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Radiation sterilization of polyethylene glycols

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Summary

Polyethylene glycols (PEGs) are used in ophthalmic ointment bases and as non-aqueous vehicles in injections, which are required to be sterile. The present study is aimed at investigating the feasibility of sterilizing some PEGs by gamma-radiation. Physicochemical and pharmacological studies were carried out on samples sterilized by irradiation at 25 kGy (2.5 Mrad) and the findings were compared with those of control and heat-sterilized samples to assess the suitability of radiation as a possible alternative method of sterilization for PEGs.

Polyethylene glycols are widely used as components of water-soluble ointment bases and as non-aqueous vehicles in injections for subcutaneous and intramuscular use (Newton et al., 1973; Gupta, 1967; Korttila et al., 1976; Bodin et al., 1955). The use of PEGs in ophthalmic ointments and injections necessitates their sterilization. The recommended methods of heat sterilization (B.P.C., XI Edition) are not suitable when ophthalmic ointments or injections contain heat-sensitive medicaments. Such preparations are therefore processed under aseptic conditions which are costly and cumbersome, and there is no certainty that the final product will be sterile. Gamma-radiation has emerged as a useful, efficient and economic tool for the sterilization of many drugs in the solid state and in ophthalmic ointments in their final containers (Gopal, 1978). However, the adoption of this method requires detailed investigations to ensure that no untoward changes take place, as ionizing radiation has been reported to cause degradation in some pharmaceuticals (Jacobs, 1976; Hartman, 1975).

The present investigation is aimed at studying the feasibility of sterilizing PEGs by 25 kGy gamma-radiation, and thereby offer an alternative to the conventional

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TABLE 1

PHYSICOCHEMICAL CHARACTERISTICS OF CONTROL AND STERILIZED SAMPLES OF PEGs

Characteristic	PEG	Specified limit	Control [a]	Irrad. (25 kGy)	Control [a]	Heat sterilized
Peroxide [d] content (μEq. of $Na_2S_2O_3$ per 100 g)	400	–	15.73 ± 1.62	9.21 ± 1.69	nil	7.54 ± 2.86
	1500		6.61 ± 0.32	7.60 ± 1.47	–	18.04 ± 1.14
	4000		60.78 ± 8.49	56.08 ± 8.31	27.29 ± 1.29	59.79 ± 8.57
pH [b,c]	400	4.5–7.5	6.3	5.9	6.8	6.2
	1500		6.6	6.6	–	5.0
	4000		4.6	4.7	5.2	3.9
Ethylene oxide [e] limit (%)	400	≯ 0.02	0.004	0.004	0.018	0.001
	1500		0.002	0.004	–	0.011
	4000		0.009	0.010	0.003	0.100

[a] Two controls in case of PEG 400 and 4000 are samples from two different batches.
[b] B.P. 1980.
[c] U.S.P. XX and N.F. XV.
[d] McKenzie (1970).
[e] Schenck (1968).

dry-heat sterilization. PEG 400, 1500 and 4000 were selected for the study as they are the most widely used members and serve as representatives of liquid, semisolid and solid PEGs. The PEGs, in sealed vials and stoppered containers of neutral glass, were irradiated by gamma-radiation of cobalt-60 to a dose of 25 kGy. A batch of the PEGs was also sterilized by heating at 150°C for 1 h. The irradiated PEG samples were tested to detect any changes in physicochemical characteristics like colour, pH, viscosity, freezing point, hydroxyl value and ethylene glycol and diethylene glycol content by pharmacopoeial procedures (B.P. 1980; U.S.P. XX). In addition, peroxide content was determined by iodometry (McKenzie, 1970) and ethylene oxide content was determined by a titrimetric procedure (Schenck, 1968). The results of these tests were compared with those obtained on an unsterilized (control) sample and the heat-sterilized sample.

The results of the physicochemical characteristics indicated that the viscosity, freezing point, hydroxyl value, average molecular weight and ethylene glycol and diethylene glycol content of the PEGs were not significantly altered by either method of sterilization. The irradiated PEG samples showed no change in colour and complied with the B.P. colour test. The heat-sterilized samples of all three PEGs, however, showed a slight yellowish tinge and failed in this test. The other characteristics which showed marked changes are peroxide content, pH and ethylene oxide content (Table 1). The radiation-induced change in peroxide content was not significant in PEG 1500; however, a decrease was observed in PEG 400 and 4000. A significant decrease (nearly half that of the control) was especially observable in PEG 400. On the other hand, the heat-sterilized samples of all the three PEGs have shown a marked increase in the peroxide content. This could be attributed to the fact that conditions of high temperature increases the formation rate of peroxide-like impurities in PEGs (McKenzie, 1970; McGinty et al., 1976), which may cause oxidative changes in some active ingredients incorporated in PEG bases (Coates et al., 1961; Azaz et al., 1977).

The pH values of irradiated and heat-sterilized PEG 400 and those of irradiated PEG 1500 and 4000 samples have shown no significant variation. However, the pH values of heat-sterilized samples of PEG 1500 and 4000 have shown a considerable decrease. This decrease in pH could be an after-effect of the increase in the peroxide content, as peroxides are generally intermediates in the degradation of glycols to carboxylic acids (McKenzie, 1970; McGinty et al., 1976). The ethylene oxide content of the irradiated PEG 400 sample has shown no change, but the heat-sterilized sample has shown a considerable decrease. Both the heat-sterilized and irradiated samples of PEG 1500 and 4000, however, showed an increase in the ethylene oxide content, the increase being greater in the heat-sterilized samples. No plausible reason could be attributed to these variations.

Pre-sterilization microbial counts (bioburden) of control samples of the PEGs, assessed by the colony count method, indicated that they had a very low level of contamination of less than 500 colony-forming units per gram. Both the irradiated as well as the heat-sterilized samples of the PEGs complied with the sterility test.

As radiation damage may induce toxicity, it was necessary to assess the safety of the irradiated PEG samples by pharmacological studies. Control and irradiated

samples of the PEGs were tested for primary skin irritation by application on the intact and abraded skin of albino rabbits by patch test technique (Draize et al., 1944). No signs of irritation like erythema or edema were caused by any of the irradiated samples.

To assess the acute toxicity of irradiated PEG samples, the LD_{50} values of PEG 400 (oral LD_{50}) and of PEG 1500 and 4000 (intraperitoneal LD_{50}) were determined on albino mice of the Haffkine strain. The LD_{50} values of control and irradiated samples of each PEG were calculated (Litchfield et al., 1948) and compared. No significant variation was observed between the LD_{50} values of the control and irradiated samples of the PEGs.

This investigation, within the limits of its experimental design, has not indicated any harmful effect of radiation on PEG 400, 1500 and 4000, when sterilized at 25 kGy.

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References

Azaz, E. and Segal, R., The stability of vitamin A acetate in cetomacrogol solutions. J. Pharm. Pharmacol., 29 (1977) 322–323.

Boding, J.J. and Taub, A., PEG 400 as a stabilizing solvent in parenteral pentobarbital sodium solutions. J. Am. Pharm. Ass. (Sci. Edn.), 44 (1955) 296.

Coates, L.V., Pashley, M.M. and Tattersall, K., The stability of antibacterials in PEG mixtures, J. Pharm. Pharmacol., 13 (1961) 620–624.

Draize, J.H., Woodward, G. and Calvery, H.O., Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Ther., 82 (1944) 377–390.

Gopal, N.G.S., Radiation sterilization of pharmaceuticals and polymers. Radiat. Phys. Chem., 12 (1978) 35–50.

Gupta, S.D., Polyethylene glycol compounds in ointment bases. Indian J. Hosp. Pharm., 4 (1967) 133–136.

Hartman, A.W., Nesbitt, R.V., Smith, F.M. and Nuessle, N.O., Viscosities of acacia and sodium alginate after sterilization by cobalt-60. J. Pharm. Sci., 64 (1975) 802–805.

Jacobs, G.P. and Melumad, D., Sterilization of barbiturates by gamma radiation. Pharm. Acta Helv., 51 (1976) 313–314.

Korttilla, K., Sothman, A. and Anderson, P., Polyethylene glycol as a solvent for diazepam: bioavailability and clinical effects after i.m. administration, comparison of oral, i.m. and rectal administration, and precipitation from i.v. solutions. Acta Pharmacol. Toxicol., 39 (1976) 104–117.

Litchfield, J.J., Jr. and Wilcoxon, F., A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther., 96 (1948) 99–112.

Mc Ginty, J.W., Patel, T.R., Naqvi, A.H. and Hill, J.A., Implications of peroxide formation in lotion and ointment dosage forms containing polyethylene glycols. Drug Dev. Commun., 2 (1976) 505–519.

McKenzie, D.A., A study of peroxide formation and decomposition in certain glycol systems, Technical Service Report, Union Carbide Corp., Feb. 1970.

Newton, D.W., Becker, C.H. and Torosian, G., Physical and chemical characteristics of water-soluble, semisolid anhydrous bases for possible ophthalmic use. J. Pharm. Sci., 62 (1973) 1538.

Schenck, G.H., Organic Functional Group Analysis: Theory and Development, Pergamon Press, Oxford-London, 1968, p. 66.

British Pharmacopoeia Vol. I, Her Majesty's Stationary Office, University Press, Cambridge, 1980, p. 262.

The Pharmaceutical Codex, XI Edn., The Pharmaceutical Press, London, 1979, p. 504.

The United States Pharmacopoeia XX and The National Formulary XV, Mack Publishing, Easton, PA, 1980, pp. 1244–1245.