East and Central African Journal of Pharmaceutical Sciences
Vol. 11 (2008) 9-15

Drug-loaded Cellulose Acetate and Cellulose Acetate Butyrate Films as Ocular Inserts

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The purpose of this research work was to evaluate the contribution of formulation variables on release properties of matrix type ocular films containing chloramphenicol as a model drug. This study investigated the use of cellulose acetate and cellulose acetate butyrate as film-forming agents in development of ocular films. Formulation variables were concentration of polymer and plasticizer. Prepared films were evaluated for thickness, tensile strength, water vapor transmission rate and *in vitro* dissolution study. All formulations showed extended drug release over a period of 12 hours. The levels of polymer and plasticizer had a significant influence on the drug release in initial periods. Diffusion exponents of all formulations were less than 0.5, which confirmed that drug release occurred without swelling of inserts. Water vapor transmission rate was influenced by concentration of plasticizer. The best formulation showed 81.26% drug release *in vivo* at the end of 12 h with cellulose acetate and 79.06% with cellulose acetate butyrate. The *in vitro-in vivo* release correlation was evaluated and the regression coefficient was found to be 0.9767 and 0.9007 for cellulose acetate and cellulose acetate butyrate formulation, respectively indicating good correlation between the *in vitro* and *in vivo* drug release.

Key words: Ocular films, cellulose acetate, cellulose acetate butyrate, chloramphenicol

INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavours faced by the pharmaceutical scientist. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The development of newer, more sensitive diagnostic techniques and therapeutic agents render urgency to the development of successful ocular drug delivery systems.

Topical delivery into the conjunctival cul-de-sac is, by far, the most common route of ocular drug delivery. The topical application of ophthalmically active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders. It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor [1, 2]. The conventional ocular dosage forms pose various constraints like short residence time, large drainage factor, frequent instillation and pulsed dosing of drug. The therapeutic efficacy of drug for ophthalmic use can be greatly improved by prolonging its contact with the corneal surface. Some of the newer, sensitive and successful ocular drug delivery systems like inserts, biodegradable polymeric systems and collagen shields are being developed in order to attain ocular bioavailability and sustained action of drugs.

Ocular inserts offer an attractive alternative approach to the difficult problem of prolonging pre-corneal drug residence time by providing a controlled release of the drug. They are composed of a polymeric support containing drug(s) incorporated as dispersion or solution in the polymeric support.

Chloramphenicol is a broad-spectrum antibiotic originally isolated from *Streptomyces venezuelae*. It is primarily bacteriostatic and acts by inhibition of protein synthesis by interfering with the transfer of activated amino acids from soluble RNA to ribosomes.

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The aim of the research work was to formulate and evaluate sustained release ocular inserts using Cellulose Acetate (CA) and Cellulose Acetate Butyrate (CAB) as polymeric films in view to sustain the release of drug in the eye cavity.

MATERIALS AND METHODS

Materials

Chloramphenicol was obtained as a gift sample from Ophthal Remedies (Surendranagar, India). Cellulose acetate and cellulose acetate butyrate were procured from Rolex Chemical Industries (Mumbai, India) while glycerin and dibutyl phthalate were obtained from S. D. Fine Chemicals Ltd. (Mumbai, India).

Formulation of ocular films

Cellulose acetate and cellulose acetate butyrate were used as film forming polymers in three different concentrations with dibutyl phthalate or glycerin as plasticizers in two different concentrations. Ocular films containing chloramphenicol were prepared by solvent casting technique using Anumbra® petridish (Bharat Enterprises, New Delhi, India). Cellulose acetate or cellulose acetate butyrate was dissolved in the required amount of acetone using a magnetic stirrer. The drug was dissolved separately in 2 ml acetone and added to the polymeric solution. The plasticizer was added and stirred for 10 min using magnetic stirrer. The resulting solution was poured into Anumbra® petridish of diameter 9 cm. Evaporation of solvent was carried out in a controlled manner using an inverted funnel at room temperature for 24 h. After complete drying, the prepared films were wrapped in aluminium foil and packed in air-tight bags till further use. Ocular films of 9 mm diameter containing 1 mg chloramphenicol were cut using a cork borer at the time of use. Tables 1 and 2 outline the composition of the different formulations prepared using cellulose acetate and cellulose acetate butyrate respectively.

Evaluation of ocular films

Drug content uniformity: Ocular films of 9 mm diameter were kept in 10 ml vials and equilibrated with 5 ml isotonic sodium phosphate buffer (pH 7.4) for 24 h. The vials were shaken at various intervals during this period. Samples were withdrawn, diluted

Table 1: Formulation composition for ocular films based on cellulose acetate

Ingredients	A1	A2	A3	A4	A5	A6
Cellulose acetate (mg)	300	300	400	400	500	500
Chloramphenicol (mg)	96	96	96	96	96	96
Glycerin* (% w/w)	30	40	30	40	30	40
Acetone (ml)	15	15	15	15	15	15

*Plasticizer was used as percentage of dry weight of polymer.

Table 2: Formulation composition for ocular films based on cellulose acetate butyrate

Ingredients	B1	B2	B3	B4	B5	B6
Cellulose acetate butyrate (mg)	400	400	500	500	600	600
Chloramphenicol (mg)	96	96	96	96	96	96
Dibutyl phthalate* (% w/w)	30	40	30	40	30	40
Chloroform (ml)	13	13	13	13	13	13
Acetone (ml)	2	2	2	2	2	2

*Plasticizer was used as percentage of dry weight of polymer.

appropriately and assayed spectrophotometrically at 278 nm to determine the drug content. The readings were recorded in triplicate and the drug content expressed as mean ± SD of three determinations.

Thickness: Thickness of each formulation was measured using Baker Digital Caliper (Baker Gauges India Pvt Limited, Pune, India) at five different points. Readings were recorded and mean thickness and standard deviation calculated.

Water vapor transmission study: The studies were carried out using 10 ml vials containing 1 g of $CaCl_2$. These vials were tightly covered with film formulation using an adhesive tape and kept in a desiccator maintained at 84 % r.h. using a saturated KCl solution. The vials were weighed initially before placing in the desiccator and re-weighed at 24 h intervals up to 7 days. Water vapor transmission rate was calculated using equation I:

$$\text{Rate} = \frac{\text{Final weight - Initial weight (mg)}}{\text{Time (h)}} \text{.....I}$$

Tensile strength: The tensile strength was determined using films of 1 cm width and 4 cm length. The films were fixed onto the tensile strength apparatus (DigiSTRENGTH™, Paramount Instruments, Pvt Ltd, New Delhi, India) in such a way that the length of films between the jaws was initially 2 cm. The distance travelled by the pointer in order to break the film (ΔL) and the weight required (break force) were noted. Tensile strength was calculated using equation II:

$$\text{Tensile stength} = \frac{\text{Break force x } (1+\Delta L/L)}{\text{a x b}} \text{....II}$$

Where:

a = width, b = thickness, L = length, ΔL = elongation at break.

In-vitro dissolution study: Ocular films of 9 mm diameter were placed in a 100 ml beaker containing 25 ml isotonic sodium phosphate buffer (pH 7.4). A wire net was placed over the film to prevent movement of the film. The beaker was placed on magnetic stirrer and the solution stirred vigorously. Samples were withdrawn after every hour for 12 hours and replaced with equal volumes of fresh buffer. The samples were analyzed for drug content against isotonic sodium phosphate buffer as a blank at wavelength of 278 nm using double beam UV visible spectrophotometer (Shimadzu 1700PC, Kyoto, Japan) .The drug release and % drug release at the end of every hour was calculated from slope of the calibration standard curve. Figures 1 and 2 are plots of % drug release against time for CA and CAB formulations, respectively.

Treatment of dissolution data with different release models

To determine the mechanism of drug release from ocular films, the dissolution data obtained from the above experiments were treated to the different release kinetic models [4, 5] according to the following equations:

Zero order kinetics:

$$Q = K_0 t \quad \text{……III}$$

Where Q is the amount of drug released and K_0 is zero order release rate constant.

Higuchi's square root of time model:

$$Q = K_H t^{1/2} \text{ ……..IV}$$

Where Q is the amount of drug released and K_H is Higuchi release rate constant.

Korsmeyer and Peppas kinetics:

$$F = (M_t/M_\infty) = K_m t^n \text{ ……..V}$$

where M_t is drug release at time t, M_∞ is total amount of drug in the formulation, F is fraction of drug release at time t, K_m is constant dependent on geometry of dosage form and n is diffusion exponent indicating the mechanism of drug release. For films, a value of n = 0.5 indicates Fickian diffusion, n = 0.5-1.0 indicates anomalous transport and n = 1.0 indicates case-II transport.

Sterilization and test for sterility

The optimized formulations from both systems (A3 and B5) were sterilized separately in their final package container by exposing them to UV radiation at 254 nm for 90 min [6]. The irradiated ophthalmic inserts were tested for sterility according to the Indian Pharmacopoeia (IP) specifications [7]. The tests were carried out under aseptic conditions to avoid accidental contamination of the product during the test.

In vivo studies

In vivo studies were carried out after obtaining clearance from the Ethical Committee of K.L.E. Society's College of Pharmacy. Sterilized formulations A3 and B5 were selected for *in vivo* drug release study. Five male albino rabbits each weighing 2-2.5 kg were selected. The study was carried out by placing one insert of optimized formulation in the conjuctival cul-de-sac of the right eye and blank film in the conjunctival cul-de-sac of the left eye, which served as the control [8-9]. The ocular inserts were carefully removed after 1, 2, 3, 6 and 12 h and analyzed for drug content by UV spectrophotometry at 278 nm. The drug content obtained was used to calculate the amount of drug released in the rabbit's eye. The studies were carried out in triplicate and results are expressed as mean $\pm$ SD.

The *in vitro* data and *in vivo* results obtained were correlated by plotting the *in vitro* drug release against *in vivo* drug release. The regression coefficient was calculated using Microsoft Excel®.

RESULTS AND DISCUSSION

The results of thickness, water vapour transmission, tensile strength and drug content uniformity are shown in Table 3. The drug content range for formulations based on CA was 0.927-1.011 mg while that for CAB formulations was 0.964- 1.003 mg. The standard deviation was found to be negligible thus establishing the content uniformity of the film produced. The maximum thickness observed was 0.126 mm and 0.124 mm for CA and CAB formulations, respectively, which is an acceptable limit as compared to similar products in the market. It was clearly seen that there was an increase in thickness with increase in polymer concentration of formulation. Formulations based on CA showed higher transmission rates than those based on CAB. The difference in water vapor transmission rate can be attributed to the difference in film porosity, which is known to vary depending on the type and concentration of plasticizers and film former used [10]. The results of tensile strength clearly indicate that CAB films were stronger and more flexible than CA films.

The dissolution profiles (Figures 1 and 2) show that there was retardation in drug release with increase in polymer concentration in both CA and CAB formulations. Formulation A3 exhibited a controlled drug release spread over 12 h. Formulation A5 showed highest retardation, as it released 65% of drug by the end of 12 h which was not acceptable. The increase in plasticizer concentration showed increase in drug release initially. This may suggest that increasing plasticizer concentration may cause increase in film porosity and therefore increase the drug release. Similar observations of *in vitro* drug release were seen with CAB formulations, where B2, B4 and B6 showed relatively higher drug release. Formulation B5 showed better drug release with only 22.44 % drug being released at the end of 1 h and 73.57 % drug being released at the end of 12 h.

The dissolution data of different formulations is shown in Table 4. The dissolution of most formulations fitted well into the Higuchi model with regression coefficients that indicated the release of drug from the ocular films to be through a diffusion mechanism. The dissolution data were analyzed using Korsmeyer Peppas model. The values of diffusion coefficients were found to range from 0.29 to 0.45 for CA films and 0.18 to 0.47 for CAB films. Since values of diffusion exponent (n) were found to be less than 0.50, the mechanism of drug release from films was characterized as Fickian diffusion [4].

Table 3: Evaluation of CA and CAB ocular films

Formulation	Drug Content (mg)	Water vapour transmission rate (mg/hr)	Thickness (mm)	Tensile strength (kg/mm^2)
A1	0.981 ± 0.037	5.870 ± 0.005	0.066 ± 0.005	0.3169
A2	0.965 ± 0.013	3.395 ± 0.005	0.074 ± 0.005	0.3491
A3	1.011 ± 0.033	5.609 ± 0.005	0.100 ± 0.007	0.3438
A4	0.927 ± 0.005	7.770 ± 0.005	0.102 ± 0.004	0.3466
A5	0.979 ± 0.083	4.718 ± 0.005	0.114 ± 0.005	0.4305
A6	0.980 ± 0.031	4.814 ± 0.005	0.126 ± 0.005	0.4466
B1	0.964 ± 0.026	0.948 ± 0.029	0.074 ± 0.005	0.3111
B2	0.982 ± 0.036	1.013 ± 0.052	0.078 ± 0.005	0.3714
B3	0.989 ± 0.032	0.851 ± 0.034	0.108 ± 0.004	0.4292
B4	0.998 ± 0.027	0.942 ± 0.025	0.118 ± 0.004	0.4934
B5	0.996 ± 0.025	0.462 ± 0.042	0.124 ± 0.005	0.4166
B6	1.003 ± 0.016	0.744 ± 0.035	0.124 ± 0.005	0.4675

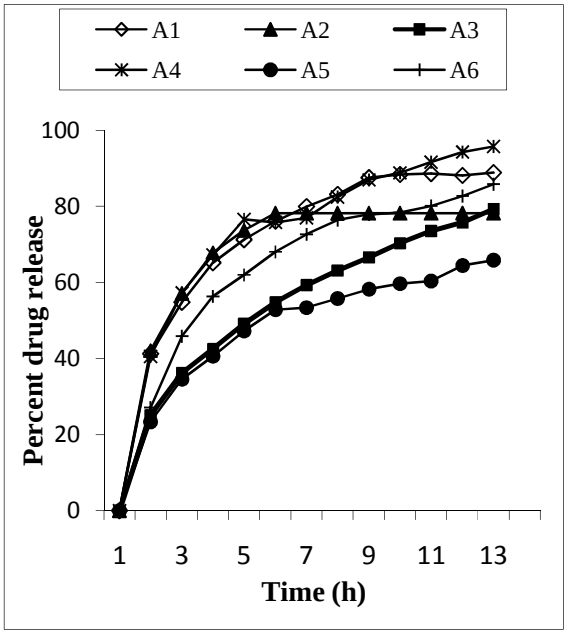

Figure 1: Dissolution profile of cellulose acetate formulations.

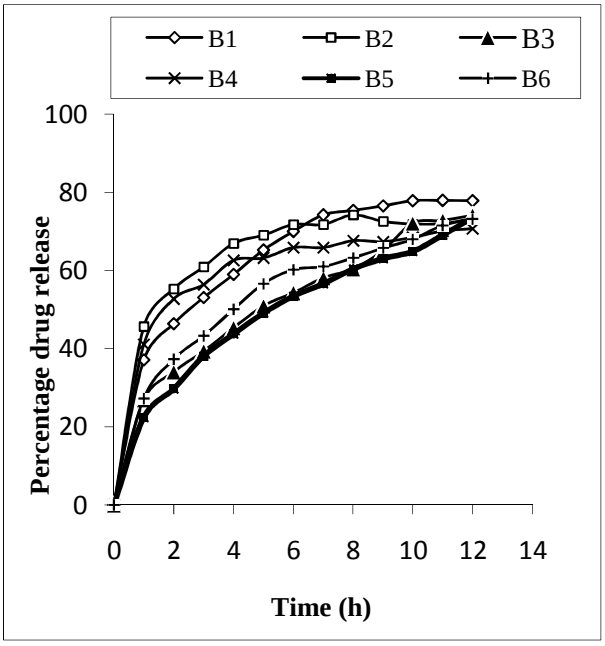

Figure 2: Dissolution profile of cellulose acetate butyrate formulations.

Table 4: Dissolution data treatment of CA and CAB based formulations

Batch	Zero order Kinetics		Higuchi's $t^{1/2}$		Korsmeyer Peppas Kinetics		
	K_0	r^2	K_H	r^2	n	r^2	K_m
A1	5.5599	0.7062	18.98	0.9223	0.3094	0.9627	1.6475
A2	5.6492	0.7052	19.115	0.9228	0.3043	0.9615	1.6614
A3	5.516	0.8874	21.59	0.9973	0.4543	0.9985	1.4138
A4	5.461	0.6859	18.105	0.9099	0.2911	0.9462	1.6677
A5	4.316	0.8002	16.053	0.9594	0.3953	0.9721	1.4088
A6	5.694	0.7809	21.44	0.9302	0.4234	0.9395	1.5067
B1	4.9958	0.7383	17.364	0.9452	0.3169	0.978	1.5792
B2	3.7949	0.5227	10.145	0.8102	0.185	0.9041	1.6892
B3	5.1739	0.8952	19.989	0.9932	0.4246	0.9923	1.4104
B4	3.7247	0.5668	10.395	0.8811	0.1998	0.9368	1.6485
B5	5.1134	0.9022	20.301	0.9962	0.4764	0.9971	1.3487
B6	4.8447	0.8233	18.082	0.9786	0.3914	0.9890	1.4533

The sterile inserts of A3 and B5 complied with the test for sterility as per the IP specifications. The results of *in vivo* studies showed 81.26% and 79.06% drug released at the end of 12 h for CA and CAB formulations respectively (Table 5). The *in vitro-in vivo* release correlation was carried out and the regression coefficient was found to be 0.9767 and 0.9007 for CA and CAB formulation respectively indicating good correlation between the *in vitro* and in *vivo* drug release. The stability studies indicated that there was no significant difference in drug content and percentage cumulative release initially and at the end of 6 weeks.

Table 5: *In vivo* drug release data of formulations A3 and B5

Time (h)	% Drug release			
	A3		B5	
	In vitro	*In vivo*	*In vitro*	*In vivo*
1	25.28 ± 4.75	23.85 ± 1.52	22.44 ± 0.77	31.25 ± 1.19
2	36.18 ± 3.11	38.44 ± 1.71	29.80 ± 0.66	51.00 ± 2.81
3	42.63 ± 5.02	53.73 ± 1.79	38.13 ± 1.03	59.83 ± 1.57
6	59.28 ± 5.97	67.79 ± 2.48	53.45 ± 2.81	66.08 ± 2.48
12	79.26 ± 4.84	81.26 ± 1.56	73.57 ± 2.97	79.06 ± 2.51

CONCLUSION

From the experiment conducted, it can be concluded that CAB and CA may be used as film forming agents especially for ocular drug delivery for better and sustained drug release. Both CA and CAB films showed good drug release for up to 12 h in selected formulations of chloramphenicol. From the evaluation results and appearance of films, it was found that CAB films were more suitable for designing drug loaded ocular inserts to provide sustained release of the drug in the ocular cavity.

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