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Some studies into the properties of indomethacin suspensions intended for ophthalmic use

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Summary

The formulation of eye drops containing indomethacin creates a number of problems since indomethacin is unstable in alkaline media but poorly soluble in acidic media. This paper outlines the formulation of a suitable suspension buffered to pH 5.6 and containing either hydroxypropylmethylcellulose (HPMC) or polyvinylalcohol (PVA) as viscolizers. Accelerated stability demonstrated satisfactory stability during storage under ambient conditions with a $T_{10\%}$ (time for 10% to degrade) of = 280 days and an activation energy of 25.4 kcal/mol. Particle size measurements (Coulter Counter) indicated that no significant alterations occurred in the particle size distribution of indomethacin in the presence of PVA or HPMC following heating at 100 °C with a bactericide for 30 min and following 2 months subsequent storage. The same behaviour for indomethacin particles was not observed in the absence of PVA or HPMC.

Introduction

Indomethacin, topically applied to the eye, may reduce the short-term risk of cystoid macular oedema associated with cataract or retinal detachment surgery due to a postulated involvement of prostaglandins (Miyake, 1977; Miyake et al., 1980). Pre- and post-operative administration of indomethacin eye drops prevents surgically induced miosis (American Medical Association, 1986). Since a commercial product is not currently available, attempts have been made to formulate suitable eye drops at neutral or slightly alkaline pH, e.g. a pH of 7.4 (Cox and Van der Graaff, 1981). Although indomethacin is more stable at a lower pH (Krasowska, 1974) no published papers describing the preparation of indomethacin eye drops at lower pH values are available, partly due to the very low solubility of indomethacin which, for instance, is 3–5 mg/100 ml at a pH of 5.6 (O'Brien et al., 1984).

The principal drug properties concerning corneal penetration are lipophilicity, reflected by the drug's partition coefficient, and its pK_a which determines the proportion of the drug in its favoured absorbable form at any given pH (Kishida and Otori, 1980; Schoenwald and Ward,

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1981; Lee and Robinson, 1986). Since indomethacin is lipophilic and has a pK_a of 4.5 (O'Brien et al. 1984) it is probable that it will readily penetrate the corneal layers from a preparation buffered to pH 5.6 where the drug would partly be in its unionized form. This pH is still acceptable to the eye. Furthermore alkaline solutions induce greater lacrimation than acid ones (Conrad et al., 1978). It seems reasonable to assume that for a poorly water-soluble substance ophthalmic delivery by suspension would be acceptable and is a practical method of achieving good bioavailability. These considerations lead to the development of the following formula:

	Indomethacin	1.0% w/v
Either	Hydroxypropylmethylcellulose (HPMC)	0.5% w/v
Or	Polyvinylalcohol (PVA)	1.4% w/v
	Phenylmercuric nitrate (PMN)	0.002% w/v
	Sodium phosphate buffer solution (pH 5.6)	to 100 ml

The concentration of the polymers were those commonly used in commercial products.

The purpose of this paper is to examine the chemical stability of indomethacin and the age-induced changes in the particle size distribution of indomethacin in suspensions buffered in the pH range 5.6–8.1 with an overall assessment of the suitability of such formulations for use as ophthalmic products. In ophthalmic products the size of any suspended particles must be carefully examined because of potential problems regarding their dissolution rate (hence bioavailability) and their irritation potential. For instance, should the particles be large enough to irritate the eye, lacrimation will be induced with subsequent drainage of the instilled dose reducing bioavailability. Thus the influence of viscolizers, method of sterilization and of storage on the particle size distribution of indomethacin is considered.

Materials and Methods

Indomethacin and PVA-type II-low molecular weight were supplied by Sigma Chemical Co. HPMC (Methocel E4M Premium) was supplied by Colorcon. The other reagents and chemicals, sodium chloride, disodium hydrogen phosphate, sodium dihydrogen phosphate and phenylmercuric nitrate were all analytical grade.

Accelerated stability testing

Solutions of indomethacin were prepared by dissolving an excess of drug in suitable buffer solutions of sodium phosphate (Sørensen's buffer, pH range 5.6–8.1) and filtering through 0.22 μm membrane filters. The final pH (stated in the text) was measured by pH meter and accepted as the definitive pH value. When required, these solutions were added to viscous buffer solutions to achieve final polymer concentrations of 0.5% w/v for HPMC or 1.4% w/v for PVA or to PMN solution to achieve final preservative concentration of 0.002% w/v. Accelerated stability testing was accomplished by placing the solutions, sealed into 5 ml neutral glass ampoules and thermostatically controlled at temperatures between 60 and 100 °C. At appropriate times, samples were removed, rapidly chilled on ice, and assayed at 320 nm using the appropriate buffer solutions as references. At this wavelength the degradates of indomethacin do not interfere with the assay (Krasowska et al., 1973).

Particle size determination

The Coulter Counter TAII was employed to determine indomethacin particle size using as electrolyte 1% w/v sodium chloride, previously saturated with indomethacin and filtered through 0.22 μm membrane filter, to avoid any dissolution of the indomethacin.

Suspensions of indomethacin (1% w/v) were prepared in buffer at pH 5.6 containing 0.002% w/v PMN and either 0.5% w/v HPMC or 1.4% w/v PVA and placed into neutral glass ampoules. Particle size determinations were performed prior to and immediately after sterilization at 100 °C for 30 min and following 2 months of storage at ambient conditions. Controls, without the sterilization process, were similarly examined following storage.

Results and Discussion

Accelerated stability testing

Earlier reports on the stability of indomethacin (Krasowska, 1974; Hajratwala and Dawson, 1977) were limited to the pH range 7–10, probably due to the low solubility of indomethacin. The data in this investigation (pH 5.6–8.1) may be presented as first-order kinetics which are consistent with earlier reports. Apparent first-order rate constants were evaluated from the Arrhenius equation and increased with increase in pH (Table 1).

Following the inclusion of 0.5% HPMC, 1.4% PVA or 0.002% PMN into the buffer at pH 5.6 the apparent rate constants for indomethacin degradation were in the narrow range 6.9×10^{-4} min^{-1} (for PMN–indomethacin solution) to 9.9×10^{-4} min^{-1} (for PVA–indomethacin solution). Such results indicate that neither compound should play a significant role in controlling the stability of indomethacin. Similar occurrences were observed at pH 7.6 except that the values for apparent rate constants were increased ($1.8–3.1 \times 10^{-2}$ min^{-1}) (Table 2).

The degradation of indomethacin was also examined in buffer solution pH 7.2 wasble 3). A straight line relationship between the logarithm of the rate constants and reciprocal thermodynamic temperature was obtained. The $T_{10\%}$ for indomethacin at pH 7.2 was 25.5 days compared with a value of 44.8 days at pH 7.0 (Krasowska, 1974) that would not be considered to be adequate in developing an ophthalmic product. The data presented in Table 2 indicate that PVA, PMN or HPMC little affected the indomethacin stability at pH 5.6 or pH 7.6 and should not play a significant role in controlling the stability of indomethacin.

TABLE 1

The effect of pH on the degradation of indomethacin at 100 °C

pH	K [a] (min^{-1})	$T_{50\%}$ [b] (min)	$T_{10\%}$ [c] (min)
5.6	6.0×10^{-4}	1143	173
6.2	8.7×10^{-4}	793	146
7.0	2.7×10^{-3}	256	38.7
7.5	1.1×10^{-2}	62.7	9.5
8.1	2.2×10^{-2}	30.2	4.6

[a] Apparent first-order rate constants.
[b] Time for 50% of the indomethacin to degrade.
[c] Time for 10% of the indomethacin to degrade.

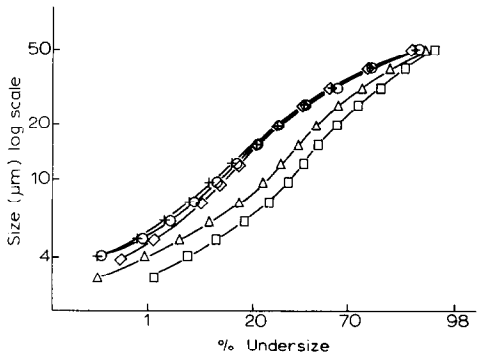

Fig. 1. The effect of storage and heat treatment for 30 min at 100 °C on the particle size of indomethacin in suspensions containing 1% indomethacin, 0.002% PMN and buffered to pH 5.6 Key: □, before treatment; +, immediately after treatment at 100 °C; △, untreated suspension after 3 weeks storage; ○, heat-treated suspension after 3 weeks storage; ◇, heat-treated suspension after 8 weeks storage.

Table 4 indicates that at 90, 95 and 100 °C 0.5% HPMC appeared to protect against the degradation of indomethacin yet at 85 °C 1.4% PVA appeared to exert greater protection. The net result is that at 25 °C the stability anticipated from Arrhenius treatment of the data implies that PVA protected the stability of indomethacin better than HPMC as reflected by the increase in $T_{10\%}$ and $T_{50\%}$ values and the increase in the activation energy. This might reflect problems in the redispersion of the HPMC gel following exposure to high temperatures rather than an influence of PVA on indomethacin stability. Solutions of indomethacin in either PVA or HPMC solutions were considered to be sufficiently stable to warrant consideration of the development of an indomethacin ophthalmic suspension, especially in considering that the increased stability of indomethacin in suspension could be expected due to the increased stability of indomethacin in the solid state over and above that of the drug in solution.

Particle size determinations

Particle size data for indomethacin are presented as cumulative plots of percentage under-

TABLE 2

The effect of viscolizers and phenylmercuric nitrate (0.002%) on the degradation of indomethacin at 100°C

	pH 5.6			pH 7.6		
	K [a] (min^{-1})	$T_{50\%}$ [b] (min)	$T_{10\%}$ [c] (min)	K [a] (min^{-1})	$T_{50\%}$ [b] (min)	$T_{10\%}$ [c] (min)
Buffer alone	9.1×10^{-4}	758	115	3.1×10^{-2}	25.2	3.8
1.4% PVA	9.9×10^{-4}	697	106	1.7×10^{-2}	41.5	6.3
0.5% HPMC	8.1×10^{-4}	854	129	1.8×10^{-2}	38.2	5.8
0.002% PMN	6.9×10^{-4}	991	150	–	–	–

[a] Apparent first-order rate constants.
[b] Time for 50% of the indomethacin to degrade.
[c] Time for 10% of the indomethacin to degrade.

TABLE 3

The effect of temperature on the Arrhenius rate constants based on first-order kinetics for indomethacin degradation at pH 7.2

Temperature (°C)	K [a] (min^{-1})	$T_{10\%}$ b (days)	E [c] (kcal·mol^{-1})
65	4.0×10^{-4}	4.4	–
70	5.3×10^{-4}	3.3	–
75	1.1×10^{-3}	1.5	–
80	1.7×10^{-3}	1.0	–
25	2.9×10^{-6}	25.5	24.3 (Estimate)

[a] Apparent first-order rate constants.
[b] Time for 10% of the indomethacin to degrade (shelf-life).
[c] Activation energy.

sized versus the logarithm of the mean diameter of the particles (Figs. 1–3). Considerable changes in the particle size distribution occurred in the samples which did not contain either HPMC or PVA following heating at 100°C for 30 min (Fig. 1). Storage, under ambient conditions, little affected the particle size of indomethacin as reflected by $D_{50\%}$ values (diameter of 50% particles smaller than a certain value) which only slightly increased from 15 to 18 μm during the subsequent eight weeks of storage (Table 5). However, attempted sterilization, by maintaining the temperature at

TABLE 4

The effect of viscolizers on the degradation of indomethacin in solutions buffered to pH 5.6 containing 0.002% w/v phenylmercuric nitrate

Temperature (°C)	Viscolizer	K [a] (min^{-1})	$T_{50\%}$ [b] (days)	$T_{10\%}$ [c] (days)	E [d] (kcal·mol^{-1})
85	0.5% HPMC	1.6×10^{-4}	–	–	–
	1.4% PVA	1.1×10^{-4}	–	–	–
90	0.5% HPMC	2.7×10^{-4}	–	–	–
	1.4% PVA	3.7×10^{-4}	–	–	–
95	0.5% HPMC	3.2×10^{-4}	–	–	–
	1.4% PVA	5.1×10^{-4}	–	–	–
100	0.5% HPMC	4.6×10^{-4}	–	–	–
	1.4% PVA	6.3×10^{-4}	–	–	–
25	0.5% HPMC	1.1×10^{-6}	428	64.8	17.7
	1.4% PVA	3.0×10^{-7}	1837	278.3	25.4

[a] Apparent first-order rate constants.
[b] Time for 50% of the indomethacin to degrade.
[c] Time for 10% of the indomethacin to degrade (shelf-life).
[d] Activation energy.

TABLE 5

The effect of viscolizers, heat treatment at 100 °C and storage on the particle size (μm) of indomethacin in its aqueous suspensions buffered to pH 5.6 containing 1% w/v indomethacin

	Mean particle size					
	Unheated			Heated at 100 °C for 30 min		
	On preparation	Storage for		Immediately after heat treatment	Storage for	
		3 weeks	8 weeks		3 weeks	8 weeks
Buffer alone	15.0	19.0	18.0	26.0	26.0	27.0
1.4% PVA	16.0	18.0	18.0	17.5	18.5	18.5
0.5% HPMC	17.0	16.0	14.0	17.5	17.0	14.5

100 °C for 30 min, greatly influenced the particle size distribution yielding a $D_{50\%}$ of 26 μm immediately after sterilization. Such values were maintained during 8 weeks, implying again the small influence of storage at ambient temperatures on the particle size distribution of indomethacin.

The corresponding data for suspensions containing PVA (Fig. 2) and HPMC (Fig. 3) did not show the same trends. After exposure of indomethacin suspension containing PVA to 100 °C for 30 min the $D_{50\%}$ was slightly increased and maintained thereafter. In the case of the suspension containing HPMC, the particle size distribution was even more uniform although a small decrease of the $D_{50\%}$ value at the end of the examining period was observed. Undoubtably $D_{50\%}$ values (Table 5) confirmed that there were no significant changes in the suspensions containing HPMC or PVA following sterilization and subsequent 2 months of storage.

It is possible that heating in the absence of the polymers allowed some of the indomethacin to dissolve with subsequent recrystallization on the remaining particles following cooling. Such findings clearly emphasize the necessity of including either HPMC or PVA into the proposed formulation of indomethacin. However, the advantages in bioavailability caused by including one of the additives as viscolizers remain to be investigated.

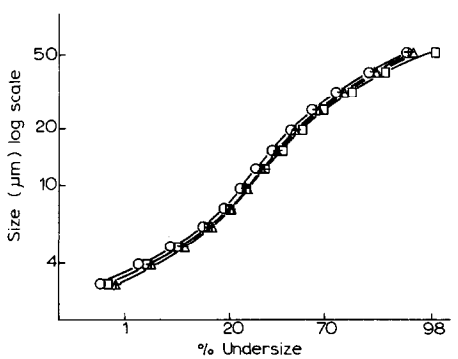

Fig. 2. The effect of storage and heat treatment for 30 min at 100 °C on the particles size of indomethacin in suspensions containing 1% indomethacin, 0.5% HPMC, 0.002% PMN and buffered to pH 5.6 Key: +, before treatment; ○, immediately after treatment at 100 °C; □, untreated suspension after 3 weeks storage; △, heat-treated suspension after 3 weeks storage. Data from 8 weeks storage excluded to clarify figure.

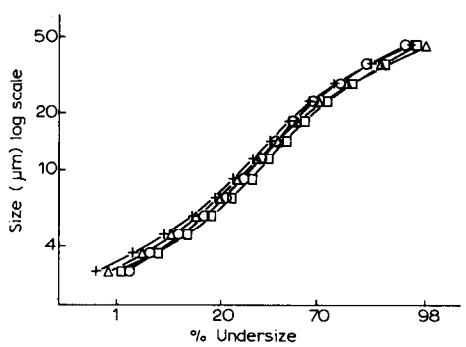

Fig. 3. The effect of storage and heat treatment for 30 min at 100 °C on the particle size of indomethacin in suspension containing 1% indomethacin, 1.4% PVA, 0.002% PMN and buffered to pH 5.6 Key: □, before treatment; △, immediately after treatment at 100 °C; ○, untreated suspension after 3 weeks storage; +, heat-treated suspension after 3 weeks storage. Data from 8 weeks storage excluded to clarify figure.

Conclusions

The degradation of indomethacin in solution followed first-order kinetics and the rate was both pH and temperature dependent. Such findings concur with the results of Hajratwala and Dawson (1977) who, however, used higher values of pH than those in this study. Satisfactory stability of indomethacin can be obtained in phosphate buffer pH 5.6 containing either 0.5% HPMC or 1.4% PVA. The $T_{10\%}$ of $\simeq 280$ days and an activation energy of 24.3 kcal $\cdot$ mol^{-1} for indomethacin solution containing PVA, after Arrhenius treatment of the data implied that such a solution could be considered sufficiently stable to be used as an ophthalmic dosage form. Heat stress considerably affected the particle size distribution of indomethacin in suspension without viscolizers. However, the addition of either 1.4% PVA or 5% HPMC protected indomethacin against crystal growth indicating that significant improvements could be gained by their inclusion into the proposed suspension.

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References

American Medical Association 'Miscellaneous Ophthalmic Preparations'. In *Drug Evaluations,* 6th edn. Chicago, IL, 1986, pp. 353–368.

Conrad, J.M., Reay, W.A., Polcyn, E. and Robinson, J.R., Influence of tonicity and pH on lacrimation and ocular drug bioavailability. *J. Parent. Drug Assoc.,* 32 (1978) 149–161.

Cox, H.L.M. and Van der Graaff, H., Indomethacin eye drops as solution. *Pharm Weekbl.,* 116 (1981) 387–338.

Hajratwala, B.R. and Dawson, J.E., Kinetics of indomethacin degradation I: Presence of alkali. *J. Pharm. Sci.,* 66 (1977) 27–29.

Kishida, K. and Otori, T., A quantitative study on the relationship between transcorneal permeability of drugs and their hydrophobicity. *Jpn. J. Ophthamol.,* 24 (1980) 251–259.

Krasowska, H., Kinetics of indomethacin hydrolysis. *Acta Pharm. Jugoslav.,* 24 (1974) 193–200.

Krasowska, H., Krowczynski, L. and Bogdanik, Z., The assay of indomethacin in the presence of its hydrolytic degradation products. *Pol. J., Pharmacol.,* 25 (1973) 417–421.

Lee, V.H.L. and Robinson, J.R., Topical ocular drug delivery: recent developments and future challenges, *J. Ocular Pharmacol.,* 2 (1986) 67–108.

Miyake, K., Prevention of cystoid macular oedema after lens extraction by topical indomethacin I: A preliminary report. *Arch. Klin. Ophthamol.,* 203 (1977) 81–88.

Miyake, K., Sakamura, S. and Miura, H., Long-term follow-up study on the prevention of aphakic cystoid macular oedema by topical indomethacin. *Br. J. Ophthamol.,* 64 (1980) 324–328.

O'Brien, M.M., McCauley, J. and Cohen, E., Indomethacin. In: K. Florey (Ed.), *Analytical Profiles of Drug Substances, Vol. 13,* Academic, London, 1984, pp. 212–238.

Schoenwald, R.D. and Ward, R.L., Relationship between steroid permeability across excised rabbit cornea and octanol-water partition coefficients, *J. Pharm. Sci.,* 67 (1981) 786–788.