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Ophthalmic Inserts of Piroxicam: Development and *in vitro* Drug Release Studies

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With the limit-ations of conventional ocular preparations the aim of the present study was to formulate once a day piroxicam releasing ocular inserts and to study the drug release of piroxicam in different release media. Piroxicam films were made with cross-linked and non-cross-linked gelatin matrix and hence the effect of cross linking on drug release was also studied. Drug release was studied separately in distilled water, simulated tear fluid and phosphate buffered saline (pH 7.4) at 37 °C. The release rates of piroxicam from cross-linked (1, 4 and 8 h) formulations were slower than the non cross-linked formulation in all the three release media. Increasing the cross-linking time decreased the release rates. The overall release rates were similar in simulated tear fluid and phosphate buffered saline (pH 7.4), while it was lower in distilled water.

Key Words: Ophthalmic inserts, Piroxicam, Gelatin, Drug release studies.

INTRODUCTION

Most ophthalmic drugs are administered topically in the form of eye drops. Although convenient and inexpensive, this type of delivery system yields low therapeutic efficacy due to the dynamics of the lachrimal system (*i.e.*, blinking, lachrimal secretion and nasolachrimal drainage). The low efficacy necessitates more frequent administration to achieve the desired therapeutic effect. This can increase the frequency and severity of both ocular and systemic side effects. Therefore, it is necessary to develop safer, efficacious and more acceptable ocular delivery systems. Delivery systems that are capable of releasing the drug in a prolonged manner are of interest because they can improve the ocular residence time. An increase in ocular

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residence time maximizes the duration for topical or local action and also minimizes the systemic side effects. Additionally, a controlled release preparation requires fewer instillations and therefore will lead to increased patient compliance.

Ophthalmic inserts can be further categorized into non-biodegradable and biodegradable. The non-biodegradable inserts possess several drawbacks as irritation, difficulty in proper retention of the device in the cul-de-sac and the need for removal from the eye at the end of dosing. The use of biodegradable inserts is preferable because they obviate the need for the removal of the device from the eye at the end of dosing. Furthermore, they can be easily removed at anytime if desired. If these devices soften upon contact with tear fluid, they will be more comfortable and better retained in the cul-de-sac.

Gelatin, the chief protein component in the skin, bones and white connective tissues of the animal body, has both clinical and pharmaceutical uses. Gelatin is practically insoluble in acetone, chloroform, ethanol, ether and methanol and soluble in water[1]. This type of gelatin is used for controlled release of active substances. The cross-linking of gelatin matrix by chemical means (formaldehyde, glutaraldehyde) is used extensively and this cross linking process permanently reduces the solubility of gelatin. Considering its well-documented properties we have preferred to use gelatin as the degradable matrix in the present formulation.

Antiinflammatory drugs are desired for ophthalmic use to treat inflammation of the eye due to various infections and in the treatment of post-operative inflammation following cataract extraction and various surgical refractive procedures. Piroxicam, one of the most potent and better-tolerated non-steroidal antiinflammatory drugs (NSAIDs) has proved effective in the topical treatment of ocular inflammations as an alternative to topical antiinflammatory steroids[2]. A wider use of NSAIDs in ocular therapy is consequent to the well-recognised dangers associated with the use of corticosteroids[3,4]. To the best of our knowledge, very few piroxicam conventional ophthalmic formulations are available and no research reports the development of sustained local delivery of piroxicam. Therefore, the aim of the present study was to develop a piroxicam containing controlled-release ophthalmic insert formulation in a gelatin polymer matrix and to study the effect of cross linking in *in vitro* release of piroxicam from these inserts in various release media.

EXPERIMENTAL

Piroxicam was a gift sample from Cross Medineeds Pvt. Ltd., Chennai. All other ingredients used in the present study were of analytical grade or better.

Fabrication of piroxicam-loaded ocular inserts: The film was prepared by the solvent evaporation technique. 1 g Hydrolyzed gelatin matrix was dissolved in 9 mL distilled water. Then, 0.3 g glycerin was added and 100 mg piroxicam was dispersed in this solution. The mixture was poured on teflon plates (5.5 × 17 cm) and evaporated at 37 °C overnight. Gelatin matrix film containing 10 % piroxicam was formed. The film was then cut into a desired form (*ca.* 2 mg; 0.6 × 0.7 × 0.1 mm width, height, thickness, respectively). The degree of the protein matrix degradation was altered by cross-linking reaction using formaldehyde. For this purpose, some of the cut films were hardened with 10 % formaldehyde solution in isopropyl alcohol for 1, 4 and 8 h and then washed with acetone and dried at room temperature.

Percentage moisture absorption[5]: Percentage moisture absorption test was carried out to check the integrity of the inserts. Individual inserts were weighed and placed in a desiccator maintained at 79.50 % relative humidity using an excess amount of salt in solution. After 3 d the inserts were taken out and reweighed. Ten identical studies were conducted and the percentage moisture absorption was calculated using the formula

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss[5]: Percentage moisture loss was carried out to check the integrity of the inserts at dry conditions. Ten inserts from each was taken for study. Inserts were weighed individually and kept in a desiccator containing anhydrous calcium chloride. After 3 d, inserts were taken out and reweighed. Percentage moisture loss was calculated using the formula

$$\text{Moisture loss (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug release studies: The drug release studies were carried out with ocular inserts placed in 10 mL of dissolution media. 10 mL of distilled water, pH 7.4 phosphate buffered saline and simulated tear fluid were used individually as medium. Stoppered vials were left in incubator with temperatures maintained at 37 °C. Three milliliters aliquots of sample were assayed at pre-determined time intervals (distilled water: 0, 1, 2, 3, 4, 5, 6 and 24 h, phosphate buffered saline (pH 7.4): 0, 1, 2, 3, 4, 5, 6, 7 and 24 h, and simulated tear fluid: 0, 1, 2, 3, 4, 5, 6 and 7 h) for piroxicam by measuring the absorption peak at 333 nm on a UV-spectrophotometer. 6 Identical studies were carried out in parallel. The release profiles were plotted as a function of time in terms of percentages. The final released amount of piroxicam at the end of the 24 h observation period was considered as 100 % and the released amounts on other sampling time points were compared

with this 100 %. The release results of piroxicam were expressed as the arithmetic mean values of the six identical studies for each of the three release media. The Student t-test and the similarity tests were performed to compare all the release results with each other for each of the three different release media and also for each of the different hardening times. For the similarity test, the equation formula below was used and a similarity factor (f_2) greater than 50 was regarded as the sign of similarity[6].

$$f_2 = 50 \log \left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left(\overline{R}(t) - \overline{T}(t) \right)^2}{n}}} \right)$$

RESULTS AND DISCUSSION

Percentage moisture absorption and moisture loss: The results of percentage moisture absorption and moisture loss are as tabulated in Table-1. The highest percentage of moisture absorption and moisture loss was observed with non cross linked formulation. The least percentage was observed with 8 h cross linked formulation. This could be due to the cross linking process. As the time of cross linking increased the inserts became harder thereby the moisture absorption and loss was restricted.

TABLE-1
PERCENTAGE MOISTURE ABSORPTION AND MOISTURE LOSS

Formulation	Moisture absorption	Moisutre loss
Non cross linked	14.36 (± 0.20)	7.58 (± 0.03)
1 h	12.49 (± 0.39)	6.78 (± 0.12)
4 h	10.52 (± 0.69)	5.22 (± 0.15)
8 h	9.02 (± 0.35)	4.69 (± 0.20)

Mean values of ten identical studies.

Release of piroxicam in distilled water: The release of drug from various formulations in distilled water are given in Fig. 1. When the effects of cross-linking times on the release rate were compared by the similarity test, it was observed that the release rates of piroxicam from the cross-linked (1, 4 and 8 h) formulations were slower than the non-cross-linked formulation and according to the similarity test, their release profiles were

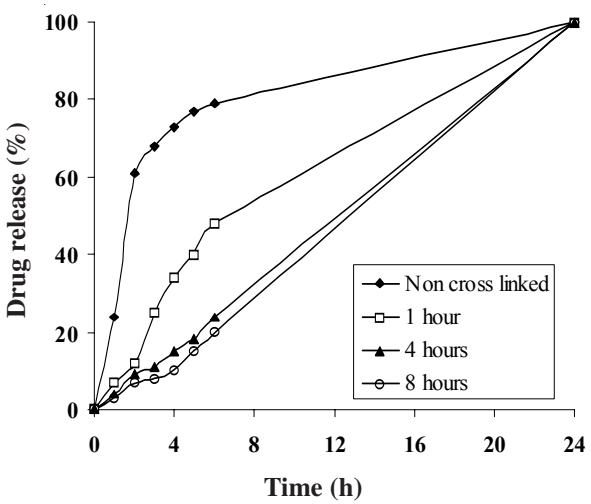

Fig 1. Release results of piroxicam in distilled water

not similar to the release profile of non cross linked formulation ($f_2 < 50$, $p > 0.05$). The effect of cross-linking times of 4 and 8 h on the release rate was found to be similar ($f_2 > 50$, $p < 0.05$) and they prolonged the release of piroxicam more effectively than 1 h cross-linking, which was not similar to these results ($f_2 < 50$, $p > 0.05$).

Release of piroxicam in simulated tear fluid: The release results in simulated tear fluid are given in Fig. 2. The non-cross-linked formulation released piroxicam faster than the cross linked formulations. The similarity test revealed that the release profiles of cross linked formulations (1, 4 and 8 h) were similar ($f_2 > 50$, $p < 0.05$).

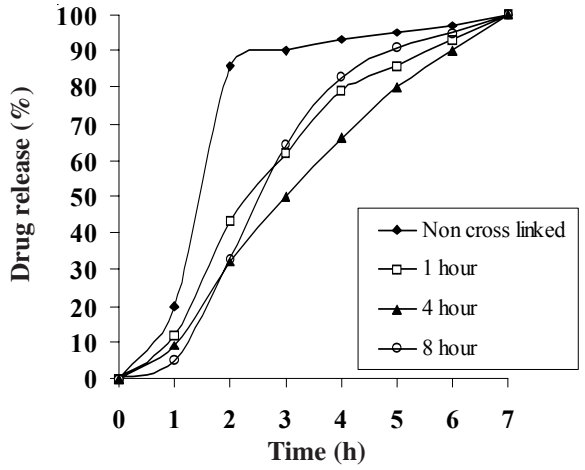

Fig. 2. Release results of piroxicam in simulated tear fluid

Release of piroxicam in phosphate buffered saline (pH 7.4): The release profiles of all formulations in phosphate buffered saline (pH 7.4) are shown in Fig. 3. The similarity test showed that the release profiles of hardened formulations (1, 4 and 8 h) were similar to each other ($f_2 > 50$, $p < 0.05$). The release of piroxicam from the non cross linked formulation was more rapid than the cross linked formulations ($f_2 < 50$, $p > 0.05$).

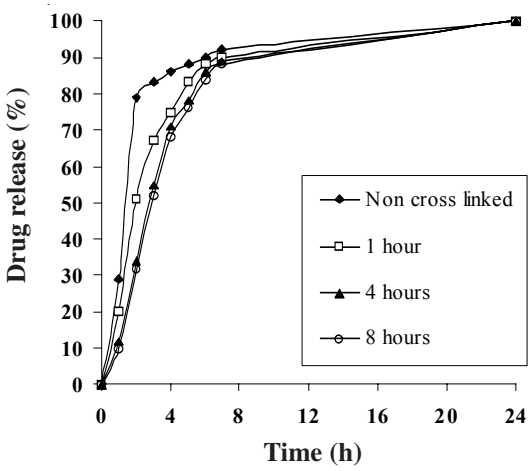

Fig. 3. Release results of piroxicam in phosphate buffered saline (pH 7.4)

The effects of release media on the release rate of piroxicam were also evaluated. All the release profiles (non-cross-linked, 1, 4 and 8 h cross linked) observed in simulated tear fluid and phosphate buffered saline (pH 7.4) were found to be similar according to the similarity test. The release of piroxicam in distilled water was slower than the other two release media.

The release profiles of all formulations were in accordance with the first-order kinetic model[7] and their release rates were calculated and found to be as given in Table-2. The fastest release rates were obtained from the non cross linked formulations. The release rates were decreased by increasing the hardening time. The lowest release rate was observed in distilled water because of the low solubility of piroxicam.

Giunchedi *et al.*[8] have reported the study of piroxicam releasing pectin microspheres. The pectin formulation reported in previous study had released 90-100 % of piroxicam within 2 h, while all the formulations employed in this study maintained their release for much better time periods. On the other hand, even with the fastest release profiles observed with phosphate buffered saline (pH 7.4) medium, 90 % drug release was observed from non cross linked gelatin inserts only by 7 h. When these two piroxicam-containing formulations are compared (pectin microspheres *vs.*

TABLE-2
RELEASE RATES (h^{-1}) OF PIROXICAM IN DISTILLED WATER, SIMULATED TEAR FLUID AND pH 7.4 PHOSPHATE BUFFERED SALINE

Cross-linking time	Distilled water	Simulated tear fluid	Phosphate buffered saline (pH 7.4)
Non cross-linked	0.220	1.238	0.336
1 h	0.128	1.050	0.368
4 h	0.049	0.627	0.395
8 h	0.044	0.521	0.422

Mean values of six identical studies.

gelatin inserts), it is quite clear that the release of piroxicam from the gelatin inserts were much more promising than the release from the pectin microspheres.

However, better judgment on the suitability of the delivery system can be made only after conducting *in vivo* release studies in animal models using these piroxicam delivery systems. The present studies are only in the elementary stage and these formulations may be improved by further laboratory work.

At present, the authors are working on different formulations including different matrix polymers and different rates of drug content to improve the release profile of piroxicam.

Conclusion

A local drug delivery device consists of a drug reservoir and a limiting element that controls the rate of drug release. This study was performed to develop a controlled-release formulation of piroxicam to be used in the ocular pocket and study the effect of cross linking and various media on drug release. Furthermore, the physical characteristics and working properties of the delivery system may influence the degree of acceptance by the professional community as well as the patient population. The present study indicates that a selective COX-2 inhibitor, piroxicam, shows a sustained rate of drug release from gelatin matrix over extended periods of time.

It was observed that cross-linked gelatin matrix is a convenient inert material for obtaining a prolonged drug release. The cross linking time has an effect on moisture absorption, moisture loss and drug release rates. While release media also have significant impact on drug release rates. The optimal dosage of the active agent is another critical issue that needs to be determined by further studies. Piroxicam is a selective COX-2 inhibitor and as yet, there exists no local delivery product of piroxicam in the market. COX-2 represents a valid pharmacologic target for the treatment and control of ophthalmic inflammation and therefore, further *in vitro* and *in vivo* studies shall be performed before starting clinical application of this formulation.

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