ORIGINAL ARTICLE

In Vitro Corneal Permeation of Etoricoxib from Oil Drops

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Abstract

Introduction: Topical administration of drugs is the most favored route for management of ocular inflammation as it provides higher ocular drug concentrations, keeping away the systemic side effects associated with the oral administration. *In vitro* transcorneal permeation of etoricoxib from oil, drops were studied using freshly excised goat cornea. **Materials and Methods:** Based on solubility of etoricoxib in several oils, formulations were well prepared (0.5% w/v in arachis, castor, mustard, olive, and sesame and 1.0% w/v in arachis, castor, and sesame oil) with or without benzyl alcohol (0.5% v/v) as a preservative. Permeation studies were conducted using all-glass modified Franz diffusion cell, and the drug permeation in receptor was measured by spectrophotometer at 234 nm, after 120 min. **Results and Discussion:** Raising drug concentration from 0.5% to 1.0% w/v increased permeation. The maximum corneal permeation was obtained with 1.0% (w/v) etoricoxib drops in sesame oil with benzyl alcohol, while minimum from 0.5% (w/v) formulation in castor oil without benzyl alcohol. Corneal hydration obtained with all the formulations were between 75% and 80% indicating no corneal damage except in castor oil with benzyl alcohol. The saturation solubility of etoricoxib in sesame oil at 4°C is 1.128% (w/v). **Conclusion:** Etoricoxib 1.0% (w/v) drops in sesame oil containing 0.5% (v/v) and benzyl alcohol showed maximum permeation (0.057 mg or 0.553%).

Key words: Corneal hydration, etoricoxib, oil drop, permeation

INTRODUCTION

Drug delivery to the eye is one of the most exciting and testing errand confronting the pharmaceutical researcher. The structures, physiology, and natural chemistry of the eye make this organ impeccably impermeable to remote substance. The challenge to the formulator is to evade the defensive boundaries of the eye without causing perpetual tissue harm. Topical administration of drugs is the most favored route for management of ocular inflammation as it provides higher ocular drug concentrations, keeping away the systemic side effects associated with the oral administration. Corticosteroids used to be the mainstay of topical therapy in the management of ocular inflammations.[1] Their use is associated with an increase in intraocular pressure, cataract formation, and risk of infections.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin,[3] flurbiprofen,[4] ketorolac, [5] and diclofenac [6] have been observed to be viable alternatives to corticosteroids in the management of ocular inflammation.

NSAIDs are potent inhibitors of cyclooxygenase-2 (COX-2) enzymes and thereby the synthesis of all downstream prostaglandins (PGs). Within the eye, PGs disrupt the blood-ocular barrier, increase vasodilation, and facilitate leukocyte migration. Consequently, topical formulations of NSAIDs have been shown in several well-designed clinical studies to reduce intraocular inflammation and macular edema after cataract and vitreoretinal surgery.[7-9] Etoricoxib, chemically 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl) pyridine, is a selective COX-2

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enzymes inhibitor. It is used for the treatment of osteoarthritis, rheumatoid arthritis, and management of pain. The pKa of etoricoxib is 4.6 and has low aqueous solubility. The drug exhibits pH-dependent solubility (i.e. high solubility in gastric media [low pH] and decreasing solubility with increasing pH).[10] The therapeutic efficacy of a topical formulation depends on its composition and the physicochemical properties of the vehicle. Use of an appropriate vehicle is critical to increasing the optimal efficacy of the pharmacologically active drugs.[11] Commonly, all the ophthalmic formulations have been administered to the eye as aqueous solutions. About 90% of the dose applied topically from such solutions is lost due to precorneal losses (nasolacrimal drainage) and tearing results in poor availability as contact time is less between drug and ocular tissue.[12] Majority of active components are lipophilic in nature, namely cyclosporine, ketorolac, and diclofenac. Both problems can be overcome by selecting an appropriate vehicle. The time-honored approach to overcome this has been through prolonging the ocular contact time of the medication. An increased ocular contact time of the drug may be achieved by formulating the drug as an oil solution. Several vegetable oils such as olive, sunflower, castor, and sesame oil have been used as a vehicle for oil-based drops to improve ocular drug delivery.[13,14] Earlier studies with pilocarpine,[15] tetracycline,[16] and ketorolac [17] revealed the higher ocular availability of drugs from oily solutions. However, no such information is available on corneal permeation of etoricoxib from oily solution. In the present study, the corneal permeation of etoricoxib from oily solutions was investigated.

MATERIALS AND METHODS

Materials

Etoricoxib (purity 99.6% w/w) was obtained as a gift sample from Cadila Healthcare Limited, India. Refined food grade vegetable oils used in the experiment were arachis (Adani Wilmar Limited, Ahmedabad, India), castor (Arora and Company, New Delhi, India), olive (Rajesh Chemicals Co., Mumbai, India), sunflower (Rajesh Chemicals Co. Mumbai, India), mustard (National Diary Development Board, Gujarat, India), and sesame oils (Tilsona, Recon oil Industries Pvt. Limited, New Delhi, India). All other chemicals purchased were of analytical grade and were used as received. Fresh whole goat eye was obtained from a local butcher shop (Berhampur, Odisha, India).

Methods

Solubility of etoricoxib in oil

An excess amount of etoricoxib was added to oils to prepare a saturated solution at 50°C. The solution of etoricoxib in oils was then cooled and left overnight at 4°C. The solution was subsequently centrifuged at 4°C at 5000 rpm (Remi Equipments Ltd., Mumbai, India). The etoricoxib oil solution (10 mL) was subjected to five successive extractions with 10 mL of 0.1N HCl solution (pH 1.2). The aqueous phases were pooled, filtered, and volume was made up to 100 mL using 0.1N HCl solution (pH 1.2). The extract was analyzed for etoricoxib at 234 nm using ultraviolet (UV)-visible spectrophotometer (1800 Shimadzu, Kyoto, Japan).

Preparation of oily formulations

The concentration of etoricoxib in test solutions was based on the solubility of the drug in different oils. The required amount of etoricoxib was dissolved in oily vehicles to give etoricoxib (0.5% w/v) solution in arachis, castor, mustard, olive, sesame, and sunflower oil and etoricoxib (1.0% w/v) oily solutions in arachis, castor, and sesame oils. Etoricoxib oily formulations containing preservative: Etoricoxib oily formulations were prepared in the same concentrations as mentioned above in the different oils, and benzyl alcohol (0.5% v/v) was added as a preservative.

Partition behavior study

Equal volumes of etoricoxib oil formulation with or without benzyl alcohol and phosphate buffer (pH 7.4) were shaken for 2 h at 37°C in a mechanical shaker at 200 rpm (Remi industries Ltd, Mumbai, India). The concentration of the drug in the aqueous phase was analyzed and the partition coefficient was calculated. The partition coefficient represents the ratio of etoricoxib distribution between oil and the aqueous phase. The experiment was done in triplicate and results were expressed as mean ± SD.

Measurement of viscosity

The viscosity of oils was determined by Brookfield DV-1þ viscometer (Brookfield Engineering Laboratories, Middle Dobro, MA) at 25°C using spindle 4 at 30 rpm.

Permeation study

The freshly excised cornea was fixed between clamped donor and receptor compartments of an all-glass modified Franz diffusion cell in such a way that its epithelial surface confronted the donor compartment. The corneal area available for diffusion was 0.64 cm^2. The receptor compartment was filled with 10 mL of freshly prepared bicarbonate ringer solution (pH 7.2), and all air bubbles were expelled from the compartment. An aliquot (1 mL) of oil drop formulation was placed on the cornea, and the opening of the donor cell was sealed with a glass cover slip; receptor fluid was kept at 37°C with constant stirring using a Teflon-coated magnetic stir bead. Permeation study was continued for 120 min, and samples were withdrawn from the receptor and analyzed for etoricoxib at 234 nm using UV-visible spectrophotometer (1800 Shimadzu, Kyoto, Japan). Results were expressed as amount permeated and percentage permeation or *in vitro* ocular availability. The permeation (%) or *in vitro* ocular availability was calculated as follows:

$$\text{Permeation} = \frac{\text{Amount of drug permeated in receptor}}{\text{Initial amount of drug in donor}} \times 100 \quad (1)$$

Corneal hydration (%)

At the end of the experiment, each cornea (freed from adhering sclera) was weighed, soaked in 1 mL methanol, dried overnight at 90°C, and reweighed. The percentage corneal hydration level (%) was calculated by the formula,

$$\text{Corneal hydration} = \frac{\text{Initial weight} - \text{Finalweight}}{\text{Initialweight}} \times 100 \quad (2)$$

The study was planned with paired corneas to avoid biological variations, i.e. one cornea of an animal received formulation without benzyl alcohol while the contralateral cornea received formulation with benzyl alcohol.

Statistical analysis

Statistical analysis was done by one-way analysis of variance (ANOVA) followed by Dunnett's test using Graph Pad Prism 5 software (GraphPad Software Inc., San Diego CA). Paired t-test was used for studies with the paired cornea. $P < 0.05$ was considered significant.

RESULTS AND DISCUSSION

The most convenient way of delivering the drug to the eye is topical application of an aqueous solution. Topically applied drug enters into the aqueous humor by partitions through the corneal epithelium, stroma and endothelium. One principal demerit of topically applied aqueous drug solution is the loss of drug due to drainage which results in the lower ocular availability of drug and a therapeutic effect of shorter duration. One way of overcoming the problem is to apply the drug in the form of an oily solution. In earlier studies, different oily vehicles such as olive, castor, and sesame oil for ocular delivery have been used for improving the delivery of poorly soluble drugs.[14,18] In healthy subjects, pilocarpine dissolved in castor oil has shown greater degree and duration of effect on the pupil compared with an aqueous solution. Statistically, significant drug effects have been noticed as long as 24 h after administration of oil-based drops.[19] Etoricoxib is poorly soluble in water. Keeping this fact in view, oil drops of etoricoxib were formulated in different vegetable oils. The concentration of etoricoxib in the oil drops was decided on the basis of saturation solubility in the respective oils. The solubility of etoricoxib in different vegetable oils was found to be between 0.675% and 1.762% w/v.

Table 1 shows the solubility of etoricoxib in different oils and its partition characteristics. Solubility was measured at 4°C. Etoricoxib was found to have maximum solubility (%w/v) in castor oil (1.762), followed by arachis (1.189), sesame (1.128), olive (0.983), sunflower (0.705), and mustard oil (0.675). The partition coefficient of etoricoxib between oil and phosphate buffer (pH 7.4) was also found to be maximum with castor oil, followed by arachis oil, while the minimum partition coefficient was observed with sesame oil. Addition of benzyl alcohol significantly ($P < 0.05$) reduced the partition coefficient value of etoricoxib from all the oils.

Table 2 presents the permeation characteristics of etoricoxib from 0.5% (w/v) oil solutions with or without benzyl alcohol through excised goat corneas (paired). Amount of etoricoxib permeated or percentage permeation was found to be maximum with sesame oil drop (0.049 mg and 0.91%) followed by mustard oil drop and minimum with castor oil (0.02 mg and 0.41%).

On comparing the permeation of etoricoxib from castor oil with other oils, it was observed that significantly ($P < 0.05$) higher permeability of etoricoxib was provided by arachis, mustard, olive, and sunflower oils with sesame oil the

Table 1: Solubility of etoricoxib in different oils and its partition characteristics from oil drops (0.5% w/v) with and without benzyl alcohol (0.5% v/v)

Oil	Solubility (% w/v)	Partition coefficient		Viscosity
		Without BA	With BA	
Arachis	1.189±0.017	1.635±0.136†	1.601±0.037*‡	54.3
Castor	1.762±0.001	1.725±0.034†	1.574±0.035*‡	625
Mustard	0.675±0.03	1.258±0.02†	1.193±0.01*‡	44.45
Olive	0.983±0.002	1.52±0.2†	1.373±0.006*‡	48.68
Sesame	1.128±0.004	1.203±0.021	1.048±0.02‡	47.7
Sunflower	0.705±0.013	1.284±0.07†	1.203±0.03*‡	41.0

Values are mean±SD (n=3), †Statistically significant ($P<0.05$) compared with sesame oil (0.5%w/v) without benzyl alcohol, as determined by 1-way Analysis of variance (ANOVA) followed by Dunnett's test, *Statistically significant ($P<0.05$) compared with sesame oil (0.5%w/v) with benzyl alcohol, as determined by one-way ANOVA followed by Dunnett's test, ‡ Statistically significant ($P<0.05$) compared without BA, as determined by one-way analysis of variance followed by Dunnett's test

maximum and castor oil with the minimum permeation. This could be attributed to the higher partitioning of etoricoxib in castor oils and lower partitioning in sesame oil. Earlier studies with ketorolac[20] also reported less permeation of drug from castor oil-based drops and higher permeation from sesame oil formulation.

Benzyl alcohol, a commonly used preservative, was added to oil formulations at 0.5% (v/v) concentration. The addition of benzyl alcohol to oil drops resulted in increased permeation of etoricoxib from all the formulations compared with the formulations without the preservative. This could be due to the higher partitioning of the drug from the oil to the aqueous phase in the presence of benzyl alcohol. The corneal hydration level of the normal mammalian cornea is between 75% and 80%.[20] Corneal hydration after permeation was found to be in acceptable range with all the oil drops except castor, mustard and olive oils.

Table 3 shows the corneal permeation of etoricoxib oil drops (1.0% w/v) with and without benzyl alcohol through excised goat cornea (paired). As compared to castor oil; mustard, olive, and sesame showed significant ($P < 0.05$) higher amount of drug permeated or percentage permeation. Maximum etoricoxib permeated or percentage permeation was observed with sesame oil drop (0.057 mg and 0.553%) with benzyl alcohol, while minimum with castor oil (0.029 mg and 0.247%) without benzyl alcohol. Addition of benzyl alcohol increased etoricoxib permeation from all the formulations as compared to formulations without benzyl alcohol. Corneal hydration was found to be in acceptable range with all the oil drops.

Table 4 shows the effects of drug concentration on the corneal permeation of etoricoxib. Increasing etoricoxib concentration in arachis, castor, and sesame oils from 0.5% to 1.0% (w/v) resulted in a significant ($P < 0.05$) increase in drug permeation. Further, the use of higher drug concentrations was associated with higher corneal hydration levels. The addition of benzyl alcohol significantly ($P < 0.05$) increased drug permeation compared with formulation without the preservative. The formulations containing 1.0% (w/v) drug and benzyl alcohol increased corneal hydration but within the acceptable range. Among all the formulations [Figure 1], etoricoxib 1.0% (w/v) drops in sesame oil containing 0.5% (v/v) benzyl alcohol showed maximum permeation with a corneal hydration of 79.72%, which shows no corneal damage.

The saturation solubility of etoricoxib in sesame oil at 4˚C is 1.128% (w/v) [Table 1]. Hence, etoricoxib 1.0% (w/v)

Table 2: Permeation characteristics of etoricoxib from oil drops (0.5% w/v) with and without benzyl alcohol (0.5% v/v) through excised goat cornea (Paired)

Oils	Without benzyl alcohol			With benzyl alcohol		
	Amount permeated (mg)	Permeation (%)	Corneal hydration (%)	Amount permeated (mg)	Permeation (%)	Corneal hydration (%)
Arachis	0.024±0.05†	0.601±0.017	76.523±0.242	0.036±0.017*‡	0.646±0.079	79.423±0.433
Castor	0.02±0.091	0.419±0.019	76.754±0.102	0.028±0.005‡	0.572±0.01	80.519±0.432
Mustard	0.033±0.08†	0.676±00.016	79.422±0.364	0.036±0.002*‡	0.71±0.052	82.457±0.323
Olive	0.032±0.001†	0.64±0.037	78.848±0.348	0.034±0.049*‡	0.683±0.008	80.223±0.235
Sesame	0.044±0.02†	0.861±0.044	76.064±0.038	0.049±0.001*‡	0.911±0.021	79.077±0.134
Sunflower	0.029±0.004†	0.591±0.0832	79.302±0.094	0.031±0.002*‡	0.627±0.058	79.552±0.423

Values are mean±SD (n=3), †Statistically significant ($P<0.05$) compared with castor oil (0.5%w/v) without BA, as determined by one-way ANOVA followed by Dunnett's test, *Statistically significant ($P<0.05$) compared with castor oil (0.5%w/v) with BA, as determined by one-way ANOVA followed by Dunnett's test, ‡Statistically significant ($P<0.05$) compared without BA, as determined by one-way ANOVA followed by Dunnett's test. ANOVA: Analysis of variance

Table 3: Permeation characteristics of etoricoxib from oil drops (1.0% w/v) with and without benzyl alcohol (0.5% v/v) through excised goat cornea (Paired)

Oil	Without benzyl alcohol			With benzyl alcohol		
	Amount permeated (mg)	Permeation (%)	Hydration (%)	Amount permeated (mg)	Permeation (%)	Hydration (%)
Arachis	0.038±0.063†	0.388±0.063	79.883±0.08	0.041±0.065*‡	0.396±0.069	80.859±0.306
Castor	0.029±0.08	0.247±0.005	80.071±0.31	0.034±0.032‡	0.269±0.011	80.92±0.421
Sesame	0.048±0.002†	0.432±0.029	76.557±0.28	0.057±0.008*‡	0.553±0.082	79.729±0.282

Values are mean±SD (n=3) †Statistically significant ($P<0.05$) compared with castor oil (0.5%w/v) without BA, as determined by one-way Analysis of variance (ANOVA) followed by Dunnett's test, *Statistically significant ($P<0.05$) compared with castor oil (0.5%w/v) with BA, as determined by one-way ANOVA followed by Dunnett's test, ‡ Statistically significant ($P<0.05$) compared without BA, as determined by one-way ANOVA followed by Dunnett's test, ANOVA; Analysis of variance

Table 4: Permeation of etoricoxib from 0.5% and 1% w/v oil drops

Oils	Drug conc. (% w/v)	Without benzyl alcohol			With benzyl alcohol		
		Amount permeated (mg)	% Permeation	% Hydration	Amount permeated (mg)	% Permeation	% Hydration
Arachis	0.5	0.024±0.05	0.601±0.017	76.523±0.242	0.036±0.017‡	0.646±0.079	79.423±0.433
	1.0	0.038±0.063†	0.388±0.063	79.883±0.08	0.041±0.065‡	0.396±0.069	80.859±0.306
Castor	0.5	0.02±0.091	0.419±0.019	80.071±0.31	0.028±0.005‡	0.572±0.01	80.519±0.432
	1.0	0.029±0.08†	0.247±0.005	76.754±0.102	0.034±0.032‡	0.269±0.011	80.92±0.421
Sesame	0.5	0.044±0.02	0.861±0.044	76.064±0.038	0.049±0.001‡	0.911±0.021	79.077±0.134
	1.0	0.048±0.002†	0.432±0.029	76.557±0.28	0.057±0.008‡	0.553±0.082	79.729±0.282

Values are mean±SD (n=3), †Statistically significant ($P<0.05$) compared with castor oil (0.5%w/v) without BA, as determined by one-way ANOVA followed by Dunnett's test, ‡ Statistically significant ($P<0.05$) compared without BA, as determined by one-way ANOVA followed by Dunnett's test, ANOVA: Analysis of variance

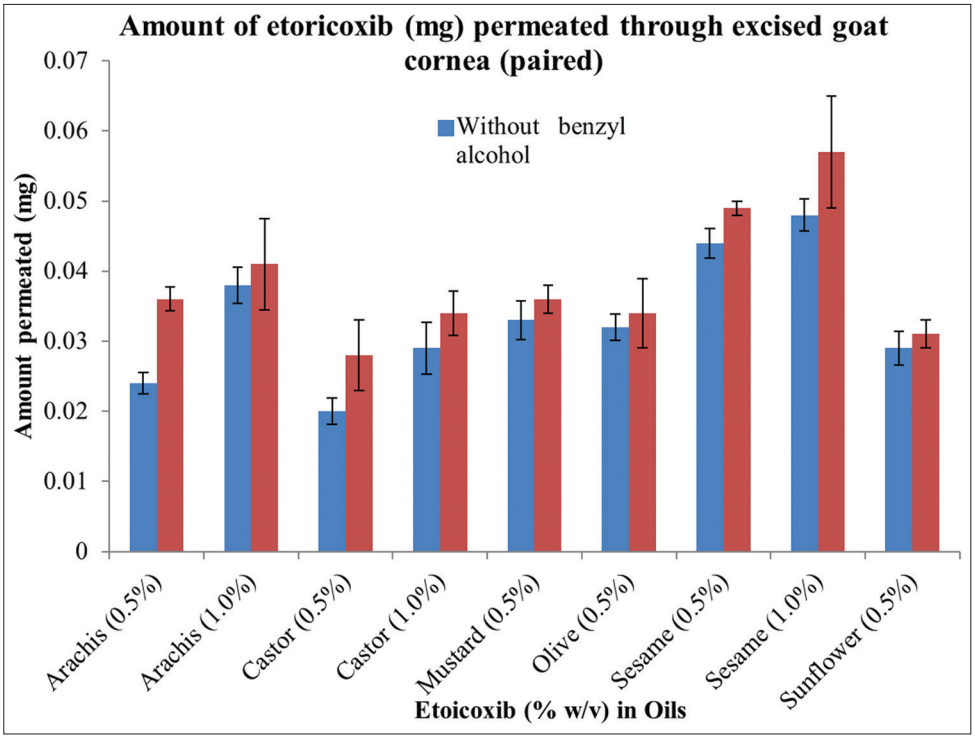

Figure 1: Effects of drug concentration on corneal permeation of etoricoxib from oil drops with and without benzyl alcohol (0.5% v/v) through excised goat cornea (Paired)

solution in sesame oil, being below the saturation level, will not precipitate at 4°C and the chances of crystallization of etoricoxib from the solution due to climatic change leading to physical instability appear to be remote. Permeation studies of oil drops with or without benzyl alcohol were conducted with paired corneas, i.e., one cornea of an animal received formulation without benzyl alcohol while the contralateral cornea received formulation with benzyl alcohol, to avoid biological variation.[21] The results suggest that the addition of benzyl alcohol to etoricoxib oil drops increases the permeation of etoricoxib from all drops. To ascertain the reason, partition characteristics of etoricoxib between oil and aqueous phosphate buffer (pH 7.4) were evaluated. The results indicated lower partitioning of etoricoxib in the oil phase in the presence of benzyl alcohol [Table 1] which means that there would be greater tendencies for the drug to enter the aqueous phase from oil drops containing benzyl alcohol compared with drops without the preservative. It would be appropriate to mention here that in oil solutions the release rate of a drug is determined by partitioning of the drug out of the oil in the surrounding aqueous medium.[22] The partitioning phenomenon is an equilibrium process described by the apparent oil/water partition coefficient (K=C0/CW, where C0 is the concentration of drug in the organic phase in equilibrium and CW is the concentration of the drug in the aqueous phase in equilibrium). Only the fraction of the total drug concentration which is present in the aqueous phase, f, could be absorbed.

$$f = 1+a/1+Ka \quad (3)$$

Where K is the apparent oil/water partition coefficient and "a" is the ratio Vo/Vw, the volume of the oil phase to that of the aqueous phase. The equation indicates that the fraction of drug available for absorption is controlled by the partition coefficient and the ratio of the volumes of the two phases (a) and that it remains constant as long as a is constant. Since Vw is a physiologic parameter, it is usually constant, and therefore the value of "a" is determined solely by the volume of the oil phase. The rate of drug absorption is described by Equation 4

$$d(C)/dt = Ka.f.(Dt) \quad (4)$$

Where Dt is the total drug concentration in both phases and Ka is the absorption rate constant. The above discussion suggests that the rate of absorption of the drug from the oil solution would depend on f, which, in turn, depends on the partition coefficient (K). The partition coefficients of etoricoxib between the oils and aqueous phase (phosphate buffer, pH 7.4) were higher compared with the K values obtained with oil with benzyl alcohol/buffer. Equation 3 indicates that the higher the values of the partition coefficient, the smaller the fraction of drug in the aqueous phase, f, and the slower the rate of absorption (from Eq.4). Thus, theoretically, corneal permeation of etoricoxib from oil drops without benzyl alcohol should be less than drops containing the preservative. The results of our permeation studies confirm this, and permeation of the drug from oil drops without benzyl alcohol was less. Thus, the results of the permeation experiments correlate well with the partition characteristics of etoricoxib.

CONCLUSION

On the basis of the present study, it can be concluded that etoricoxib 1.0% (w/v) solution in sesame oil provides the maximum *in vitro* permeation through goat cornea while the formulation in castor oil provides minimum permeation. The presence of benzyl alcohol to oil drops increases drug permeation due to an increased partitioning of the drug in the aqueous phase. The solubility of etoricoxib was found to maximum (% w/v) in arachis oil (1.762) followed by arachis (1.189) and sesame oil (1.128). In the rest of the oils such as mustard, olive, and sunflower oil, the solubility was between 0.675% and 0.983%. However, drug permeation from 0.5% to 1.0% (w/v) etoricoxib drops in arachis, castor, mustard, olive, and sunflower oil or 0.5% (w/v) drops in sesame oil is less than that observed with 1.0% (w/v) sesame oil drops. Among all the formulations, etoricoxib 1.0% (w/v) drops in sesame oil containing 0.5% (v/v) benzyl alcohol showed maximum permeation (0.057 mg or 0.553%). The formulation showed corneal hydration of 79.72%, which is in the acceptable range. Hence, there will not be any corneal damage. The saturation solubility of etoricoxib in sesame oil at 4°C is 1.128% (w/v) [Table 1]. Hence, etoricoxib 1.0% (w/v) solution in sesame oil, being below the saturation level, will not precipitate at 4°C and the chances of crystallization of etoricoxib from the solution due to climatic change leading to physical instability appear to be remote.

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