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COMMUNICATION

Stability of Cefazolin in Pluronic F-127 Gels

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ABSTRACT

As a part of studies on the possible application of pluronic F-127 gels for drug delivery systems, an investigation was carried out to characterize cefazolin stability in aqueous pluronic F-127 gels. Pseudo-first-order rate constants for the cefazolin degradation were obtained from different concentrations of pluronic F-127 gels at temperatures of 35°, 45°, and 55°C. Rate measurements were also carried out in the gels composed of different pluronic F-127 concentrations (20%, 25%, and 30% w/v).

Key Words: *Cefazolin sodium; Pluronic F-127 gel; Stability, Temperature, and Concentration.*

INTRODUCTION

Pluronic F-127, one of a series of polyethylene–polyoxypropylene–polyoxyethylene block coploymers, possesses several properties which appear to make it particularly suitable for use in pharmaceutical formulations. These include an extremely low order of toxicity and skin irritation (1), reversal thermal gelation (2), and excellent compatibility with other ingredients (3). Owing to these favorable properties, pluronic F-127 has been considered to be potentially useful for topical drug delivery systems. Recent studies have been undertaken of in vitro drug release from pluronic F-127 gels (4–7), and their good drug release characteristics have been demonstrated by comparing with other formulations (8). Further, the applications of the gels as vehicles for ophthalmic use (9) and rectal administration (10) have been attempted in terms of improved drug delivery. In order

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to develop such drug delivery systems, it is also necessary to characterize the effects of pluronic F-127 gels on the chemical stability of formulated drug.

Cefazolin sodium is a semisynthetic cephalosphorin antibiotic. The drug can be used to treat infections of the respiratory tract, skin, soft tissue, bone, joints, and urinary tract; and endocartitics and septicemia caused by susceptible organisms (11,12).

Although a few studies on drug stability in the aqueous form of some pluronics have been reported (13,14), the degradation kinetics of drug in pluronic gels have not been investigated. Thus, the present study was undertaken to assess the possible use of pluronic F-127 gels with respect to cefazolin stability. For the study, the stability of cefazolin in the gels was studied in relation to the effect of temperature and concentration of pluronic F-127.

EXPERIMENTAL

Materials Cefazolin sodium 1.0 g was obtained from Fujisawa Pharm. Corp., lot 308, Japan; pluronic F-127 was purchased from Wei-Mei Chemical Company, Taipei, Taiwan; methanol was purchased from AlPS Chemical Co., Ltd., Taipei, Taiwan; ammonium phosphate was obtained from J. T. Baker Chemical Company, Phillipsburg, NJ. All materials were used as received.

Preparation of pluronic gels All pluronic F-127 formulations were prepared on a weight/volume percentage basis by the cold process. The gel was prepared by the slow addition of appropriate amounts of pluronic F-127 to cold water in a container containing a magnetic stirring bar with gentle mixing for 30 min. The container was left overnight in a refrigerator to ensure complete dissolution. After a clear, viscous solution was formed, cefazolin was later dissolved in each gel at a concentration of 100.0 mg/ml. Gel formulations containing 20%, 25%, and 30% of pluronic F-127 and 100.0 mg/ml cefazolin were prepared.

Stability studies To study the effect of storage temperature on the cefazolin gel, the cefazolin gels were subdivided into 2-ml portions in screw-capped vials of 5-ml capacity, which were tightly capped and sealed. The vials were stored in thermostated ovens at 35°, 45°, and 55°C. At appropriate intervals, each vial was removed and immediately placed in a -20°C refrigerator in order to stop further reaction and to revert gel to solution.

To study the effect of pluronic F-127 concentration on the cefazolin gel stability, three cefazolin gels, containing 20%, 25%, and 30% pluronic F-127 and 100.0 mg/ml cefazolin were prepared and stored in the screw-capped, sealed vials of 5-ml capacity. These samples were stored at 55°C and samples were withdrawn at designated intervals and placed in a -20°C refrigerator before high-performance liquid chromatographic (HPLC) analysis. The samples for HPLC analysis were prepared by accurately weighing about 0.3 g of the solutions in a 25-ml volumetric flask and diluting with water to 25 ml.

The cefazolin content was determined by a previously described HPLC procedure (15,16).

RESULTS AND DISCUSSION

The degradation kinetics of cefazolin in pluronic F-127 gels is depicted in Fig. 1. The linearity of the plot by log % remaining versus time indicates a first-order degradation. It was observed that the degradation rate of cefazolin in high-concentration pluronic F-127 gel is slower than its degradation rate in low-concentration pluronic F-127 gels.

The effect of temperature on the cefazolin degradation was evaluated at 35°, 45°, and 55°C for cefazolin in different concentrations of pluronic F-127 gels. As shown in Fig. 2, the dependence of K_{obs} on temperature is shown in the Arrhenius plot. The Arrhenius plot of

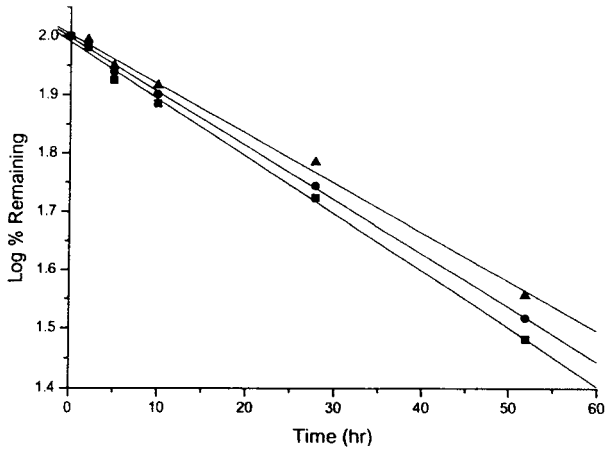

Figure 1. First-order plots for the hydrolysis of cefazolin in different concentrations of pluronic f-127 gels: ■, 20% w/v pluronic F-127 gel; ●, 25% w/v pluronic F-127 gel; ▲, 30% w/v pluronic F-127 gel.

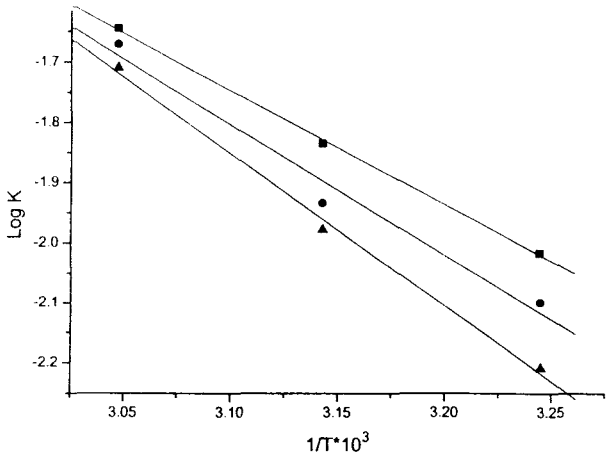

Figure 2. Arrhenius plots for the hydrolysis of cefazolin in different concentrations of pluronic F-127 gels: ■, 20% w/v pluronic F-127 gel; ●, 25% w/v pluronic F-127 gel; ▲, 30% w/v pluronic F-127 gel.

log K_{obs} versus $1/T$ was found to be a straight line, indicating that the mechanism responsible for the degradation is not altered with change in temperature. From the least squares slopes of log K_{obs} against a reciprocal of absolute temperature, $1/T$, the following values of the activation energies, Ea, were derived:

Ea_1 = 8.435 kcal/mol (in 20% w/v pluronic F-127 gel)
Ea_2 = 9.588 kcal/mol (in 25% w/v pluronic F-127 gel)
Ea_3 = 11.278 kcal/mol (in 30% w/v pluronic F-127 gel)

The results show that cefazolin degradation rate is decreased with increasing pluronic F-127 concentration in the gel, and that its dependency was hyperbolic. These data suggests that the formulation of cefazolin with pluronic F-127 micelles is responsible for the retardation of the cefazolin degradation, since pluronic F-127 forms nonionic micelles and its gels are assumed to consist of large populations of micelles.

In conclusion, this study has demonstrated that cefazolin degradation is retarded in higher-concentration pluronic F-127 gel. From the data presented, it is predicted that the required for 10% cefazolin degradation is 130.6 hr in the 30% pluronic F-127 gel at 4°C.

REFERENCES

1. BASF Wyandotte Corp., Industrial Chemical Group, Pluronic Polyols Toxicity and Irritation Data, Wyandotte, MI, 1967.
2. J. Rassing, W. P. Mckenna, S. Bandyopadhyay, and E. M. Eyring, J. Mol. Liquid, 27, 165 (1984).
3. BASF Wyandotte Corp., Organic Specialties & Fine Chemicals Dept. Technical Data Pluronic Polyols, Publ. OS796, Parsippany, NJ.
4. P. C. Chen-Chow and S. G. Frank, Int. J. Pharm., 8, 89 (1981).
5. S. Miyazaki, S. Takeuchi, C. Yokouchi, and M. Takada, Chem. Pharm. Bull., 32, 4205 (1984).
6. J. C. Gilbert, J. Hadgraft, A. Bye, and L. G. Brookes, Int. J. Pharm., 32, 223 (1986).
7. H. Tomida, M. Shinohara, N. Kuwada, and S. Kiryu, Acta Pharm. Suec., 24, 263 (1987).
8. P. C. Chen-Chow and S. G. Frank, Acta Pharm. Suec., 18, 239 (1981).
9. S. C. Miller and M. D. Donovan, Int J. Pharm., 12, 147 (1982).
10. S. Miyazaki, C. Yokouchi, T. Nakamura, N. Hashiguchi, W. M. Hou, and M. Takada, Chem. Pharm. Bull., 34, 1801 (1986).
11. J. H. Collett, J. A. Rees, and D. L. Buckley, J. Pharm. Pharmacol., 31, 80P (1979).
12. S. Y. Lin and Y. Kawashima, Pharm. Acta Helv., 60, 345 (1985).
13. *The Extra Pharmacopeia*, 28th ed., The Pharmaceutical Press, London, 1982, p. 1135.
14. K. Florey, *Analytical Profiles of Drug Substances*, Academic Press, Orlando, FL., 1975, Vol. 4, pp. 1–20.
15. Da-Peng Wang and Ming-Kung Yeh, Chin. Pharm. J., 42(2), 123 (1990).
16. Li-Chien Chang, Da-peng Wang, and Chi-Yin Wong, J. Med. Sci., 14(4), 255 (1994).