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Formulation and Evaluation of Drug-free Ophthalmic Films Prepared by Using Various Synthetic Polymers

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ABSTRACT

An attempt has been made to formulate drug-free ophthalmic films by using different polymers in single use as well as in combinations for matrix system design for ocular use and to study the effect of various plasticizers on physicochemical characteristics and permeability of the resultant films. Drug-free films of hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), polyvinyl pyrrolidone (PVP), and Eudragit RL 100 polymers were prepared by the solvent casting method on a mercury surface by employing distilled water and ethanol as solvents, and glycerol and dibutyl phthalate as plasticizers. These films were evaluated for weight variation, uniformity of thickness, tensile strength, percentage of elongation at break, folding endurance, hardness, surface pH, and water vapor permeability. Permeability characteristics of these films were studied using Ofloxacine as a model drug. Film properties of various synthetic polymers such as hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), polyvinyl pyrrolidone (PVP), and Eudragit RL 100 were studied for their utility in the formulation of ophthalmic inserts. Sterility test was carried out before performing an irritation study on *albino* rabbit eyes. There was no sign of any irritation, redness, swelling, or haziness in the rabbit's eyes even after 24 hours after removal of the film.

Key words: Eudragit RL 100, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, ophthalmic inserts, polyvinyl alcohol, polyvinyl pyrrolidone

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INTRODUCTION

The ocular route of drug delivery has become popular recently and its importance has been extensively pointed out. To achieve controlled and constant release of drug, ocular systems require suitable rate-controlling membranes and drug reservoirs. The permeability of drugs through the polymeric free films is dependent on characteristics of the polymer, the casting solvent, and the plasticizers used. Preparation of polymeric ocular films for ocular use requires plasticizers for various reasons: To reduce the brittleness, to impart flexibility, to increase strength, and also to improve adhesiveness of the films with surfaces or membranes. Plasticizers interpose themselves between the polymer chains and interact with the chains to extend and soften the polymer matrix. Plasticizers commonly used in the formulation of ocular films are phthalate esters, phosphate esters, fatty acid esters, and glycol derivatives.

Local therapy is preferred over systemic therapy for the eye to avoid risk of eye damage from high blood concentrations of the drug. The unique anatomy, physiology, and biochemistry of the eye render this organ impervious to foreign substances, thus presenting a constant challenge to the formulator to circumvent the protective barriers of the eye without causing permanent tissue damage. Most ocular

treatments, like eye drops and suspensions, call for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but suffer from the inherent drawback that the majority of the medication they contain is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac. It is then rapidly drained away from the precorneal cavity by constant tear flow and lacrimo-nasal drainage. Therefore, because only a very small fraction of the instilled dose is absorbed by the target tissue, concentrated solutions and frequent dosing are required for the instillation of the drug to achieve an adequate level of therapeutic effect.[1] One of the new classes of drug delivery systems, polymeric film ophthalmic drug delivery systems, which are becoming more popular worldwide, release drugs at a preprogrammed rate for a longer period by increasing precorneal residence time.[2] Various synthetic polymers such as hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), polyvinyl pyrrolidone (PVP), and Eudragit RL 100 were selected to study their suitability for ophthalmic formulation.

The aims of the present study were to i) prepare plasticized, drug-free ocular films of hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), polyvinyl pyrrolidone (PVP), and Eudragit RL 100, and ii) to evaluate their weight variation, uniformity of thickness, tensile strength, percentage of elongation at break, folding endurance, hardness, surface pH, and water vapor permeability. Glycerol and dibutyl phthalate were used as plasticizers. These films were subjected to permeability studies using ofloxacine, a model drug to investigate the effect of plasticizers on the permeability characteristics of films.

EXPERIMENTAL

Materials

Eudragit RL 100, polyvinyl alcohol (PVA), and hydroxypropyl cellulose (HPC) were obtained as gift samples from Colorcon Asia pvt Ltd., Goa. Hydroxypropyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP) were obtained as gift samples from Nison Soda, Japan and Zydus Health Care, Ahmedabad, India respectively. Dibutyl phthalate and glycerol were obtained from SD Fine Chemicals, Mumbai, India.

Method for preparation of placebo[11]

Ophthalmic films were prepared by the solvent casting technique. In the present study, eleven formulations were formulated using different polymers. Glycerol or dibutyl phthalate was incorporated as a plasticizer at a concentration of 30% w/w of the polymer. Distilled water or ethanol was used as a casting solvent. These formulations are designated as F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, and F11. The detailed compositions of the drug-free films are given in Table 1. The casting solutions were prepared by dissolving the appropriate polymers (2% w/v) and plasticizer (30% w/w) in suitable solvents using a magnetic stirrer for 30 minutes to get a uniform dispersion. Mercury was used as the substrate and was poured into a petridish (24.6176 cm^2 area). The mould was kept on the smooth horizontal surface of the mercury and 10 mL of the solution was poured into the mould. After 24 h, the dried films thus obtained were taken out and stored over fused calcium chloride in a desiccator at room temperature for further use.[3,12,14]

Evaluation of the drug-free films

Uniformity of thickness[4]

Transverse sections of the films were taken at five different points and the thickness was determined using the optical microscopic technique.

Weight variation[12,13]

The weight variation test was done by individually weighing twenty films using a digital balance. The average weight of the films was taken as the original weight.

Hardness[6,14]

The hardness test was performed on three different films from each batch using a fabricated hardness instrument and the average was calculated. The hardness apparatus consists of a wooden stand 8 cm in height with a top area of 8 × 8 cm. A hole of 0.2 cm diameter was made in the center of the wooden top. A small plastic pan was fixed horizontally onto one end of a 2 mm-thick, smooth iron rod, whose other end had been reduced to a sharp point. This rod was inserted into the hole in the wooden top with its lower sharp end placed on a metal plate. An electric circuit was set up with a 3 Volt battery in such a way that the bulb lighted up only when the circuit was completed through the contact of the metal plate and the sharp end of the rod. The sample patch was placed between the metal plate and the sharp end of the iron rod. Weights were gradually added on to the pan and the total weight required to penetrate the patch, as indicated by the lighted bulb, was noted.

Tensile Strength[6]

The tensile strength of the ocular films was measured using a tensile strength instrument. An average reading was taken

Table 1: Composition of drug-free films formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
HPMC	400 g	200 g	-	-	-	-	-	-	-	-	-
HPC	-	-	400 g	200 g	-	-	-	-	-	-	-
PVA	-	-	-	-	400 g	200 g	-	-	-	-	-
PVP	-	200 g	-	200 g	-	200 g	-	44.44 g	80 g	133.33 g	200 g
Eudragit –RS 100	-	-	-	-	-	-	400 g	355.56 g	320 g	266.67 g	200 g
Dist. water	20 mL	20 mL	20 mL	20 mL	20 mL	20 mL	-	-	-	-	-
Ethanol							20 mL	20 mL	20 mL	20 mL	20 mL
Glycerol (% w/w)*	30	30	30	30	30	30	-	-	-	-	-
DBP (% w/w)*	-	-	-	-	-	-	30	30	30	30	30

*Based on polymer weight

of three patches from each batch as the tensile strength. A small patch strip (2 × 1 cm) was cut on a glass plate with a sharp blade. One end of the film strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to the hook, passed over the pulley and the small pan attached to the other end to hold the weights. A small pointer was attached to the thread, which traveled over the graph paper affixed on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force until the patch was broken. The elongation was determined by noting the distance traveled by the pointer on the graph paper before the breaking of the patch. The weight required to break the patch was noted as break force. Tensile strength was calculated using the following formula:

$$\text{Tenile strength} = \frac{\text{Break Force}}{ab\left(1+\frac{\Delta L}{L}\right)}$$

Where a, b and L are width, thickness, and length of strip respectively and ΔL is the elongation at break.

% Elongation at break

Substitute the original length of the patch from the length of patch at the break and divide the value by the initial length of the patch and multiply the value by 100.

% Elongation at break was calculated using the following formula:

$$\% \text{ Elongation at break} = I_B - I_O / I_O \times 100$$

Where I_O = Original length of patch

I_B = length of patch at break when stress is applied.

Folding Endurance[5]

Folding endurance of the film was determined repeatedly by folding a small strip of film (2 cm × 2 cm) at the same place until it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Surface pH[7]

Surface pH of the film was determined by allowing it to swell in a closed petridish at room temperature for 30 minutes in 0.1 mL of double distilled water. The swollen devices were removed and placed in a digital pH meter to determine the surface pH.

Water vapor permeability[8]

Glass vials of 5 mL capacity were washed thoroughly and dried to constant weight in an oven. One gram of fused calcium chloride was taken in the vials and the polymer films were fixed over the brim with the help of an adhesive tape. These preweighed vials were stored in a humidity chamber at 80% RH with the temperature set to 30°C for a period of 24 hours. Weight gain was determined every hour up to a period of 24 hours (predetermined equilibration period).

Sterilization and test for sterility for ophthalmic films[9,10,13]

In the present study, all films were sterilized separately by exposing them to UV radiation for 30 minutes.

The irradiated ophthalmic films were tested for their sterility as per the Indian Pharmacopoeia to detect the presence of viable forms of bacteria, fungi, and yeast in or on sterilized preparations. The tests were carried out under aseptic conditions to avoid accidental contamination of the product during the test.

Irritation study[12]

Albino rabbits were selected for this study. The ophthalmic film was placed in rabbits' eyes which were observed after 24 hours for signs of any irritation, redness, swelling, or haziness. The primary eye irritation test was performed on seven healthy albino rabbits weighing between 2.0 to 3.5 kg. Ethical clearance for the handling of experimental animals was obtained from the Institutional Animal Ethical Committee (IAEC) constituted for the purpose. Drug-free films of 1cm^2 area were prepared and used as test films. The test films were placed on the left and right eyes of the rabbit. The films were removed after 24 h with the help of swabs and the eyes were examined for irritation, redness, swelling, or haziness.

RESULTS AND DISCUSSION

The casting method using the mercury surface was found to be satisfactory to get thin and transparent films.

Uniformity of thickness

The prepared films were evaluated for thickness using Vernier calipers. The average of three readings was taken and the mean thickness and standard deviation were calculated. The low standard deviation of the measured thickness of all 11 formulations may indicate uniform distribution of the drug and excipients in the prepared inserts. It was found to be in the range of 0.0489 ± 0.005 to 0.0508 ± 0.002 mm [Table 2].

Uniformity of weight

The weights of all the films were found to be in the range of 0.0054 (± 0.00015) to 0.0062 (± 0.00015) g [Table 2]. The uniformity of the weights of the films indicates good distribution of the drug, polymer, and plasticizer.

Folding endurance

Folding endurance measures the ability of a film to withstand rupture. The folding endurance was measured manually by folding the film repeatedly at a point until it broke; the breaking time was considered as the end point. Folding endurance was found to be the highest for F5 (300.18 ± 6.15) and lowest for F8 (276.50 ± 4 .95) as shown in Table 2. It was found that folding endurance of the films was increased by the use of different polymers in the following order: PVA > PVP > Eudragit RS 100. The folding endurance values of the films were found to be optimal and therefore, the films exhibited good physical and mechanical properties.

Surface pH

The surface pH of the prepared ocular films was found be in range of 6.84 to 7.13 [Table 2]. This indicates that the prepared inserts would not alter the pH of the tear fluid in the eyes and no irritation would occur in the eye after application of the films. All the films were permeable to water vapor at 80% relative humidity, 30ºC, and followed nearly zero order kinetics.

Table 2: Evaluation data of drug-free ophthalmic films

F. C.	Weight* (g)	Thickness * (mm)	Tensile strength* (kg/mm^2)	% Elongation at break	Folding Endurance*	Surface pH	Hardness* (g)	WVP
F1	0.0054 (0.00015)	0.0489 (0.005)	0.200 (0.0007)	18.09 (0.31)	285.09 (5.22)	6.95(0.021)	124.25 (7.78)	4.477
F2	0.0059 0.00015)	0.0495 (0.006)	0.208 (0.001)	18.15 (0.21)	297.29 (5.50)	7.04 (0.028)	123.75 (10.61)	4.619
F3	0.0057 (0.00011)	0.0502 (0.007)	0.216 (0.002)	18.29 (0.08)	298.25 (4.40)	7.02 (0.042)	125.50 (3.54)	4.673
F4	0.0060 (0.00011)	0.0495 (0.003)	0.222 (0.002)	18.25 (0.26)	289.15 (4.15)	6.99 (0.035)	123.75 (9.19)	4.864
F5	0.0058 (0.00015)	0.0508 (0.002)	0.197 (0.001)	21.99 (0.21)	300.18 (6.15)	6.85 (0.021)	112.75 (7.78)	4.282
F6	0.0062 (0.00015)	0.0506 (0.005)	0.195 (0.001)	21.67 (0.15)	296.20 (5.11)	6.87 (0.014)	115.25 (4.95)	4.478
F7	0.0054 (0.00011)	0.0501 (0.004)	0.209 (0.002)	19.20 (0.23)	278.67 (5.66)	6.84 (0.015)	118.75 (6.36)	3.488
F8	0.0057 (0.00011)	0.0498 (0.001)	0.199 (0.002)	19.18 (0.15)	276.50 (4.95)	6.92 (0.021)	119.25 (4.24)	3.582
F9	0.0056 (0.00011)	0.0508 (0.003)	0.174 (0.001)	17.14 (0.29)	312.99 (5.10)	7.06 (0.014)	129.25 (9.90)	3.769
F10	0.0061 (0.00011)	0.0502 (0.005)	0.179 (0.001)	17.47 (0.30)	299.36 (5.35)	7.13 (0.035)	128.75 (9.19)	3.882
F11	0.0059 (0.0015)	0.0492 (0.005)	0.182 (0.003)	17.36 (0.35)	281.14 (6.11)	7.04 (0.049)	131.75 (5.66)	3.972

Above values are average of three observations. Figures inside the parentheses are standard deviation values. WAP and F.C. indicates water vapor permeability and formulation code respectively. You could actually state your results (which formulation—solvent, plasticizer—gave better characteristics) in the abstract, discussion and conclusion

Tensile strength

The tensile strength of the film(s) was found to vary with the nature of the polymer and plasticizer between 0.174 to 0.222 kg/mm^2. The tensile strength of the films can be arranged in the order of F9 < F10 < F11 < F6 < F5 < F8 < F1 < F2 < F7 < F3 < F4. The percentage elongation at break showed flexibility of the film; it varied from 17.14 to 21.99.

Films plasticized with 30% w/w plasticizer were found to be optimal with respect to smoothness, flexibility, and transparency. Films require a certain amount of hardness to withstand the mechanical shocks in handling, packaging, and at the time of application. The hardness of the films varied from 112.75 to 131.75 g. Thus, hardness, tensile strength, and percentage elongation at break were dependent on the properties of the polymers and plasticizers. Sterilization of films was carried out by exposing the ocular films to UV radiation. The sterile films complied with the test for sterility as per the Pharmacopoeial procedure. The positive control test showed the growth of microorganisms, which confirms that the media is suitable for test conditions. The negative control test did not show any growth of microorganisms, which confirms that all the apparatus used for the test were sterile and aseptic conditions were maintained. The sample test also did not show any growth of microorganisms, which suggest that the films were sterile. There was no sign of any irritation, redness, swelling, or haziness in the rabbit's eyes used for the study, indicating that ophthalmic films were free from ocular toxicity and safe for ocular use. The physicochemical evaluation data have been presented in Table 2.

CONCLUSION

The present study showed that the type of the plasticizer used and its concentration has considerable influence on the physicochemical characteristics and permeability properties of the polymeric films. It is evident from these studies that formed polymeric films have appreciable strength and safety. Hence, these films can be used in ophthalmic formulations.

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