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Development and Evaluation of Ocular Films of Cromolyn Sodium

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Cromolyn sodium ocular films were prepared by solvent casting technique using polyvinyl alcohol and sodium alginate with glycerin and polyethylene glycol 400 as plasticizers. The physicochemical parameters like thickness, percent elongation at break, tensile strength and drug content uniformity of the ocular films were evaluated. *In vitro* drug release from the formulations was studied and the formulation that shows better release behavior was subjected to *in vivo* studies on rabbits. The results of formulations F_3 (1% polyvinyl alcohol) and F_4 (1.5% sodium alginate) indicated a strong positive correlation of *in vitro* and *in vivo* drug release, which follow zero order kinetics and non-fickian in nature. It was also concluded that sodium alginate and poly vinyl alcohol are good film forming agents and in the presence of plasticizer (PEG 400) they are promising controlled release ocular delivery systems for cromolyn sodium.

Cromolyn sodium is an antiallergic agent, which is useful in the treatment of allergic disorders. It is available as 2 % and 4 % solutions; these solutions are effective against ocular allergies. The drug is administered 4-6 times daily as eye drops[1]. The half-life of the drug is approximately 80 min with more than 90 % being eliminated within 24 h. When administered to a normal volunteer approximately 0.07 % cromolyn sodium was absorbed following an ocular dose[2].

Traditional topical ophthalmic formulations have poor bioavailability because of rapid pre-corneal elimination, conjunctival absorption, solution drainage by gravity, induced lacrimation and normal tear turnover. This leads to frequent instillations of concentrated medication to achieve a therapeutic effect. These observations suggest that increasing contact time between drug and corneal tissue could both be beneficial for patient compliance and to improve therapeutic efficucy[3].

Present study is undertaken to prepare an ocular film with an aim of increasing the contact time, achieving controlled release, reducing the frequency of administration, improving patient compliance and obtaining greater therapeutic efficacy. Main objective of the ocular film is to increase the contact time between the film and conjunctival tissue to ensure a sustained release formulation suitable for topical or systemic treatment.

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MATERIALS AND METHODS

Cromolyn sodium was obtained as a free gift sample from Cipla Ltd., Mumbai, sodium alginate[5] was procured from Loba Chemicals, Mumbai and polyvinyl alcohol [PVA] from BDH Chemicals, Mumbai. Plasticizers, glycerin and polyethylene glycol 400 were procured from Nice Chemicals, Cochin and P.C.L, Pune respectively.

Preparation of ocular films:

Method used for the preparation of ocular film is solvent casting technique[6] using purified water as solvent. A total number of five formulations were designed. Table 1 shows composition of cast films for each ocular insert. Sodium alginate and/or polyvinyl alcohol were dissolved in 15 ml of water using magnetic stirrer in a beaker to get desired concentration of the polymer. Cromolyn sodium was added and the plasticizer system was then incorporated to the above solution under continuous stirring using a magnetic

bead at 100 rpm. After complete mixing, 10 ml solution was poured into a clean Petridish (Anumbra® Area 38.5 cm^2 approximately) placed on a horizontal plane. Water was allowed to evaporate slowly by inverting a glass funnel on the Petridish at 24.2° for 24 h. After complete evaporation of solvent, cast film was obtained[6], from these cast films; ocular inserts with 7.0 mm diameter were cut with the help of cork borer and wrapped individually in aluminium foil.

Evaluation of polymeric ocular films:

The prepared ocular films were evaluated for thickness, percent elongation at break, tensile strength and drug content uniformity. The film thickness[7] was measured using a dial caliper (Mitutoyo, Japan) at different points and the mean values were calculated. Readings were taken over a circular film of area of 38.5 mm^2. The standard deviation in thickness was computed from the mean value.

To perform percent elongation at break and tensile strength, a small filmstrip measuring 4 cm x 1 cm was cut with a sharp blade. One end of the film was fixed by placing in the film holder. Another end of the film was fixed with the help of forceps having triangular ends to keep the strip straight while stretching and a hook was inserted. A thread was tied to the hook, passed over the pulley and a small pan attached to the other end to hold weights. A small pointer was attached to the thread that travels over the graph paper affixed on the base plate. To determine elongation and tensile strength[7,8], the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. Elongation was determined simultaneously by noting the distance traveled by the pointer on the graph paper before the film was broken. The weight necessary to break the film was noted as break force. Percent elongation at break and tensile strength was calculated using the fallowing formulae, Percent elongation at break=I_B-I_O/I_Ox100 where I_O is the original length of film and I_B is the length of film at break when stress was applied. Tensile strength=Break force/a b (1+ΔL/L) where a, b and L are width, thickness and length of the strip respectively and ΔL is the elongation at break. Break force=weight required to break the film (Kg).

To check the uniformity of the drug in the cast film, inserts were cut at different places in cast films and each insert was placed in vials containing 5 ml of isotonic sodium phosphate buffer of pH 7.4 to extract cromolyn sodium and the solution was analysed by spectrophotometer at 238 nm using isotonic sodium phosphate buffer as blank. Same procedure was adopted for other formulations of cast films in triplicates and mean drug content and standard deviation of variance were calculated[7].

***In vitro* drug release studies:**

Ocular films of cromolyn sodium in triplicates from each batch were used for *in vitro* release study[6]. Each inserts were placed in 10 ml capacity vials containing 5 ml of pH 7.4 isotonic sodium phosphate buffer (simulating tear pH) that was previously warmed at 37±1°; these vials were placed over hot plate (maintained at temperature 37±1°) that was positioned on a sieve shaker. Shaker was kept at minimum shaking speed. Aliquots of one ml samples at 1, 3, 5, 7, 9 and 11 h were withdrawn carefully using pipette and equivalent amount of fresh dissolution fluid was replaced. The aliquots withdrawn were suitably diluted with pH 7.4 isotonic phosphate buffer solution and was analysed at 238 nm using Shimadzu UV-spectrophotometer against blank.

***In vivo* drug release studies:**

Study was conducted on healthy male rabbits of New

TABLE 1: COMPOSITION OF FORMULATIONS

Formulation code	Polymers (% w/v)		Plasticizers (% w/w) #	
	Polyvinyl Alcohol	Sodium Alginate	Glycerin	PEG 400
F_1	-	1.5	40.0	-
F_2	1.0	-	40.0	-
F_3	1.0	-	-	40.0
F_4	-	1.5	-	40.0
F_5	0.5	0.5	40.0	-

Based on dry polymer weight. In each of the formulations cromolyn sodium 2.64% was incorporated using 20 ml of distilled water. From this solution 10 ml is poured into Anumbra® petridish to prepare a circular cast film.

Zealand white strain, with prior approval of Institutional Animal Ethics Committee. Out of the five formulations, F3 and F4 which showed better r *in vitro* drug release were taken for *in vivo* studies[6]. The inserts were sterilized by using UV radiations for 1 h before the study. Male rabbits, weighing 2.5 to 3.0 kg were selected for the experiment. The animals were housed in individual cages and customized to laboratory conditions for a day and received free access to food and water.

On the day of experiment the sterilized ocular inserts were placed into the lower conjunctival cul-de-sac of rabbits. The inserts were inserted into one eye of six healthy rabbits at same time and another eye served as control. After 1, 3, 5, 7, 9 and 11 h, the inserts were carefully removed and analyzed for drug content. The drug remaining was subtracted from initial drug content of insert, which gave the amount of drug released in the rabbit eye. Observation for any fall out of the insert was also recorded throughout the experiment. After the washout period of one week the experiment was repeated for two times as before.

RESULTS AND DISCUSSION

The physicochemical evaluation data presented in Table 2 indicates that the thickness of the ocular films varies from 0.148±0.004 to 0.183±0.006 mm. All the formulations exhibited uniform thickness with low standard deviation values ensured the uniformity of the films prepared by solvent casting method. The formulations did not produce any irritation when placed in the cul-de-sac.

The formulation F_1 shows the maximum percent elongation at break whereas the least one was found with formulation F_3. Presence of plasticizers in the form of glycerin imparts flexibility to polymers. Glycerin and PEG 400 forms hydrogen bonds with the polymer molecule, there by imparting flexibility to the filmstrip. Tensile strength measures the ability of film to withstand rupture. The formulation F_1 shows the maximum value of 0.184±0.007 as shown in Table 2. This might be due to formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture. All the formulation found to contain almost uniform quantity of drug as per content uniformity studies indicating reproducibility of the technique.

In vitro release study of formulations F_3 and F_4 shows 94.5% and 98.2% drug release at the end of 11th h, respectively. The use of PEG 400 in the films shows increase in the drug release pattern due its permeation enhancer role in addition to plasticizer. Formulations F_1 and F_2 that contain glycerin don't exhibit significant drug release where as F_5 with combination of polymers shows slight improvement in drug release. The drug release pattern for all the formulation followed the zero order kinetics and non-fickian in nature.

In vivo drug release for formulations F_3 and F_4 through conjunctival cul-de-sac of rabbits was 66.2% and 70.4% at the end of 11th h, respectively. The release pattern followed zero order kinetics. *In vitro* and *in vivo* correlation was carried out for the therapeutic efficacy of the pharmaceutical formulation. The correlation coefficient of formulations F_3 and F_4 were found to be 0.995 and 0.989 respectively, indicating that the correlation was strong and positive. There was no drag out of circular inserts at the time of experiment, which suggests that the dimension of the inserts (7.0 mm diameter) were suitable for ocular use. Rabbits subjected for *in vivo* study did not show any signs of irritation, inflammation and abnormal discharge that confirmed the safety of the polymers used in the formulation. Compatibility between for-

TABLE 2: PHYSICOCHEMICAL EVALUATION DATAS OF CROMOLYN SODIUM OCULAR FILM FORMULATIONS.

Film Code	Mean Thickness (mm) n=3	Mean Percent Elongation at Break (Kg/cm2) n=3	Mean Tensile Strength (Kg/mm2) n=3	Mean Content Uniformity (mg) n=3
F_1	0.148±0.004	22.33±0.288	0.184±0.007	6.27±0.030
F_2	0.172±0.003	19.16±2.886	0.133±0.010	6.54±0.025
F_3	0.176±0.002	09.00±2.598	0.069±0.010	6.38±0.020
F_4	0.161±0.004	11.66±1.443	0.129±0.011	6.31±0.030
F_5	0.183±0.006	15.66±1.154	0.115±0.080	6.48±0.025

All the values are mean±S.D of triplicates.

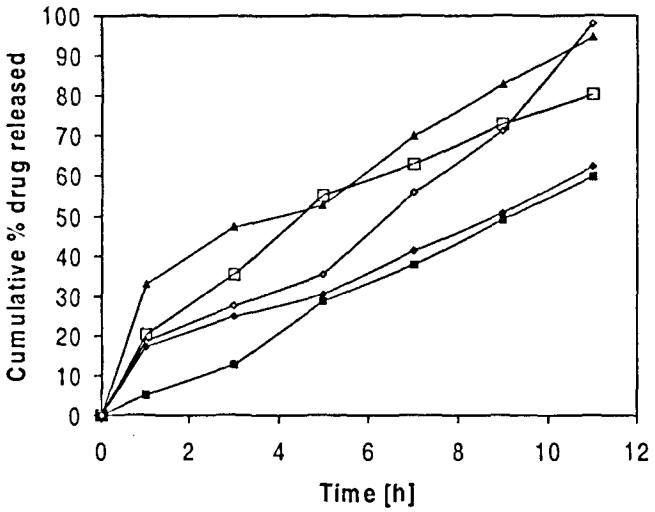

Fig.1: *In vitro* cumulative percent drug release Vs Time [h] profiles for formulations.

Release profiles of cromolyn sodium ocular films prepared using sodium alginate with glycerin F1 [□], polyvinyl alcohol with glycerine F2 [■], polyvinyl alcohol with PEG 400 F3 [▲], sodium alginate with PEG 400 F4 [◇] and combination of sodium alginate and polyvinyl alcohol with glycerin F5 [□].

mulation ingredients and effect of uv-radiation was studied by performing TLC. It was found that drug is compatible with formulation ingredients without any interaction.

From the results it can be concluded that formulations F_3 (1.0 % polyvinyl alcohol) and F_4 (1.5% sodium alginate) of cromolyn sodium has achieved the objectives of increased

TABLE 3: DATA SHOWING *IN VITRO* AND *IN VIVO* CUMULATIVE PERCENTAGE DRUG RELEASED AFTER 11 HOURS

Formulation Code	*In-vitro* Drug* Release [%]	*In-vivo* Drug* Release [%]
F_1	62.37	-
F_2	59.95	-
F_3	94.51	66.21
F_4	98.20	70.36
F_5	80.20	-

*Values expressed as mean of triplicates.

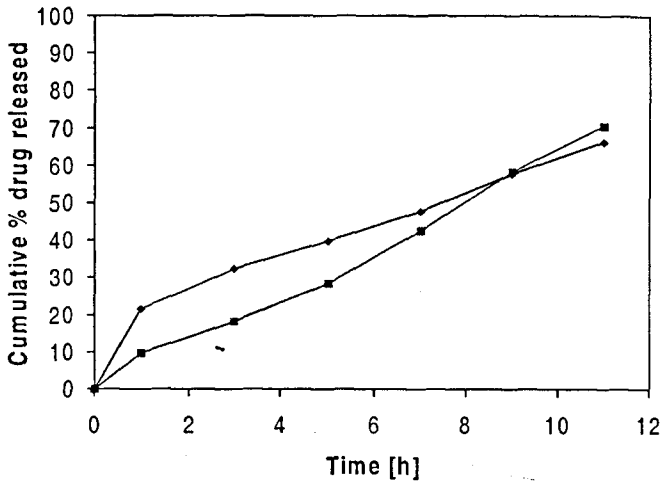

Fig. 2: *In vivo* cumulative percent drug released Vs Time [h] for formulation F_3 and F_4.

***In vivo* drug release in cul de sac of rabbit eyes for select formulation F3 [□] and F4 [■].**

contact time, prolonged release, decreased frequency of administration and thus can be used for better control of allergic disorders by formulating as an ocular insert.

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