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In vitro and *in vivo* evaluation of the Gelrite® gellan gum-based ocular delivery system for indomethacin

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The poor bioavailability and therapeutic response exhibited by the conventional ophthalmic solutions due to pre-corneal elimination of the drug may be overcome by the use of *in situ* gel forming systems, wich upon instillation as drops into the eye undergo a sol-gel transition in the cul-de-sac. This may result in better ocular availability of the drug. The purpose of this work was to develop an ophthalmic delivery system of the NSAID indomethacin, based on the concept of ion activated *in situ* gelation. Gelrite® gellan gum, a novel ophthalmic vehicle, which gels in the presence of mono or divalent cations present in the lacrimal fluid, was used as the gelling agent. The developed formulations were therapeutically efficacious (in a uveitis induced rabbit eye model) and provided sustained release of the drug over an 8-hour period *in vitro*.

Keywords: gellan, indomethacin, ocular delivery

In ocular delivery, the physiological constraints imposed by the protective mechanisms of the eye lead to low absorption of drugs, resulting in a short duration of the therapeutic effect. When a drug solution is dropped into the eye, effective tear drainage and blinking action of the eye result in a 10-fold reduction of the drug concentration in 4–20 minutes (1). Limited permeability of the cornea contributes to the low absorption of ocular drugs. Due to tear drainage, most of the administered dose is absorbed via the naso-lacrimal duct to the GI tract, leading to side-effects. Rapid elimination of the eye drops administered often results in a short duration of the therapeutic effect making a frequent dosing regimen necessary.

Ocular therapy would be significantly improved if the pre-corneal residence time of drugs could be increased. Several new preparations have been developed for ophthalmic use, not only to prolong the contact time of the vehicle on the ocular surface, but also to slow down the drug elimination (2, 3). Successful results were obtained with inserts (3) and collagen shields (4), although these preparations involve some disadvantages, such as non-compliance, especially by elderly people, and many patients some-

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times lose the device without noticing it. From the point of view of patient acceptability, a liquid dosage form is preferable.

This problem can be overcome by using *in situ* gel forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol-gel-sol) and pseudo-plastic behavior to minimize interference with blinking (5). Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye, which upon exposure to physiological conditions shifts to the gel phase, thus increasing the pre-corneal residence of the delivery system and enhancing ocular bioavailability.

Depending on the method employed to cause sol to gel phase transition on the ocular surface, the following three types of systems have been recognized: pH-triggered systems including cellulose acetate hydrogen phthalate latex (6, 7), Carbopol (8), temperature-dependent systems including pluronics (9, 10) and tetronics (11, 12), and ion-activated systems including Gelrite® (13) and gellan (14). Gellan is a high molecular mass; linear anionic heteropolysaccharide produced aerobically from the bacterium *Auromonas* (*Pseudomonas*) *elodea*, renamed *Sphingomonas paucimobilis*.

The objective of the present study was to develop an ion-activated *in situ* gelling system of indomethacin, a NSAID used as an alternative to steroids in the treatment of uveitis (15, 16) and other external inflammations of the eye. Gellan was investigated as a vehicle for the formulation of eye drops of indomethacin (1%, *m/V*), which undergo gelation when instilled into the cul-de-sac of the eye and provide sustained release of the drug during the treatment of uveitis.

EXPERIMENTAL

Materials

Indomethacin was generously provided by Jagsonpal Pharmaceuticals Ltd. (India). Gelrite® gellan gum was purchased from Sigma (USA). Bovine serum albumin (BSA), lysozyme and γ-globulin were purchased from CDH Ltd. (India). All other reagents used were of analytical grade.

Methods

Preparation of formulations. – Gellan was dissolved in hot phosphate buffer pH 7.4 (prepared from potassium dihydrogen ortho phosphate and sodium hydroxide in fresh water for injection at 70 °C under laminar flow), with or without different proportions of sodium citrate, by continuous stirring at 40 °C. The quantity of indomethacin required to give a final drug concentration of 1% (*m/V*) was added to the polymeric solution and stirred until dissolved. The formulations were filled in 10-mL amber colored glass vials, capped with rubber bungs and sealed with aluminum caps. In their final pack, the formulations were terminally sterilized by autoclaving at 121 °C and 15 Pa for 20 minutes. Sterilized formulations were stored in a refrigerator (4–8 °C) until use.

Evaluation of the formulations

Drug content uniformity. – The vials ($n = 3$) containing the preparation were shaken for 2–3 minutes manually and 100 μL of the preparation was transferred aseptically to sterile 25-mL volumetric flasks with a micropipette and the final volume was made up with acetate buffer pH 5.0 (0.2 mol L^{-1} CH_3COONa + 0.1 mol L^{-1} CH_3COOH). Indomethacin concentration was determined at 318.5 nm (Shimadzu, UV-1601, Japan).

Gelation studies. – Gelation studies were carried out in gelation cells, fabricated locally (Instrumentation Center, Banaras Hindu University, India) using Teflon®. The cells were cylindrical reservoirs capable of holding 3 mL of gelation solution (simulated tear fluid, STF). Within the cells at the bottom, a 250-μL transparent plastic cup was located to hold the gel sample in place after its formation. The studies were carried out using STF of composition 1 (sodium chloride 0.670 g, sodium bicarbonate 0.200 g, calcium chloride dihydrate 0.008 g and purified water sufficient to make 100 g) (8) and of composition 2 (BSA 0.268 g, lysozyme 0.268 g, γ-globulin 0.134 g, calcium chloride dihydrate 0.008 g, *D*-glucose 0.15 g, sodium chloride 0.65 g and distilled water sufficient to make 100 g) (17), which simulated either the divalent cation content or both the protein and divalent cation content of the tear fluid.

The preparation (100 μL) was carefully placed into the cavity of the cup using a micropipette and 2 mL of gelation solution (composition 1 or 2) was added slowly. Gelation was assessed by visual examination.

Rheological studies. – Viscosity determinations of the prepared formulations were carried out on a cone (0.8°) and plate geometry viscometer (Brookfield, USA) using spindle cp 40. Viscosity of sample solutions was measured at different angular velocities at a temperature of 37 ± 1 °C. A typical run comprised changing of the angular velocity from 0.5 to 100 rpm at a controlled ramp speed. After 6 seconds at 0.5 rpm, the velocity was increased to 100 rpm with a similar wait at each speed. The hierarchy of angular velocity was reversed (100 rpm to 0.5 rpm) with a similar wait of 6 seconds. The average of two readings was used to calculate the viscosity. Evaluations were conducted in triplicate.

In vitro *release studies*. – The drug release kinetics from the prepared formulations was studied using a modified method reported earlier (18). The test solution (2 mL) was placed in a circular plastic cup (2.5 cm internal diameter and 1.2 cm depth). This was in turn placed on an inverted USP basket kept inside a 250-ml beaker. Dissolution medium (200 mL of STF of composition 1) was added and stirred with a star-headed magnetic bead. Temperature of 37 ± 1 °C was maintained throughout the study. Samples (5 mL) were withdrawn at regular time intervals and replaced with an equal volume of prewarmed medium. The samples were analyzed for indomethacin as stated above.

Pharmacodynamic studies. – A total of 6 albino rabbits weighing 2–2.5 kg (2.18 ± 0.34 kg) were used for the present study. Prior to the commencement of the study, the animals with observed ocular abnormalities were excluded after thorough examination. The animals were housed in individual cages, and the experiments were conducted in a sanitized room at a temperature maintained around 24 °C. Uveitis was induced into both eyes of each rabbit by an intra-vitreal injection (30 g needle) of a sterile solution of BSA (0.5 mL per eye of 50 μg mL^{-1} sterile solution). Two days after the intra-vitreal injec-

tion of BSA, the eyes of individual rabbits were submitted to slit-lamp examination for induction of uveitis. The following clinical parameters; congestion, keratitis (keratopathy), flare, aqueous cells, clot and synechias were evaluated (15) and scored as shown in Table I. Based on the pretreatment scores of the above descriptors, the eye (left or right) showing more severe uveitis was selected for instilling the formulations (2 drops each of the prepared formulation and a standard indomethacin dispersion). Animal studies were conducted after obtaining the approval of the Departmental Ethical Committee in accordance with rules set forth by the appropriate leguratory authority of India.

Results are expressed as mean ± SD. Student's *t*-test was used. Differences were considered to be statisticaly significantly at $p < 0.05$.

Table I. Grading of the various clinical parameters of uveitis monitored[a]

Grading	Congestion	Keratitis	Clot	Flare	Aqueous cells
0	No congestion	No inflammation	No clot	Complete absence	No cell
+	Slight to moderate circum-corneal congestion	Slight diffuse stromal edema	Small clot in the lower angle of papillary area	Faint	5 to 10 cells per field
++	Marked circum-corneal ciliary congestion	Moderate epithelial and stromal edema with thickening and folds in Decemet's membrane	Clot occupying the lower third of anterior chamber	Moderate	10 to 20 cells per field
+++	Marked circum-corneal, diffuse episcleral and conjuctival congestion	Diffuse epithelial and stromal edema and folds in Descemet's membrane; peripheral vascularisation.	Clot filling the lower half of anterior chamber	Marked	20 to 50 cells per field
++++	Marked circum-corneal, diffuse episcleral and conjuctival congestion with edema	Severe edema of the stroma	Solid clot, filling almost the entire anterior chamber	Intense	More than 50 cells per field

[a] Synechia: there are no scores like for other parameters, either present or absent.

RESULTS AND DISCUSSION

The composition of various batches of the fabricated eye drops are shown in Table II. Concentration of gellan was kept at a maximum of 0.5% (*m/V*). Increasing the concentration beyond 0.5% caused gelation upon cooling to 40 °C. Gellan at a concentration of 0.6 % (*m/V*) was used earlier (13, 14) to prepare eye drops of timolol maleate and methylprednisolone.

Table II. Composition of the prepared indomethacin gelling systems[a]

Batch code	Gellan (%, *m/V*)	Sodium citrate (%, *m/m*)
GI_1	0.1	–
GI_2	0.2	–
GI_3	0.3	–
GI_4	0.4	–
GI_5	0.5	–
GI_6	0.5	10
GI_7	0.5	20
GI_8	0.5	30
GI_9	0.5	40

[a] Indomethacin 1% (*m/V*) was added in all the cases and mannitol 5% (*m/V*) was used as the isotonic agent.

Evaluation of formulations

The physico-chemical properties of the prepared formulations are shown in Table III. The drug content, clarity and pH of the formulations were found to be satisfactory and the formulations were liquid both at room temperature and when refrigerated.

The two main prerequisites of a gelling system are viscosity and gelling capacity (speed and extent of gelation). The formulation should have an optimum viscosity, which will allow its easy instillation into the eye as a liquid (drops), which will then un-

Table III. Physico-chemical properties of the prepared gelling systems

Batch code	DCU (%)[a]	Gelling capacity	
		STF 1	STF 2
GI_1	99.64 ± 0.86	++	++
GI_2	98.18 ± 0.48	+++	+++
GI_3	99.09 ± 0.51	+++	+++
GI_4	99.43 ± 0.68	+++	+++
GI_5	98.78 ± 0.76	+++	+++
GI_6	98.81 ± 0.88	+++	+++
GI_7	99.66 ± 1.04	+++	+++
GI_8	99.84 ± 0.91	+++	+++
GI_9	98.93 ± 0.43	+++	+++

[a] Percent of indomethacin present in the prepared gelling systems, mean ± SD, $n = 6$.
++ gelation immediate, remains for a few hours (less stiff);
+++ gelation immediate, remains for extended periods and forms stiff gels.
DCU – drug content uniformity.

dergo rapid sol to gel transition due to ionic interaction. Moreover, to facilitate sustained release of the drug to the ocular tissues, the *in situ* formed gel should preserve its integrity without dissolving or eroding for a prolonged period of time. All the formulations showed instantaneous gelation when contacted with gelation fluids (STF 1 and 2). However, the nature of the gel formed depended upon the polymer concentration. The batch GI_1 formulation showed the weakest gelation, which could be due to the presence of a minimal amount of gellan (0.1%). The nature of the components of the gelation medium did not seem to influence the nature of the gel formed indicating that the gelation occurred primarily due to the presence of cations in the fluid.

Rheological studies

The formulations exhibited pseudoplastic rheology, as evidenced by shear thinning and an increase in the shear stress with increased angular velocity. The viscosity was directly dependent on the polymeric content of the formulations. No change in the viscosity of the formulations was observed after autoclaving. Addition of sodium citrate in the formulations reduced the viscosity significantly ($p < 0.05$) compared to the corresponding batches without sodium citrate (Figs. 1 and 2).

The administration of ophthalmic preparations should influence as little as possible the pseudo-plastic character of the pre-corneal film (19). Since the ocular shear rate is very high, ranging from 0.03 s^{-1} during inter-blinking periods to 4250–28500 s^{-1} during blinking (20), viscoelastic fluids with a viscosity that is high under the low shear rate conditions and low under the high shear rate conditions are often preferred.

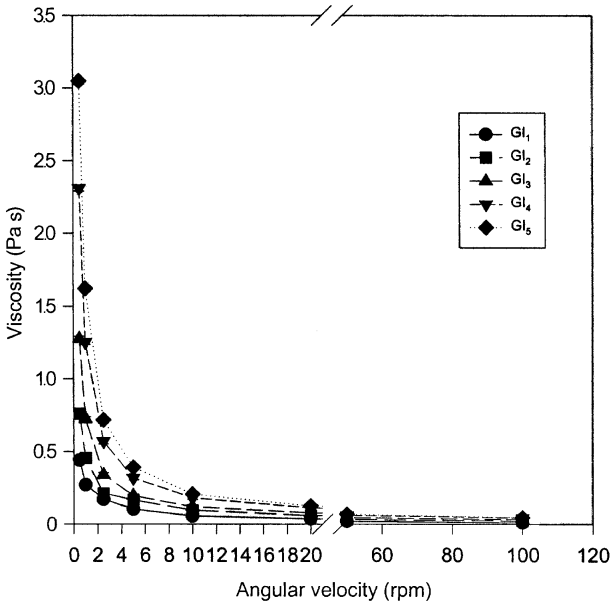

Fig. 1. Viscosity of gelling preparations of indomethacin. Effect of gellan concentration. Mean ± SD values are presented ($n = 3$).

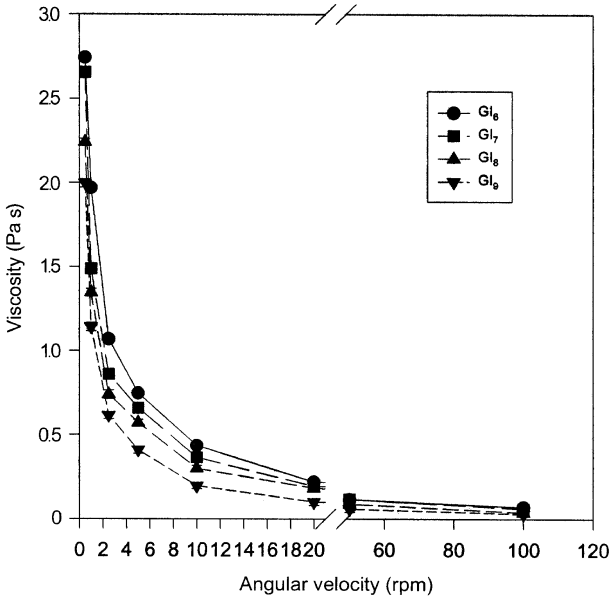

Fig. 2. Effect of sodium citrate concentration on arheological behaviour of gelling system of indomethacin. Mean ± SD values are presented ($n = 3$).

In vitro *release studies*

The gelling studies showed that the nature of gelation of the formulations with STF of either composition 1 or 2 was similar. STF 1 was selected as the dissolution medium to avoid interference in the analysis of the release study samples for indomethacin content of the protein components used in STF 2. First sampling was done 1 minute after the gelling system came in contact with the dissolution medium in order to account for the drug released before the complete formation of the gel and also to evaluate the effect of increasing polymer concentration on the nature of the gel formed. The results showed that the amount of drug released in the first minute decreased with increasing polymer concentration (Fig. 3) and this trend continued for the entire duration of the study. The initial fast release of indomethacin from the prepared systems could be explained by the fact that these systems were formulated in an aqueous vehicle. The matrix formed on gelation was already hydrated and hence hydration and water permeation could no longer limit the drug release. A similar release pattern was reported for pilocarpine, wherein the initial fast release (burst effect) decreased with an increase in polymer concentration from alginate systems (21). These results correlated with the results of the gelation study. The formulations containing sodium citrate (batches GI_6 to GI_9) showed a significantly higher release ($p < 0.05$) than the corresponding batches without sodium citrate, presumably due to the formation of a less stiff gel, resulting in a faster diffusion of indomethacin from the gel to the dissolution medium. The release index (n) of the formulations studied ranged from 0.52 to 0.59, indicating the square root of time release kinetics.

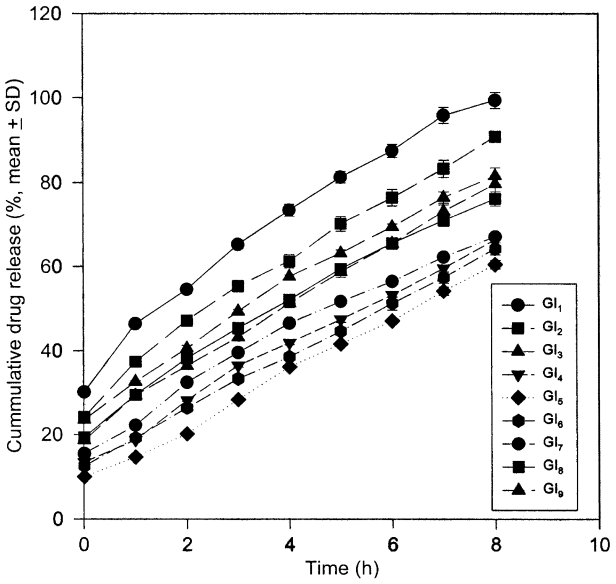

Fig. 3. *In vitro* release of the prepared gelling system of indomethacin. Mean ± SD values are presented (n = 3).

The eye drops formed an opaque matrix immediately upon addition to the dissolution medium, due to the cation interaction in the STF (composition 1). Hence the release of indomethacin from this matrix was possibly influenced by diffusion and/or erosion of the matrix. The combination of these processes seemed to result in the overall diffusion-controlled release kinetics, as indicated by the n values. These results are in agreement with those reported earlier (14) for methylprednisolone from gellan eye drops.

The *in vitro* release study conditions may be very different from those likely to be encountered when instilled into the eye. However, the results showed that the formed gels had the ability to retain indomethacin for the duration of the study (8 h). In the cul-de-sac, the gels would probably undergo rapid dissolution due to the shearing action of the eyelid and eyeball movements.

Pharmacodynamic studies

Pharmacodynamic evaluation of the indomethacin formulations in the uveitis induced rabbit eye model is shown in Table IV.

In the case of eyes treated with the standard dispersion, no significant improvement in the clinical parameters was observed after initial 4 hours (where improvement was observed in some parameters) indicating the need of frequent dosing to produce the optimum therapeutic effect, whereas the *in situ* gelling formulation (batch GI_5) showed improvements in the clinical parameters up to 24 hours post instillation suggesting the propensity of the prepared systems to sustain drug release with a minimal loss due to drainage.

Table IV. Pharmacodynamic studies of indomethacin gelling systems

Batch	Animal No.	Treated eye	Clinical parameters														
			Congestion					Flare					Keratitis				
			0	4 h	8 h	12 h	24 h	0	4 h	8 h	12 h	24 h	0	4 h	8 h	12 h	24 h
GI_5	1	R*	++++	++++	+++	++	++	+++	++	+	0	0	++++	+++	++	+	0
		L	++	++	++	++	++	++	++	++	++	++	+	+	+	+	+
	2	R*	+++	++	++	+	0	++	+	+	0	0	+++	+++	+	+	0
		L	+	+	+	+	+	0	0	0	0	0	+	+	+	+	0
	3	R	+	+	+	+	+	0	0	0	0	0	+	+	+	+	0
		L*	++	+	0	0	0	++	+	+	0	0	+++	++	++	+	+
Std	1	R*	+++	++	++	++	++	++++	++++	+++	+++	+++	++++	++++	+++	+++	+++
		L	+	+	+	0	0	++	++	++	++	+	+++	+++	+++	++	++
	2	R	+	+	+	+	0	++	++	++	++	++	+	+	+	0	0
		L*	+++	+++	+++	+++	+++	++++	+++	+++	+++	+++	+++	++	++	++	+
	3	R	++	++	++	++	++	+	0	0	0	0	+	+	+	+	0
		L*	+++	+++	++	++	++	++	++	++	+	+	+++	+++	+++	+++	++

			Clot					Aqueous cells					Sinekese				
			0	4 h	8 h	12 h	24 h	0	4 h	8 h	12 h	24 h	0	4 h	8 h	12 h	24 h
GI_5	1	R*	++++	++++	+++	+++	++	++++	++++	++	++	+	P	P	P	P	P
		L	++	++	++	++	++	+	+	+	+	+	P	P	P	P	P
	2	R*	++	++	+	+	+	++	++	++	++	+	P	P	P	P	P
		L	+	+	+	+	+	0	0	0	0	0	P	P	P	P	P
	3	R	0	0	0	0	0	0	0	0	0	0	P	P	P	P	P
		L*	++	++	+	0	0	++	++	+	+	0	P	P	P	P	P
Std	1	R*	++++	++++	++++	+++	+++	++++	+++	+++	+++	+++	P	P	P	P	P
		L	++	++	+	+	+	++	++	++	++	+	P	P	P	P	P
	2	R*	+++	+++	+++	+++	+++	+++	+++	++	++	++	P	P	P	P	P
		L	+	+	+	+	+	+	+	+	0	0	P	P	P	P	P
	3	R	++	++	+	+	0	++	++	+	+	+	P	P	P	P	P
		L*	+++	+++	++	++	++	+++	+++	++	++	++	P	P	P	P	P

* implanted eye, Std – standard dispersion of indomethacus; R – right eye; L – left eye.

No repeated dose study was attempted since the aim of the study was to develop a suitable formulation for the once daily application. The formulation (GI_5) used for the pharmacodynamic study was seen to form a translucent gel immediately after instillation into the eye. Gross examination of the ocular tissues showed that the formulations caused no undue irritation and no leakage of the gelled material was observed from any part of the eye.

CONCLUSIONS

Indomethacin was successfully formulated as an *in situ* gelling system using gellan. The formulated systems provided sustained release of the drug over an 8-hour period *in vitro* and the developed formulations were devoid of any deleterious effect on the ocular tissues. The formulations demonstrated better therapeutic efficacy compared to the standard suspension because they were successful in improving the clinical parameters monitored for prolonged periods (24 hours). Hence, this can be viewed as a viable alternative to conventional eye drops by virtue of its ability to enhance pre-corneal residence time and thereby ocular bioavailability. The ease of administration coupled with its ability to provide sustained release could probably result in less frequent administration, thus enhancing patient compliance.

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S A Ž E T A K

In vitro i *in vivo* evaluacija oftalmološkog pripravka za indometacin na temelju Gerlite® gume

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Slaba bioraspoloživost i terapijski učinak postignut konvencionalnim oftalmološkim otopinama radi prekornealne eliminacije ljekovite tvari može se prevladati uporabom sustava koji *in situ* stvara gel. Lijek se daje u obliku kapi za oči koje u dodiru s okom prelaze iz sol u gel stanje. Cilj istraživanja bio je razviti oftalmološki pripravak nesteroidnog protuupalnog lijeka indometacina na temelju ionski aktiviranog *in situ* geliranja. Kao gelirajuće sredstvo upotrebljena je guma Gelrite®, nova oftalmološka pomoćna tvar koja gelira u prisutnosti jednovalentnih i dvovalentnih kationa iz suzne tekućine. Dobiveni pripravci bili su učinkoviti u terapiji induciranog uveitisa na pokusnim zečevima i omogućili su produljeno oslobađanje ljekovite tvari *in vitro* tijekom 8 sati.

Ključne riječi: gelan, indometacin, oftalmološka primjena

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