Investigation of an Ocular Irritation Threshold for Leachables and Impurities in Pharmaceutical Products

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Introduction

Low levels of degradant and leachable impurities are sometimes found in ophthalmic drug products due to the solution/suspension formulation of the product, the container system, and/or the secondary packaging. There are currently no official Regulatory guidance documents on how to manage extractables and leachables for ophthalmic products. However, the US FDA has previously presented concentrations of 1, 10 and 20 ppm as an internal starting point for reporting, identification and qualification thresholds, respectively (Ng, 2011). Data supporting the 20 ppm qualification threshold is currently not available in the public domain.

In contrast to systemically administered drugs, the primary toxicity endpoints of concern for non-carcinogenic leachables from topical ophthalmic products are local effects including ocular irritation/safety and sensitization. However, if a leachable is identified in an ophthalmic drug product, there is often a paucity of information on safety/ocular irritancy potential of the chemical at relevant concentrations.

Therefore to address this, in these studies, the potential to establish a threshold for ocular irritation is investigated. To do this, relevant chemical classes for irritation, were identified and from each class, chemical(s) which have demonstrated the greatest irritation potential were selected for evaluation. The identified chemicals were then tested for ocular irritancy potential in rabbits in multi-dose studies at concentrations of 20 ppm and 100 ppm (5-fold safety factor).

Selection of test compounds

The compounds selected are described in Table 1. Nine chemical classes were identified as likely either to be found as an impurity, or as representatives of classes known to be severe ocular irritants. Out of these classes the most severely irritating representative, or the representative demonstrating the highest irritation potential at the lowest concentration, was chosen for evaluation. Where possible, an established Draize score was used as the criteria to determine severity; however other information was taken into account as appropriate.

Experimental

Each chemical for test was formulated to 20 ppm and 100 ppm concentrations. Where appropriate the vehicle was phosphate buffered saline (PBS). For chemicals insoluble in PBS, cottonseed oil was used as the vehicle. In each case, the vehicle was also used as the control solution in the contralateral eye of the rabbit. Each chemical was evaluated first at 20 ppm, and then proceeded only to 100 ppm if there was no evidence of irritation.

All rabbit studies were conducted by the Moog Medical Device Group (Rush, NY). Adult New Zealand White rabbits with clinically normal eyes were weighed prior to treatment initiation on Day 1 and Day 3. The rabbits' eyes were examined by the McDonald-Shadduck method using a slit lamp and fluorescein stain before study initiation. Eyes were also macroscopically examined and scored before study initiation using the Draize Method.

A preliminary study was conducted to evaluate the tolerability of cottonseed oil in the rabbit eye (data not shown). It was determined that cottonseed oil resulted in mild redness to the palpebral conjunctiva when dosed six times daily. As a result of this, all chemicals which used cottonseed oil as a vehicle (2-chloroethyl acrylate, p-toluenesulfonyl chloride, 2,4-di-tert-butylphenol) were dosed only four times daily in order to eliminate the inherent irritation to the palpebral conjunctiva caused by this particular vehicle. The remaining chemicals were dosed six times daily.

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Table 1 Chemical Classes and Representative Selection

Selected Class of Chemical	Reason for selection	Chemical Representative	Known irritation level
Acids	Hydrolysis products; corrosive effects	Lactic Acid	Corneal irritation (neat) = 80/80 Draize score
Acrylates	Major source of extractables/leachables; Common in curing and resins	2- chloroethyl acrylate	Corneal irritation (neat) = 9/10 (Smyth et al 1951)
Acyl Halides	Highly reactive intermediates used in chemical synthesis; known lachrymators	p-toluenesulfonyl chloride	Serious eye damage (Category 1 as per GHS)
Alcohols	Solvents; Common degradation products	1-Hexanol 2,4-di-tert-butylphenol	Modified Maximum Average Score (MMAS) Draize = 64.8 Irritant R36 (EEC)
Aldehydes	Common degradation products	Methacrylaldehyde	Corneal irritation (neat) = 9/10 (Smyth et al 1951)
Alkalis	Used for cleaning and pH control	Sodium Hydroxide	Draize score at 10% = 108/110; Draize score at 1% = 25.8/110
Amines / Non-Alcohol solvents	Provides depth for solvents; prevalent in manufacturing processes including dyes and pharmaceuticals	Diethylamine	103% corneal swelling at a 2% concentration in solution
Surfactants (Anionic)	Detergents; Foaming agents	Sodium Lauryl Sulfate	MMAS Draize = 58.0 (10%)
Surfactants (Cationic)	Commonly used as antistatic agents, softeners, disinfection agents; Preservatives	Benzethonium Chloride Cetyltrimethylammonium Bromide (CTAB)	Maximum Average Score (MAS) = 76.3 (10%) MAS = 69.0 (10%)

Experimental (cont.)

On Days 1 - 3 of the studies, six instillations of 50 µl of test solution were administered to the right (test) eyes of each animal at approximately 1.5 hour intervals. The test solution was placed into the inferior ocular cul de sac. The left (control) eyes of each animal received 50 µl of the control solution in the same manner.

The rabbits' eyes were examined daily macroscopically by Draize Method prior to the 1st dose and a minimum of ten (10) minutes after the 6th dose. One additional Draize observation was made 20 minutes after the first dose on Day 1 only. The animals were also examined microscopically via the McDonald-Shadduck method using a slit lamp. This microscopic examination was conducted on Day 3 following the final Draize evaluation. The rabbits were also evaluated daily for any signs of systemic toxicity.

Conversion of Concentration (ppm) to Total Daily Intake (ug)

As a point of reference, for a product delivered topically in a volume of 50 µL QID in both eyes, the toal daily intake at 20 and 100 ppm would be:

20 ppm ⇨ 8 µg TDI
100 ppm ⇨40 µg TDI

Results and Discussion

The results of the ocular irritation tests conducted for each chemical species are summarized in Table 2. Each chemical species was evaluated at 20 ppm and then, 100 ppm by both macroscopic and microscopic examination.
There was no evidence of irritation caused by any of the chemical species when macroscopically examined and scored using the Draize Method. The conjunctiva, iris, and cornea all appeared clinically normal at each time point during the study. Following the final Draize evaluation, each animal was also examined microscopically via McDonald-Shadduck method using a slit lamp. There was no evidence of irritation using this means of evaluation as well. There was no evidence of systemic toxicity under the conditions of the test. All animals appeared clinically normal throughout the duration of the study for each chemical species evaluated.

Table 2 Test Results

Chemical Tested	Concentration	Draize Score (Avg.)	Slit Lamp Score (Avg.)
Lactic Acid	20 ppm	0	0
	100 ppm	0	0
2- chloroethyl acrylate	20 ppm	0	0
	100 ppm	0	0
p-toluenesulfonyl chloride	20 ppm	0	0
	100 ppm	0	0
1-Hexanol	20 ppm	0	0
	100 ppm	0	0
2,4-di-tert-butylphenol	20 ppm	0	0
	100 ppm	0	0
Methacrylaldehyde	20 ppm	0	0
	100 ppm	0	0
Sodium Hydroxide	20 ppm	0	0
	100 ppm	0	0
Diethylamine	20 ppm	0	0
	100 ppm	0	0
Sodium Lauryl Sulfate	20 ppm	0	0
	100 ppm	0	0
Benzethonium Chloride	20 ppm	0	0
	100 ppm	0	0
Cetyltrimethylammonium Bromide (CTAB)	20 ppm	0	0
	100 ppm	0	0

Recommendations /

Conclusions

These studies provide support for 20 ppm as an ocular irritation threshold for topical ophthalmic products. Each chemical under evaluation is known to be a severe ocular irritant with the potential to cause serious damage to the eye at concentrations much higher than expected levels of impurities in ophthalmic formulations. That these chemicals showed no evidence of irritation in the rabbit eye at five times the proposed threshold indicates it is unlikely that any chemical would be irritating to the tissues of the eye at a concentration of 20 ppm. As such these data support a threshold of 20 ppm under which chemical impurities need not be qualified for their potential to cause ocular irritation for topical ophthalmic products. Further work may be needed verify this threshold and to establish thresholds for other endpoints of concern.

References

- ICH Harmonised Tripartite Guideline "Impurities in New Drug Products Q3B(R2)" 2 June 2006
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