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Solubility Enhancement of Opthalmic Indomethacin

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ABSTRACT

In recent years, there have been increased efforts to find safer and effective drugs to treat various ocular conditions as well as to develop novel dosage forms and delivery systems to improve the topical delivery of existing drugs. Today, topical ophthalmic application is considered the preferred way to achieve therapeutic levels of the drug used to treat ocular diseases. The conventional preparations for this route fall into several categories: solutions, suspensions, semisolids and others. Bioavailability, particularly for ocular solutions, ranges from 1 to 10% of the total administered dose. Oily eye drops can be used for three reasons namely to produce an emollient effect, to protect a compound liable to hydrolysis and to obtain an enhanced effect. Some drugs are broken down in an aqueous solution and are supplied as oily drops to prevent this. Some drugs are broken down in an aqueous solution and are supplied as oily drops to prevent this. Since, lipophilic substances cross the epithelial barriers more easily than hydrophilic ones, it would appear logical to provide drugs in the former state rather than the later. Topically applied agents produce effective levels mainly in the anterior segment. As far as the optometrist is concerned, the topical route is the only one that is applicable.

Keywords: topical drug delivery, Oil based preparation, sterile eye drops, lipophilic substances.

INTRODUCTION

In recent times, great emphasis has been placed on the importance of formulation with the recognition that they can significantly influence the physiologic availability of drugs. It is becoming increasingly evident that the rate of dissolution or release of the drug from the formulation is of paramount importance and that even minor changes unknowingly can greatly influence this property in some cases. In dealing with the formulation of new products, as the variety and complexity of materials and techniques have increased, it has become necessary to

apply the best research methods and tools, in order to develop, produce and control the potent, stable and effective dosage forms [1].

Ocular topical drug delivery is particularly challenging because of inherent difficulties associated with absorption of topically applied drugs into the eye. Ophthalmic doses forms are administered via the topical route to treat both surface and intraocular conditions [2]. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) have been used to treat various ailments for over 100 years. As a class, these drugs posses anti-inflammatory, anti-allergic, analgesic and antipyretic activity and widely used to treat chronic inflammatory states, such as arthritis, psoriases and asthma. NSAIDs include a variety of different agents of different chemical classes. Most of these drugs are analgesics, but the degree of anti-inflammatory activity varies, some (such as aspirin and indomethacin) being strong anti-inflammatory, some (such as naproxen and maclofenamate) being moderately anti-inflammatory, while some (such as paracetamol) have essentially no anti-inflammatory activity at all [3-5].

EXPERIMENTAL SECTION

Drug Indomethacin was generously gifted by Alchem Laboratories, Bombay and Labrafil M 2125 CS [6] by Torrent Research Center, Gandhinagar, Gujarat. All other excipients were obtained from commercial sources and were of analytical grade.

1 Determination of solubility of indomethacin

Indomethacin is a low soluble drug (specifically in water). Its solubility was determined in various solvents and their combinations and also in presence of solubilizing agents, by placing an excess quantity of drug in a vial along with the solvent. The tightly closed vials were then agitated for 24 hr at 30º C $\pm$ 2º C. The solutions were filtered through a 0.45μm filter and the filtrate was analyzed for drug content on a UV / Vis spectrophotometer (Jasco – V550) after appropriate dilutions.

2 Compatibility Studies:

1% solution of indomethacin base was prepared in Labrafil and Labrafil-castor oil combination (50:50) respectively. 5ml of each solution was mixed with benzyl alcohol (1% v/v), methyl paraben (0.05%), propyl paraben (0.015%) and span 80 (1%) (Concentrations as per Inactive Ingredient Guide). Each mixture was filled in flint vial, stoppered with rubber stopper, sealed and kept at different temperature conditions. Sample of plain drug solution without any excipient alone was kept as control.

2.1 Physical compatibility:

The samples stored at room temperature, (25˚C/60%RH), (30˚C/65%RH) and (40˚C/75%RH), samples were observed visually for clarity and discoloration after different time intervals.

2.2 Chemical compatibility:

Above drug solutions kept in different storage conditions were analyzed for drug content at 320 nm on a UV/Vis Jasco V-550 spectrophotometer after proper dilution with dichloromethane. (Initial drug content was 100.05%).

3. Sterilization of formulations

Formulations were prepared with 1 % drug and other excipients filled in vials and sealed. These vials were autoclaved for 20 minutes. In some other vials, solutions were filled by filtration through 0.2µm Millex, Millipore filter.

Table no. 1 Effect of sterilization on drug content of indomethacin eye drops

Sample	Drug content before sterilization	Drug content after autoclaving	Drug content after filtration
IND (1%) + 50% Labrafil + 50% Castor Oil + 1% Benzyl alcohol + 1% span 80	100.20%	99.7%	99.8%
IND (1%)+ Labrafil + 1% Benzyl alcohol + 1% Span 80	100.15 %	99.5%	100.0%

4. Viscosity determinations of oil bases:

Viscosity of oils bases in the formulation with and without combinations and excipients proposed to be used in the formulation development of indomethacin eye drops was determined using Brookfield-Programmable Rheometer (Model – DVIII).

Table no. 2 Viscosity of oil bases of eye drop formulation

S.No.	Bases	Viscosity (at 20˚C)
1.	Labrafil – M2125	85 m Pas
2.	Castor Oil	980 m Pas
3.	Labrafil + Castor Oil (1:1)	695 m Pas
4.	Labrafil + Benzyl alcohol (1 %) + Span 80 (1%)	88 m Pas
5.	Labrafil + Castor oil (1:1) + Span 80 (1%) + Benzyl alcohol (1 %)	705 m Pas

3. Preparation of eye drop formulation:

On the basis of results obtained during preformulation studies, the weighed quantity of Labrafil or a mixture of Labrafil and castor oil was kept in 250-ml beaker. The beaker was then kept on a water bath maintained at 30-35°C. Weighed quantities of indomethacin base and other excipients were mixed and dissolved in the above vehicle with constant stirring. The formulated clear solution was filled in 10-ml vials after filtration through 0.2 µm filter under aseptic area and sealed.

Table no. 3. Formulation of indomethacin oil based drops

S. No.	Formulation Code	Ingredients	Quantity	Application
1	INDOD1	Indomethacin Span 80 Benzyl alcohol Castor Oil+Labrafil (1:1)	1 % (w/v) 1 % (v/v) 1 % (v/v) q. s. to 100% (v/v)	Drug Solubiliser Preservative Vehicle
2	INDOD2	Indomethacin Span-80 Benzyl alcohol Labrafil-M-2125	1% (w/v) 1% (v/v) 1% (v/v) q.s. to 100% (v/v)	Drug Solubiliser Preservative Vehicle

3.3 Packaging of products:

Since indomethacin is reported to be a light sensitive drug, so 10 ml, 20 mm USP type–I flint glass vials were used as containers. For closing these vials, 20-mm Grey bromo-butyl slotted rubber stoppers were used. These packaging materials were tested as per USP [7].

4. Evaluation of formulated products

4.1 Assay Procedure

1 ml of each formulation was accurately taken and transferred to a 100 ml volumetric flask. It was diluted to 100 ml dichloromethane. 10 ml of this was again diluted with solvent to 100 ml. Two dilutions of each sample were prepared at a time for cross check. Absorbance of each dilution was measured at 320 nm on a Jasco–V-550, UV/Vis spectrophotometer. The results are recorded in table no.5.

Table no. 4. Assay of formulated indomethacin eye drops

Formulation code	Concentration
INDOD1	10.42 mg/ml
INDOD2	10.47 mg/ml

4.2 Sterility testing

Prepared indomethacin eye drops were tested for sterility as per USP. The test was done by direct inoculation method. Fluid Thioglycollate was used for aerobes and facultative anaerobes while Soyabean Casein Digest Broth was used for aerobes and fungi. Test mixtures were incubated in culture tubes and media was examined for microbial growth. Incubation was continued for a total of 14 days from the original incubation at 32.5 $\pm$ 2.5ºC. Control samples of aerobes, anaerobes and fungi were prepared in both the medium.

4.3 Stability Study of formulated indomethacin eye drops

Stability study protocol

The formulated products were subjected to stability studies at different storage conditions as per ICH guidelines. The sealed vials containing different formulations were kept in the temperature / humidity control ovens (Newtronics). Some vials were also kept in inverted position to check any interaction between rubber closure and formulation. The drug content of each formulation was determined after different time intervals and percent residual drug was calculated.

Table no.5. Stability study protocol for formulated products

S.No.	Test	Storage Condition	Period	Limits during stability
A	Physical test Appearance pH	2-8˚C 25˚C / 60% RH 30˚C / 65% RH	Initial 7days 15 days	- -
B	Chemical test assay	40˚C / 75% RH	1 month 3 months	5% change

RESULTS

The successful formulation of poorly water-soluble drugs is one of the major problems in pharmaceutical manufacturing. Poorly water-soluble drugs, such as indomethacin, may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of the gastrointestinal tract.

From solubility studies, it is clear that we cannot prepare a 1% solution of indomethacin in water using any of the above co-solvents or solubilizing agents. But, in castor oil and labrafil, indomethacin is having good solubility, so these two can be used to make a formulation of 1% concentration. The results of table no. 1 showed that, there was no significant difference in the drug content of indomethacin formulation before and after autoclaving or filtration, so both the methods can be used for sterilization of eye drops in the present studies. The viscosity range of

the bases showed that they can be used alone and in combination in the formulation development of indomethacin eye drops. All the formulations passed test of sterility.

Looking into the advantages of eye-drop preparation, it may be recommended that eye-drop of indomethacin should be prepared commercially. The formulations prepared by author are showing satisfactory results. However, it would be desirable to carry out exhaustive clinical-pharmacological evaluations before they can be approved for the actual use.

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