermic

peak at 138.53 °C.[39] In the range of about 60–110 °C, the appearance of a broad endothermic signal may be an indication of moisture removal from the HPMC.[15,38] The absence of an endothermic peak observed with the film formulation indicating significant amorphization of aspirin.

In vitro *release of drug*

Drug release profiles of various formulations are shown in Fig. 4A. The aspirin-in-HPMC film formulation showed the sustained effect of release of aspirin. HPMC as the hydrophilic matrix polymer in the film formulation inhibited the crystal growth in general and maintained aspirin in the amorphous state.[18] The high viscosity grade of HPMC (K100M) extended the drug release in a controlled manner over a period of 6 h. The percent release of drug from film AH1, AH2, AH3 and AH4 was found to be 92.0, 83.75, 77.1 and 67.4 %, respectively, at the end of 6 h as shown in Fig. 4A. Formulation AH1 showed the highest (92.0 %), and formulation AH4 showed the lowest (67.4 %) drug release after 6 h due to the presence of HPMC in highest amount in the film and consequently, the highest percentage swelling (2216.5 %) rather than the other formulations. Maximum erosion of the formulation AH1 exhibited relatively the highest release of aspirin. With increasing content of HPMC, as the polymer matrix in the film formulation, the drug release was gradually sustained at 6 h ($P < 0.02$).

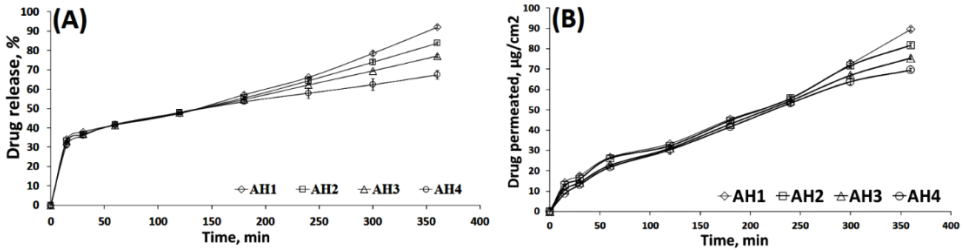

Fig. 4. A) *In-vitro* drug release profile of the film formulations; B) *ex-vivo* corneal permeation of the films.

Ex vivo *permeation study*

Ex vivo permeation profiles of aspirin through the corneal mucosa are shown in Fig. 4B. The amount of drug permeated for formulation AH1, AH2, AH3 and AH4 was found to be 89.59, 81.82, 75.48 and 69.51 % respectively. The amount of drug permeated after 6 h was highest in the case of AH1 relative to the other formulations.

The fact that AH4 showed the lowest amount of drug permeation after 6 h may be due to higher concentration of HPMC compared to the other formulations. Drug permeation was observed to be more sustained with the increasing

content of HPMC in the film formulations, drug release was gradually sustained at 6 h ($P < 0.01$).

Korsmeyer–Peppas power law fits well with the permeation pattern. The r^2 value ranged from 0.964 to 0.996 and the permeation exponent (n) value was closer to 0.5 (0.561 to 0.654), the mechanism of permeation could be a diffusion--controlled process (Table II). According to the Peppas–Sahlin model, the k_1 value is greater than the k_2 value in both the cases of drug release and permeation confirming the drug release from the hydrogel matrix to be by the Fickian diffusion mechanism (Table III). Flux of the film was decreased with increasing content of HPMC and found in the order: AH1 > AH2 > AH3 > AH4 (13.0, 12.9, 12.6 and 12.2 μg min^{-1}, respectively, Table II).[16,18]

Anti-inflammatory activity of aspirin

The anti-inflammatory action is depicted in Fig. 5. In a variety of animal models, carrageenan is commonly used for inducing cytokine mediated acute inflammation.[42]

Freund's adjuvant used for inducing chronic inflammation may last for more than 14 days, whereas carrageenan induced inflammation can be recovered within 24 h.[43] Carrageenan was injected in the upper palpebral conjunctiva of the right rabbit eye for induction of inflammation. The normal eye was used as control where no signs of inflammation were seen. Watery eye with continuous lacrimation, redness and swelling of the conjunctiva (as signs and symptoms of inflamemation) were observed after 1 h of the injection. AH4 was hydrated by the tear fluid and resulted in continuous release of drug just after application of the film in the cul-de-sac of the rabbit eye. Reduced inflammation was noticed within 2 h and the redness had also almost vanished.[15,20] Thus, aspirin-in-HPMC formulation could be explored in ophthalmic anti-inflammation. Embedding the drug in the HPMC matrix also made it more tolerable to the ocular environment.[36] A similar anti-inflammatory study was performed by Nandi *et al.* 2021 by administering vildagliptin film formulation in the eye for reduction of inflammation by inhibiting DPP-4.[36]

CONCLUSION

Aspirin-in-HPMC film formulations were successfully prepared with sufficient flexibility and swelling property for better patient comfort. Both the drug release and corneal permeation were sustained for more than 6 h and exhibited a diffusion-controlled mechanism. The signs of acuteness of inflammation induced by carrageenan were alleviated within 2 h of placing the film indicating ocular anti-inflammatory activity. Aspirin-in-HPMC film formulation could be a better option for controlling ocular anti-inflammation for an extended period of time with better patient compliance.

TABLE II. The rate of swelling and the release/permeation kinetics of the prepared film formulations

Film code	K_S / min^{-1}	Release					Permeation					J_{SS}[a] / μg min^{-1}
		First order	Higuchi		Peppas		First order	Higuchi		Peppas		
		r^2	K / % min$^{-1/2}$	r^2	n	r^2	r^2	K / % min$^{-1/2}$	r^2	n	r^2	
AH1	2.19±0.23	0.878	3.566	0.925	0.292	0.892	0.874	4.645	0.935	0.561	0.964	15.84±0.87
AH2	2.47±0.16	0.936	3.188	0.957	0.279	0.927	0.952	4.463	0.959	0.580	0.976	14.29±0.37
AH3	3.36±0.08	0.935	2.816	0.976	0.259	0.947	0.980	4.282	0.975	0.619	0.988	12.78±0.49
AH4	3.88±0.06	0.878	2.301	0.997	0.236	0.991	0.993	4.090	0.986	0.654	0.996	10.88±0.88

[a]Mean±*SD*; $n = 3$

TABLE III. Peppas–Sahlin model parameters

Formulation code	Drug release			Permeation		
	k_1 / min^{-m}	k_2 / min^{-2m}	m	k_1 / min^{-m}	k_2 / min^{-2m}	m
AH1	9.683	1.375	0.273	1.813	0.068	0.545
AH2	1.968	0.083	0.520	1.968	0.083	0.520
AH3	11.893	2.181	0.219	1.823	0.082	0.518
AH4	13.571	2.929	0.184	1.060	0.575	0.447

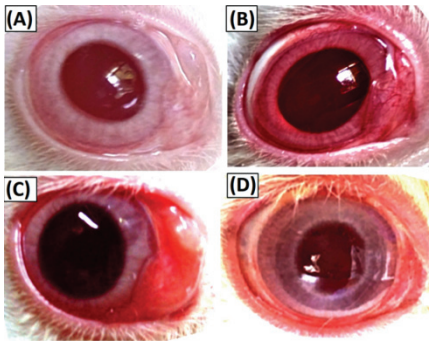

Fig. 5. Anti-inflammatory activity study: A) normal eye; B) inflamed eye 1 h after carrageenan injection; C) application of film formulation 1 h after inflammation; D) revival to the normal eye 2 h after application of the film formulation.

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ИЗВОД

ОКУЛАРНИ ФИЛМ АСПИРИН–ХИДРОГЕЛ ЗА ПОВРШИНСКО НАНОШЕЊЕ У ЛЕЧЕЊУ ОЧИЈУ И ПРОТИВ УПАЛЕ

ASHIRBAD NANDA[1,2], SHUBHASHREE DAS[2], RUDRA N SAHOO[1,2], SOUVIK NANDI[1], RAKESH SWAIN[1], SUNIL PATTANAIK[1], DEBAJYOTI DAS[1] и SUBRATA MALLICK[1]

[1]*School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India, 751003 и* [2]*Centurion University of Technology and Management, Odisha, India*

Примена лекова у облику хидрогел филмова за лечење очију има неколико предности у поређењу са уобичајеним начинима примене. Извршена су испитивања површинске примене аспирина за третман против-упалних офталмолошких процеса. Припремљен је хидрогел матрикс од хидроксипропил-метилцелулозе (HPMC) методом додавања и упаравања растварача, уз додатак триетаноламин (TEA) за повећање еластичности. Испитивана је пропустност рожњаче као и потенцијал анти-упалног ефекта аспирина на моделу зечијег ока иритираног карагенином. Утврђено је да је апсорпција влаге у опсегу 17,097 и 19,139 % за све формулације филмова. Висок садржај HPMC у филму повећава апсорпцију влаге и оток. Присуство полимера за формирање матрице подржава отпуштање лека и пропустност рожњаче више од 6 сати у контролисаном процесу према дифузионом механизму. Акутна упала изазаване карагенином је инхибирана потпуно у току 2 сата након постављања филма на зечије око, док у позитивној контролној групи постоји континуитет црвенила и лучења суза. Окуларна формулација која садржи аспирин може се применити за анти-инфламаторно дејство на очима у продуженом периоду са бољим утицајем.

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