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Pluronic F-127 Gels as a Novel Vehicle for Rectal Administration of Indomethacin[1,2]

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Polyoxyethylene–polyoxypropylene surface-active block copolymers (Pluronics®) were evaluated as a vehicle for rectal administration of indomethacin.

The effects of the concentration of Pluronic F-127, temperature, and drug concentration on the drug release were studied by means of an *in vitro* release method using a cellulose membrane. With increasing concentration of Pluronic F-127 in the vehicle, a corresponding decrease in the apparent release rate of the drug occurred. The apparent release rate increased with increasing temperature from 20 to 44 °C. Increase in drug concentration increased the drug release rate.

Indomethacin gel preparations made by dissolving the drug in Pluronic F-127 aqueous gel were administered rectally to rabbits and the drug plasma levels were compared with those after rectal administration of commercial suppositories. When a commercial suppository was given to rabbits, the plasma concentration reached the maximum level 30 min after administration. On the other hand, the gel preparation did not show a sharp peak of plasma concentration and produced a sustained plateau level of indomethacin from 15 min to 10 h without a lag time.

Thus, it appeared that indomethacin preparations based on Pluronic F-127 aqueous gel may be practically useful as a rectal preparation with prolonged action and with reduced side effects.

Keywords——Pluronic F-127 gel; indomethacin; drug vehicle; sustained release; rectal administration; rabbit; rectal delivery system

Surface-active block copolymers of polyoxyethylene–polyoxypropylene (Pluronics®) are widely used in pharmaceutical formulations as solubilizing and wetting agents.[4] Some Pluronics possess several properties which appear to make them particularly suitable for use in the formulation of topical dosage forms; these include the relatively low toxicity and ability to form clear gels in aqueous media.[5,6] Pluronic F-127 is of particular interest since concentrated solutions (>20% w/w) of the copolymer are transformed from low viscosity transparent solutions to solid gels on heating to body temperature. This suggests that when poured onto the skin or injected into a body cavity, the gel preparation will form a solid artificial barrier and sustained release depot. Furthermore, Pluronic F-127 was reported to be the least toxic of commercially available copolymers.[5]

In recent years, Pluronic F-127 has been employed in novel dosage forms for dermatological use[5,7,8] and topical ophthalmic application.[9] In our previous paper, the possible use of Pluronic F-127 as a vehicle for topical administration of anticancer agents has been examined.[10] The Pluronic F-127 gels appear to have good potential for use in topical drug delivery systems since they exhibit reverse thermal gelation behavior and have good drug release characteristics and low toxicity.

Indomethacin has been used extensively in therapy for various inflammatory diseases.[11] However, the clinical usefulness of indomethacin is severely restricted by the gastrointestinal side effects. In order to minimize this side effect, rectal administration of the drug has been

attempted.[12,13] Furthermore, sustained release suppositories of indomethacin were prepared to obtain desirable plasma concentrations, since a high plasma level of the drug has an adverse effect on the nervous system.[14]

In this work, the suitability of Pluronic gels as a vehicle for rectal administration of indomethacin was examined, as a part of an investigation into the pharmaceutical application of Pluronic gels.

Experimental

Materials——Indomethacin was obtained from Sigma Chemical Co., St. Louis. Indomethacin suppository (JP) was a product of Hisamitsu Seiyaku Co., Tokyo. Pluronics were a gift from Asahi Denka Kogyo Co., Tokyo and BASF Wyandotte Co., Parsippany, and were used as received (Pluronic F-68; Pluronic F-88; Pluronic F-98; Pluronic F-108; and Pluronic F-127). These Pluronics were selected to obtain a group with various values of molecular weight and relative degree of hydrophilicity. Some of the physical characteristics of these polymers are summarized in Table I.

Preparation of Pluronic Gels——All Pluronic formulations were prepared on a weight percentage basis using the cold method described by Schmolka.[5] A weighed amount of Pluronics was slowly added to cold phosphate buffer at pH 7.2 in a vial containing a magnetic stirring bar with gentle mixing. The container was left overnight in a refrigerator to ensure complete dissolution. Eventually, a clear and viscous solution formed. These gels exhibit reverse thermal behavior and are therefore fluid at refrigerator temperature (4—5 °C). An appropriate amount of indomethacin was then added to the cold solutions. Dissolution of the drug was promoted by incubation of the mixture at 30 °C.

Measurement of Drug Release Rate from Pluronic Gels——Indomethacin release rates were measured by using plastic dialysis cells similar to that described previously.[10] The capacity of each half-cell was 4 ml and the surface area of the membranes was 3.14 cm^2: An aqueous formulation was placed in the donor compartment and an equal volume of pH 7.2 phosphate buffer in the receptor compartment. The gel donor phase and aqueous receptor phase were separated by a cellulose membrane (Visking Co., type 36/32). The assembled cell was shaken horizontally at the rate of 60 strokes/min in an incubator. The total volume of the receptor solution was removed at certain intervals and replaced by fresh buffer solution.

Release rates of indomethacin from the Pluronic gels were compared with those from commercial suppositories according to the method of Muranishi *et al.*[15] using a suppository release apparatus (Toyama Sangyo Co., Tokyo). The gel preparation (3 ml) in a cylindrical cell was separated from the extraction phase by a membrane filter (Toyo type TM-300) and was slowly stirred (25 rpm) to simulate the rectal environment. The release phase was the same medium as described above, which was stirred at 100 rpm.

The drug concentration of the sample was determined with a spectrophotometer at 266 nm. All experiments were carried out at least in triplicate and average values were plotted.

Rectal Administration——White male rabbits weighing 3.0—3.6 kg were fasted for 36 h prior to the experiments but allowed free access to water. Pluronic F-127 gel preparation was administered into the rectum 3—5 cm above the anus through a stomach sonde needle for rats (KN-348, Natume Seisakusho, Tokyo) fitted on a glass syringe: the gel was chilled prior to filling the syringe to facilitate this procedure. Indomethacin gel preparation was given as 3 ml of 25% (w/w) Pluronic F-127 gels containing 25 mg of the drug. At predetermined intervals, 1 ml of blood sample was collected from the ear vein and centrifuged at 3000 rpm for 10 min.

Measurement of Indomethacin in Plasma——The plasma concentration of indomethacin was determined chromatographically by the method of Skellern and Salole[16] with slight modifications. Plasma (0.4 ml) was mixed with 0.4 ml of citrate buffer (pH 5.0), 0.4 ml of water, and 40 μl of flufenamic acid (internal standard) solution (250 μg/ml). The drug was extracted with 2 ml of diethyl ether by mechanical shaking for 15 min and centrifuged at 3000 rpm for 15 min. The organic phase was evaporated to dryness on a water bath at 30 °C. The residue was

TABLE I. Physicochemical Characteristics of Selected Pluronics

Pluronics	F-68	F-88	F-98	F-108	F-127
Molecular weight	8350	10800	13500	15500	11500
POE : POP ratio	80 : 20	80 : 20	80 : 20	80 : 20	70 : 30
Hydrophobe weight (POP)	1750	2250	2750	3250	3850
Melting point (°C)	50	55	56	57	56

POE: polyoxyethylene. POP: polyoxypropylene.

dissolved in 0.2 ml of mobile phase. After filtration through a membrane filter (0.45 μm), 10 μl of the solution was injected into the chromatograph (Shimadzu LC-6A with a Shimadzu SPD-6A detector). A 25 cm × 4.6 mm i.d. column, packed with reverse-phase packing material (Zorbax NH_2, Shimadzu-du Pont. Kyoto) was used. Elution was carried out with acetonitrile–0.1 M acetic acid (8 : 2) at a rate of 1.3 ml/min.

Results and Discussion

Choice of an Appropriate Pluronic Gel

As a first step, the gel-forming properties of aqueous solutions of non-medicated Pluronic gels were measured. A series of 5 Pluronic gels (10 ml) were prepared in pH 7.2 phosphate buffer at concentrations of 20, 30, and 40% (w/w) by the cold method and their gel-forming properties were observed qualitatively as a function of the copolymer concentration after standing at 25 and 37 °C for 1 h. A list of Pluronics tested and their gel-forming properties is given in Table II, where the gel-forming properties are expressed as gel-formation (+) or no gel-formation (−). Concentrated solutions (20—40% w/w) of Pluronic F-98, Pluronic F-108, and Pluronic F-127 were transformed from low viscosity transparent solutions to solid gels on heating from 5 to 25 or 37 °C, except for 20% (w/w) Pluronic F-98 and Pluronic F-108 at 25 °C. At sufficiently high polymer concentration and temperature, Pluronic F-68 and Pluronic F-88 will form gels.

Release patterns of indomethacin from 5 Pluronic gels (30% w/w) at 37 °C are shown in

Table II. Gel-Forming Property of Selected Pluronics

Concentration of Pluronics (%)	Temperature (°C)	Pluronics				
		F-68	F-88	F-98	F-108	F-127
20	25	−	−	−	−	+
20	37	−	−	+	+	+
30	25	−	−	+	+	+
30	37	−	+	+	+	+
40	25	−	+	+	+	+
40	37	+	+	+	+	+

+: gel-formation. −: no gel-formation.

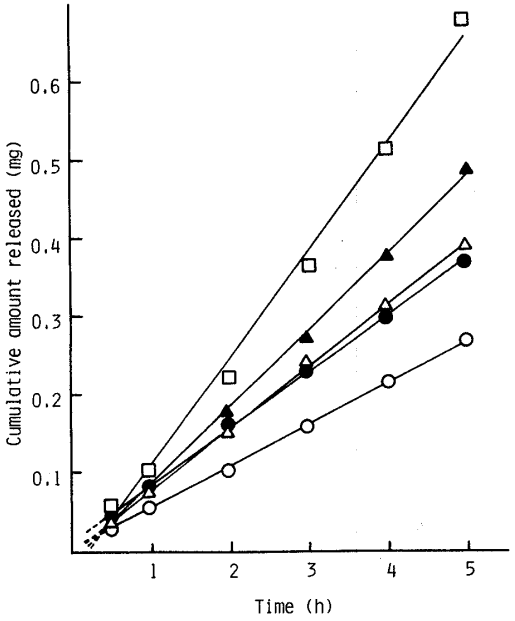

Fig. 1. Release of Indomethacin from 30% (w/w) Pluronic Gels at 37 °C

○, Pluronic F-127; ●, Pluronic F-108; △, Pluronic F-98; ▲, Pluronic F-88; □, Pluronic F-68.
Concentration of indomethacin was 0.5% (w/v). Each value represents the mean of 3 experiments.

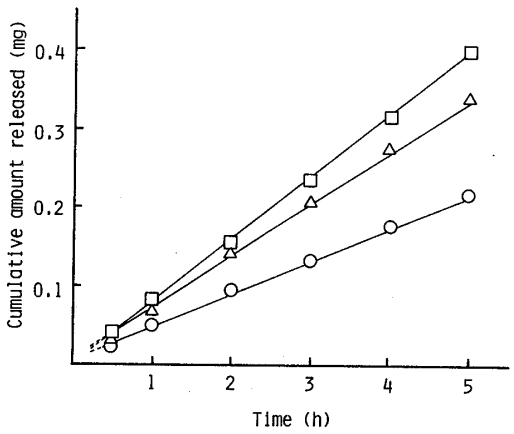

Fig. 2. Effect of Pluronic F-127 Concentration on Indomethacin Release at 30 °C

□, 20%; △, 25%; ○, 30% (w/w) Pluronic F-127 gels.
Concentration of indomethacin was 0.5% (w/v). Each value represents the mean of 3 experiments.

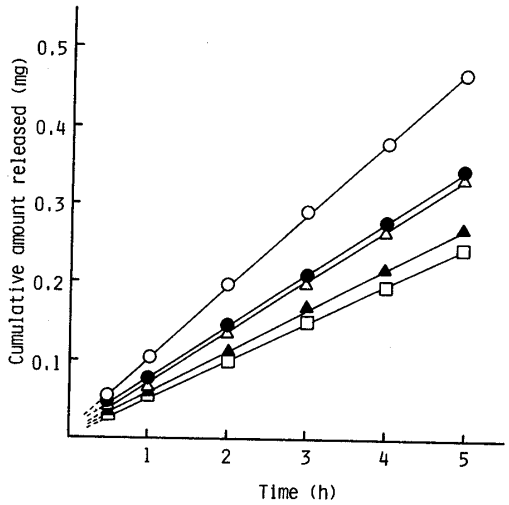

Fig. 3. Effect of Temperature on Indomethacin Release from 25% (w/w) Pluronic F-127 Gel

□, 20 °C; ▲, 25 °C; △, 30 °C; ●, 37 °C; ○, 44 °C.
Concentration of indomethacin was 0.5% (w/v). Each value represents the mean of 3 experiments.

Fig. 1. Release was fastest from Pluronic F-68 and slowest from Pluronic F-127. Pluronic F-68 did not form a gel at a concentration of 30% (w/w) at 37 °C. In a comparison of the release of indomethacin from Pluronic F-88, Pluronic F-98, and Pluronic F-108, the rates of release were F-88 > F-98 > F-108. This order seems to be the reverse of the order of viscosity of the gels at 37 °C.[17,18] Since slow release was desired, Pluronic F-127 was used for further studies of the release behavior of indomethacin *in vitro* and *in vivo*.

Release Rate of Indomethacin from Pluronic F-127 Gels

Effect of Pluronic F-127 Concentration on Drug Release——For studying the effect of Pluronic F-127 concentration on the drug release kinetics, the release of indomethacin dissolved in vehicles composed of different concentrations of Pluronic F-127 was investigated. In this study, both the initial concentration of drug in the vehicle (0.5% w/v) and the temperature (30 °C) were held constant, while the concentration of Pluronic F-127 was varied (20, 25, and 30% w/w).

Figure 2 shows plots of the data, expressed as the cumulative amount of indomethacin released *versus* time. The release of indomethacin from the gels shows a typical zero-order pattern. The apparent release rate (k) in each experiment was determined by measuring the slopes (mg/h) of the lines by the least-squares method. The values for the vehicles with 20, 25, and 30% (w/w) Pluronic F-127 concentrations were 0.79, 0.67, and 0.43 mg/h, respectively. With increasing concentration of Pluronic F-127 in the vehicle a corresponding decrease in apparent release rate of the drug occurred. The reason for the decreased release rate may be a reduction in the size of the water channels and an increase in the micro-viscosity of the water channels of the gel.[8] It was reported that the higher the Pluronic F-127 concentration, the greater the yield strength[5] or viscosity.[18]

Effect of Temperature on Drug Release——The release patterns of indomethacin were measured at 20, 25, 30, 37, and 44 °C, and the results are shown in Fig. 3. In this study, both the initial concentration of drug (0.5% w/v) in the vehicle and the Pluronic F-127 concentration (25% w/w) were held constant; the higher the temperature, the greater the drug release.

The activation energy of release, as determined from the slope of a plot of log k *versus* the

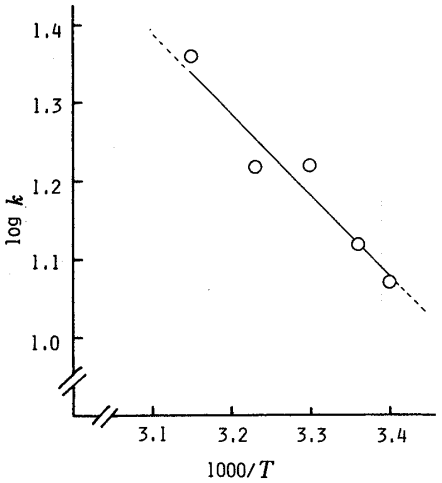

Fig. 4. Temperature Dependency of the Release Rate of Indomethacin from Pluronic F-127 Gel (Data from Fig. 3)

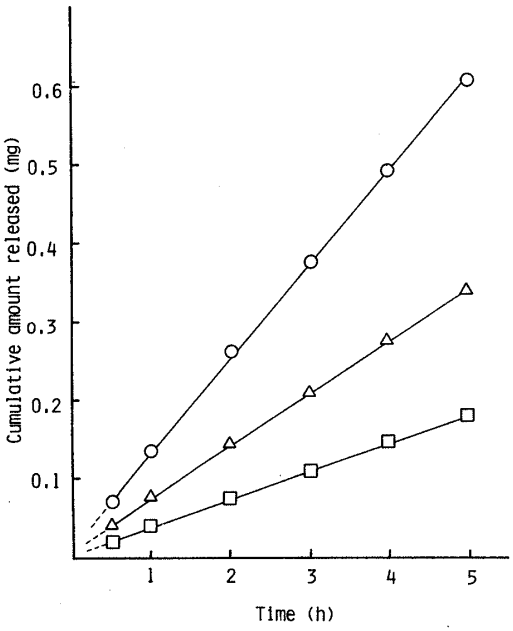

Fig. 5. Effect of Initial Indomethacin Concentration on Release from 25% (w/w) Pluronic F-127 Gel at 30 °C

□, 0.3%; △, 0.5%; ○, 0.8% (w/v).
Each value represents the mean of 3 experiments.

reciprocal of the absolute temperature (Fig. 4), was 4.79 kcal/mol. The energy required for indomethacin release from the 25% (w/w) Pluronic F-127 gel is close to the value for lidocaine (5.10 kcal/mol)[8] and in the range of 4.5—5.0 kcal/mol reported for the diffusion of low-molecular-weight non-electrolytes in liquids.[19] Since Pluronic F-127 gels exhibit reverse thermal behavior, their viscosity increases as the temperature is increased.[8,18] However, the apparent release rate for indomethacin increased with increasing temperature from 20 to 44 °C. Chen-Chow and Frank[8] suggested that the rate of drug release is determined by the micro-viscosity of the extramicellar fluid of the gel rather than the macro-viscosity. The viscosity of the extramicellar water channels would be expected to decrease with increasing temperature. Since Pluronic F-127 gels are viscous isotropic liquid crystals consisting of micelles,[8,20] it is likely that the drug is released by diffusion through the water channels of the gel matrix.

The linear increase in release with increasing temperature suggests that the release characteristics of the copolymer would change within the body temperature range. This finding indicates that special care may be necessary in applying this dosage form.

Effect of Initial Drug Concentration on Drug Release——The effect of initial drug concentration on the release pattern was tested at three drug concentrations (0.3, 0.5, and 0.8% w/v), and the results are shown in Fig. 5. It is evident that variation in the initial drug concentration in the vehicle affects the drug release. The smaller the drug concentration, the more slowly the drug was released.

These results suggest that the Pluronic F-127 gel is useful for controlling the release of drugs. The gel may be used as a reservoir from which drugs are released when placed intrarectally for systemic treatment, since the Pluronic F-127 gel forms a soft gel at body temperature.

Comparison of Indomethacin Release from Pluronic F-127 Gels and Suppositories

On the basis of release studies using dialysis cells, it was expected that Pluronic F-127 gels

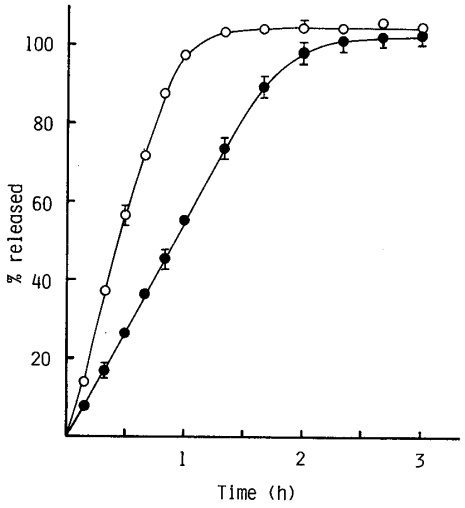

Fig. 6. Comparison of Indomethacin Release from 25% (w/w) Pluronic F-127 Gel and Commercial Suppositories at 37 °C

●, 25% (w/w) Pluronic F-127 gel; ○, commercial suppositories.

Each preparation contained 25 mg of the drug. Each value represents the mean ± S.E. of 4 experiments.

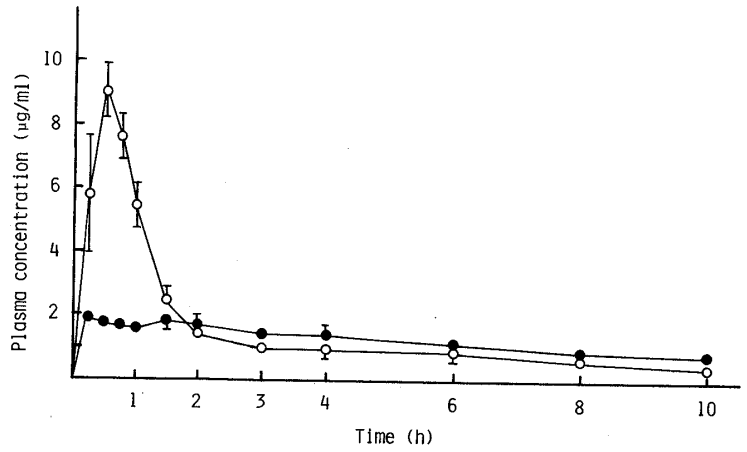

Fig. 7. Plasma Concentration of Indomethacin after Rectal Administration to Rabbits

Key, see Fig. 6.

Each value represents the mean ± S.E. of 4 rabbits.

would release the drug more slowly than the conventional suppositories. The release pattern of indomethacin from 25% (w/w) Pluronic F-127 gels containing 25 mg of the drug was compared with that of commercially available suppositories.

As shown in Fig. 6, the release of indomethacin from Pluronic gel was significantly slower than that of indomethacin suppositories. The drug was completely released from the suppositories within 1 h, whereas the percentage released in this period was 55% for Pluronic gel. These *in vitro* results suggest that Pluronic gel might serve as a rate-controlling barrier and be useful as a vehicle for sustained-release preparations of indomethacin to be administered rectally.

Plasma Concentration of Indomethacin after Rectal Administration

Indomethacin gel preparations made by dissolving the drug (25 mg) in Pluronic F-127 aqueous gel were administered rectally to rabbits and the drug plasma levels were compared with those after rectal administration of commercial suppositories.

The plasma drug levels after rectal administration are shown in Fig. 7. In this experiment, there was a distinct difference in plasma concentration response between commercial suppositories and Pluronic gel preparations. The absorption of indomethacin from commercial suppositories was very rapid, and the plasma level reached a peak of 9.0 μg/ml at 30 min after administration. On the other hand, the gel preparation did not show a sharp peak

of plasma concentration, but produced a sustained plateau plasma level of indomethacin from 15 min to 10 h without a lag time. The area under the curve (AUC) was calculated by means of the trapezoidal method.[21] The mean $[AUC]_0^{10}$ value ($\pm$S.E., $n=4$) after administration of the Pluronic gel preparation ($12.71 \pm 1.28\,\mu g \cdot h/ml$) was slightly smaller than that of the commercial suppository ($15.77 \pm 1.27\,\mu g \cdot h/ml$, $p > 0.1$). Therefore, no significant difference in extent of bioavailability could be seen between the Pluronic gel and commercial suppositories.

Bechgaard *et al.*[22] reported that the frequency and severity of side effects of indomethacin are well correlated with peak plasma concentrations. Alvan *et al.*[23] observed on adverse effect of indomethacin on the nervous system at plasma concentrations exceeding $5\,\mu g/ml$. The results of the present study show that the initial high peak plasma concentration does not occur after administration of the Pluronic gel preparation, suggesting that side effects might also be reduced.

Thus, in terms of decrease in the peak of plasma concentration and maintenance of indomethacin concentration in plasma, the Pluronic gels are superior to the conventional suppositories. Indomethacin preparations using a Pluronic F-127 aqueous gel may be practically useful as a rectal preparation with reduced side effects and with prolonged action.

General Discussion

Pluronic F-127 consists (by weight) of approximately 70% ethylene oxide and 30% propylene oxide with an average molecular weight of 11500. The unique characteristic of this copolymer is reverse thermal gelation; concentrated solutions (20—40% w/w) of the copolymer are fluid at refrigerator temperature (4—5 °C), but are soft gels at body temperature (Table II). This suggests that when poured onto the skin or injected into a body cavity, the preparation will form a solid artificial barrier and sustained release depot.

The present results revealed that Pluronic F-127 gels are useful as a vehicle for rectal administration of drugs. There are several dosage forms available for the rectal delivery of drugs; suppositories; rectal gelatin capsules; and enemas.[13] Pluronic gels are potentially useful for sustained drug release in the form of enemas. There is no practical difficulty in administration of the gel preparation.

Although this study was limited to rectal administration, it seems likely that the Pluronic gels will also be particularly suitable for topical and nasal administrations because of their reverse sol–gel property.

Indomethacin administration has been limited to oral and rectal routes. More recently, an indomethacin ointment has been developed for topical application.[24] For application to the skin, such water-based polymeric gels offer several advantages over traditional oleaginous bases in terms of ease of application, cosmetic acceptability (colorless and water-washable) and good drug release characteristics. It was reported that indomethacin topical solution is superior to the ointment in terms of ease of application for the therapy of rheumatism.[25]

Similarly, for nasal use, semi-solid gels are better retained in the nasal mucous membranes. A study on the use of Pluronic gels as a vehicle for nasal administration of drugs is in progress.

It has been suggested that bioadhesive polymers which adhere to the esophagus or gastrointestinal tract will be effective and lead to significant improvements in oral drug delivery.[26,27] The reversible sol–gel property of Pluronics gels would allow the cool solution to flow into the esophagus. Our previous report[10] on the use of Pluronic gels as a vehicle for anticancer agents indicated that Pluronic gels are good potential bioadhesives for drug delivery in the therapy of esophageal carcinoma.[28]

Thus, Pluronic gels should find application for drug delivery in the rectum, the nose and the gastrointestinal tract (including the esophagus), as well as the skin and the eye.

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References and Notes

1) Pharmaceutical Application of Biomedical Polymers, Part XX. Part XIX: S. Miyazaki, N. Hashiguchi, W.-M. Hou, C. Yokouchi, and M. Takada, *Chem. Pharm. Bull.*, in press.
2) This work was presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April 1985.
3) Present address: *Department of Dosage Form, Shanghai Institute of Pharmaceutical Industry, 1320 Beijing Road West, Shanghai, China.*
4) I. R. Schmolka, *J. Am. Oil Chem. Soc.*, **54**, 110 (1977).
5) I. R. Schmolka, *J. Biomed. Mater. Res.*, **6**, 571 (1972).
6) Asahi Denka Kogyo Co., PLURONIC and TETRONIC, Publication No. 04'81-1.
7) H. P. Gregor, H. T. Hsia, S. Palevsky, R. S. Neuwirth, and R. M. Richart, "Controlled Release Polymeric Formulations," ed. by D. R. Paul and F. W. Harris, American Chemical Society, Washington D.C., 1976, pp. 147—156.
8) P. C. Chew-Chow and S. G. Frank, *Int. J. Pharm.*, **8**, 89 (1981).
9) S. C. Miller and M. D. Donovan, *Int. J. Pharm.*, **12**, 147 (1982).
10) S. Miyazaki, S. Takeuchi, C. Yokouchi, and M. Takada, *Chem. Pharm. Bull.*, **32**, 4205 (1984).
11) L. Helleberg, *Chin. Pharmacokinet.*, **6**, 245 (1981).
12) L. P. J. Holt and C. F. Haukins, *Br. Med. J.*, **1**, 1354 (1965).
13) A. G. Boer, F. Moolenaar, L. G. J. Heede, and D. D. Breimer, *Clin. Pharmacokinet.*, **7**, 285 (1982).
14) T. Umeda, A. Matsuzawa, T. Yokoyama, K. Kuroda, and T. Kuroda, *Chem. Pharm. Bull.*, **31**, 2793 (1983).
15) S. Muranishi, Y. Okubo, and H. Sezaki, *Yakuzaigaku*, **39**, 1 (1979).
16) G. G. Skellern and E. G. Salole, *J. Chromatogr.*, **114**, 483 (1975).
17) M. Vadnere, G. Anudon, S. Lindenbaum, and J. L. Haslam, *Int. J. Pharm.*, **22**, 207 (1984).
18) S. C. Miller and B. R. Drabik, *Int. J. Pharm.*, **18**, 269 (1984).
19) G. L. Flynn, S. H. Yalkowsky, and J. J. Roseman, *J. Pharm. Sci.*, **63**, 479 (1974).
20) J. Rassing and D. Attwood, *Int. J. Pharm.*, **13**, 47 (1983).
21) W. A. Ritschel, "Handbook of Basic Pharmacokinetics," Drug Intelligence Publications, Hamilton, 1976, pp. 235—243.
22) H. Bechgaard, R. R. Brodie, L. F. Chasseaud, P. Houmoller, J. O. Hunter, P. Siklos, and T. Taylor, *Eur. J. Clin. Pharmacol.*, **21**, 511 (1982).
23) G. Alvan, M. Orme, L. Bertelsson, R. Ekstraud, and L. Palmer, *Clin. Pharmacol. Ther.*, **18**, 364 (1975).
24) T. Inukai, H. Awata, H. Kurokawa, M. Adachi, Y. Nakanishi, and Y. Nagao, *Yakuri To Chiryo*, **7**, 21 (1979).
25) S. Kondo, *Kiso To Rinsho*, **18**, 494 (1984).
26) K. Park and R. Robinson, *Int. J. Pharm.*, **19**, 107 (1984).
27) P. A. Swispner, S. L. Sendelbeck, and J. W. Fara, *Int. J. Pharm.*, **22**, 219 (1984).
28) T. Kamano, H. Kishino, K. Mizukami, N. Azuma, K. Kondo, Y. Watanabe, and T. Kidokoro, *Gan To Kagaku Ryoho*, **9**, 1394 (1982).