Design and Evaluation of Polymeric Ocular Drug Delivery System for Controlled Release of Tetracycline HCl

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Ophthalmic inserts of tetracycline HCl were prepared as membrane permeation controlled devices with the aim of achieving once a day administration. Drug reservoir and rate controlling membrane were prepared using different hydrophilic polymers such as HPMC, MC, PVP (K-30) and hydrophobic ethyl cellulose respectively.The ocular inserts were evaluated for their physico chemical properties, *in vitro* kinetics, and *in vivo* release characteristics. Since, the targeted zero order mode of release was observed in formulation F6 (Drug reservoir with 2% HPMC and 4% EC as rate controlling membrane), its *in vivo* release characteristics were evaluated using rabbits as animal models. Influence of changes in polymer composition of films over physical and *in vitro* release characteristics were tested using statistical tools such as ANOVA and the Students t-test.The *in vitro* release kinetic data was treated according to diffusion models proposed by Higuchi and Peppas in order to access the mechanism of drug release.

Tetracycline HCl is a broad-spectrum antibacterial agent, which is one among the commonly employed drugs in the form of eye drops for the treatment conjunctivitis[1], blepharitis, and neonatal conjunctivitis[2] caused by *Neiseria gonorrhea*. In addition to the inherent draw backs in the conventional eye drop dosage form, the frequency of administration for more than eight times[2] a day are presumed to cause non compliance to drug therapy. In spite of the impetus for developing controlled release opthalmic devices for tetracycline HCl, only few designs have been developed and reported[3]. This study was targeted to design a new opthalmic delivery system[4] that may not only improve the efficiency of the therapy but also the patient compliance.

Tetracycline HCl was a gift sample obtained from Paris Dakner Ltd, Madurai. The polymers used were hydroxy propyl methyl cellulose (15 cps), methyl cellulose (40 cps), ethyl cellulose (20 cps) and polyvinyl pyrrolidone (K-30), which were purchased from S. D. Fine Chem., Boisar. All other chemicals used were of analytical grade and used as they were procured.

Drug reservoir containing 1 mg of drug was prepared by mercury casting technique using different hydrophilic polymers such as HPMC, MC, PVP K-30 using water as the casting solvent and glycerin as plasticizer (30 % w/w of polymer). Similarly, rate-controlling membrane was prepared using ethyl cellulose and dibutyl phthalate (30% w/w of polymer) as plasticizer and used for sealing drug reservoir on either sides[5].

The *in vitro* release characteristics of the ocular inserts were tested using bi chambered donor receiver compartment model[6]. The prepared ocuserts were evaluated for moisture absorbtion[8], moisture loss[8], thickness, weight variation, and drug content. Based on the amount and mode of drug release, formulation F6 (drug reservoir with 2 % HPMC and 4 % EC as rate controlling membrane), which showed maximum release in a concentration-independent manner, was studied for *in vivo* release characteristics[6] after being sterilized using ethylene oxide.

Percent moisture absorption studies revealed that the formulation F2 and formulation F7 have shown maximum and least moisture absorption respectively. While high moisture absorption capacity of hydrophilic HPMC, and the magnitude of resistance offered by EC due to its low concentration (4%, 6%) may be the causative factors for high or least moisture absorption

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values, the ability to retain the moisture within the matrix that depends on the nature of substitution in cellulose ether and extent of hindrance offered by hydrophobic ethyl cellulose played major role in determining moisture loss values.

Formulated to ensure the patient acceptability and avoid untoward changes in release pattern, all batches were found to have thickness of 0.38-0.47 mm with minimum intra batch variability, which was confirmed from coefficient of variance values. Drug content analysis data that revealed the uniformity of content by showing statistically insignificant values ($P>0.05$) along with thickness uniformity values not only affirmed the ability of the process to give films with uniform content but also confirmed the reproducibility of the process adopted.

In order to study the changes in the *in vitro* release characteristics due to the changes in concentration and nature of the polymers, the time taken by the delivery system to release 50% of the loaded drug and amount of drug released at the end of 12 h (Table 1) was statistically analyzed using ANOVA[11] at 95% significance level. All statistical evaluations were performed using EXCEL®-Version 6.0 (Microsoft Corporation, USA). One-way ANOVA, done by using $t_{50\%}$ values, revealed that the changes in concentration of EC in rate controlling membrane at every concentration of hydrophilic drug reservoir matrix were highly significant ($P<0.05$) than that caused by concentration of HPMC matrix. This fact was later confirmed by two-way ANOVA, done on total amount of drug release at 12 h, at 95% confidence levels. While statistically significant changes caused by increase in HPMC concentration can be attributed to the significant changes in matrix erodibility and swellability, changes in the slow dissolving and limited swellability properties of EC in different concentrations could have been the reasons for the significant impact in the release profiles.

Though plots drawn according to zero and first order kinetic order equations revealed the concentration independent mode of release, Higuchi's[12] and Peppas[13] diffusion models have been adopted to find the mechanism of release. Graphical best fit for the aforementioned models were drawn according to method of least squares. The least sum of residuals shown by all formulations to Peppas (log time-log drug release) equation and slope values above 0.89, affirmed that the release pattern was of super case II transport[14] (Table 1).

As the formulation F6 fulfilled many prerequisites of a once a day delivery system, it was selected as

TABLE 1: COMPOSITION AND PHYSICO CHEMICAL EVALUATION OF FORMULATIONS

Formulation code	Drug reservoir	Rate controlling membrane			%MA*	%ML*	Thickness* (mm)	Weight *(mg)	Drug content *(mg)
	EC	HPMC	PVP	MC					
F 1	6	4	—	—	8.33	7.11	0.342	24.05	0.992
F 2	4	4	—	—	10.41	8.33	0.338	21.24	0.988
F 3	6	3	—	—	7.03	9.34	0.324	20.54	1.004
F 4	4	3	—	—	7.05	9.82	0.322	20.32	0.991
F 5	6	2	—	—	5.26	10.14	0.292	22.44	1.023
F 6	4	2	—	—	6.18	11.37	0.285	22.41	1.015
F 7	6	—	—	1	5.05	6.42	0.292	17.35	0.989
F 8	4	—	—	1	8.11	6.82	0.274	16.41	1.016
F 9	6	3	1	—	8.59	9.01	0.311	16.82	1.034
F 10	4	3	1	—	9.26	9.94	0.339	20.28	0.995

F1 to F10 represent various formulations prepared using Hydroxy propyl Methyl cellulose (HPMC), Poly vinyl Pyrrolidone (PVP), Methyl cellulose (MC) and Ethyl Cellulose (EC). %MA and %ML indicates Percent moisture absorption and Percent moisture loss respectively. *Average of three determinations.

formulation of choice for *in vivo*[6] studies, which confirmed the ability of the formulation to release the drug in a concentration-independent manner in the biological environment with excellent *in vivo-in vitro* correlation (r=0.9995). Comparative results obtained from IR spectral analysis at pre and post sterilization conditions revealed that the drug remained chemically unchanged in sterilization conditions. Validity and authenticity of the sterilization procedure was confirmed by test for sterility, which yielded negative results for the presence of aerobic and fungal organisms.

Accelerated stability study performed at three different temperatures, 30, 40, and 50° for 4 w and the graphical data treatment using method proposed by Free and Blythe[15] indicated that the shelf life of the formulation will be 72 d if stored at ambient conditions. The shelf life predictions were made at 90% confidence levels.

In conclusion, these results indicate that formulation F6 (drug reservoir with 2 % HPMC and 4 % EC as rate controlling membrane) has achieved the targets of the present study such as increased residence time, prolong zero order release, reduction in frequency of administration, and thus may improve patient compliance.

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Postcoital Antifertility Activity of the Root of *Momordica dioica* Roxb

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Aqueous and ethanol extracts from the root of *Momordica dioica* Roxb. (Cucurbitaceae) were tested for postcoital antifertility activity in female rats. Both the extracts were found to be most effective in causing significant abortifacient activity. The extracts showed moderate estrogenic activity. Histological studies of the uterus were carried out to confirm estrogenic activity.

Momordica dioica Roxb. Ex. Willd. (Cucurbitaceae) is a perennial dioiceous climber with tuberous roots found throughout India[1]. The fruits are used to prevent inflammation caused by lizard excretion[2]. The whole plant is used for treatment of eye diseases, poisoning and

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