DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 4, pp. 347–357, 2004

RESEARCH PAPER

Development of Local Injectable Dental Gel: The Influence of Certain Additives on Physicochemical Properties of Glycerylmonooleate-Based Formulations

S. Okonogi,[1,*] S. Khongkhunthain,[2] P. Bunyaratavej,[2] T. Thusaphorn,[1] and R. Umpriwan[2]

[1]Faculty of Pharmacy and [2]Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand

ABSTRACT

The current research study is based on the design and development of a sol-gel biodegradable controlled-release formulation for use in the treatment of periodontal diseases. Glycerylmonooleate (GMO) was used as a main composition in the gel base. The influence of various additives, e.g., glycerylmonostearate (GMS), methylcellulose (MC), surfactants, and triglycerides, in GMO formulations on rheologic and swelling properties and release characteristics was described. It was demonstrated that the surfactants and triglycerides affected rheologic behavior, whereas GMS and MC influenced both rheologic and swelling properties of the bases. The release study revealed that drug released from the gel bases depended on the square root of time. The kinetics can be explained by the Higuchi's diffusion theory. Some polyols could enhance drug release from the gel. The stability results suggested that the dental gels obtained should be kept in the low temperature range.

Key Words: Glycerylmonooleate; Dental gel; Periodontal disease; Rheology; Swelling; Drug release; Stability; Tetracycline hydrochloride.

INTRODUCTION

Bacteria flora presenting in periodontal pockets play an important role in the etiology of periodontal disease.[1] Systemic administration of antibiotics has proved useful in the management of subgingival flora. However, the drugs must be given in high doses to maintain the effective concentrations of drug in gingival crevicular fluid. Therefore, this type of treatment requires sufficient caution against occasional side effects, e.g., gastrointestinal disorders, and the development of resistant bacteria and superinfection.[2]

*Correspondence: S. Okonogi, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, 50200, Thailand; E-mail: sirioko@pharmacy.cmu.ac.th.

DOI: 10.1081/DDC-120030929
0363-9045 (Print); 1520-5762 (Online)

An advance in pathological researches on periodontal disease and pharmaceutical technologies, the local drug treatment for periodontal disease by sustained delivery systems, has been recently developed.[3–5] However, the techniques are still unsatisfactory for clinical use because they consist of insoluble polymers such as ethylene vinyl acetate, polyethylmethacrylate,[6] and ethyl cellulose.[7] These substances must be removed from the periodontal pocket after the completion of drug release. This occasionally causes local mechanical irritation and disturbs periodontal repair. Recently, a thermosensitive polymer, Poloxamer 407, has been introduced as a gelling polymer in dental gel base because it exhibits the sol-gel transition temperature.[8,9] However, poloxamer is not biodegradable and the formed gel is dissolved in a few hours.[10] Moreover, toxicity of poloxamer has been reported when administered systemically into rat.[11]

To overcome the disadvantages mentioned above, we attempted to develop a controlled-release injectable gel base. Glycerylmonooleate (GMO) was used as a main principle in the gel base formulation because it is a viscous injectable liquid that can be changed to a liquid crystalline phase when in contact with water.[12] This crystalline phase possesses a desirable adhesive property.[13,14] Moreover, it is biodegradable as it could be converted to oleic acid and glycerol by lysosomal enzyme liberated by neutrophils and some bacteria present in the pocket.[15] The influence of various additives on GMO gel formulations on swelling and rheologic properties and release characteristics of the gel base was studied. Tetracycline hydrochloride (TCH) was used as a model drug because it was found effective against the microorganisms associated with periodontitis in the gingival crevice.[16] The in vitro release characteristics and the effect of some polyols on the release behavior of the dental gels were carried out. The stability of TCH in dental gel formulations was also investigated.

EXPERIMENTAL

Materials

Glycerylmonooleate (GMO), glycerylmonostearate (GMS), and methylcellulose (MC) were purchased from Fluka (Switzerland). Cyclohexane was obtained from Barcelona (Spain) and dimethyl formamide was obtained from Labscan Asia Co. Ltd. (Dublin, Ireland). Sodium hydroxide and monobasic potassium phosphate were purchased from Merck (Darmstadt, Germany). Tetracycline hydrochloride (TCH) was supplied by Ningxia Pharmaceutical Factory (Ning Xia, China). Sesame oil, Tween 80, Span 80, Propylene glycol (PG), polyethylene glycol 400 (PEG 400), and glycerol were of pharmaceutical grade. All other chemicals were of reagent grade.

Preparation of Gel Bases

The meltable solid materials and liquid ingredients were mixed and heated to about 45–50°C to form a viscous liquid base. Insoluble ingredients were pulverized and only the portion with particle size <63 μm was dispersed throughout the viscous liquid base. The mixture was slowly cooled with a constant stir until congealed. The formulated gel bases were stored at 4°C for further studies.

Preparation of Drug Containing Dental Gels

The selected gel bases were allowed to melt at 45°C in a water bath. An accurate amount of TCH powder was dissolved in a certain portion of water. The solution was gradually incorporated into the gel base to give 10% (w/w) of drug concentration dissolved in the base. The dental gels were investigated immediately after preparation.

Swelling Study

An accurate weight portion of the gel (1–2 g) was placed in a series of petri dishes (5-cm diameter) as supporting containers and weighed. Each gel-containing dish was immersed in 300 mL of deaerated distilled water at 37°C. At predetermined time intervals, the dish with gel was taken off, blot-dried and reweighed. The kinetic swelling behavior was calculated as a swelling ratio (W_t/W_o), where W_t indicated the weight of sample at time t and W_o denoted the initial weight of the sample.

Study of Rheologic Properties

The rheologic behavior of gels was studied using a Brookfield rotational viscometer model DV III (Torque HA, Brookfield Co. Ltd., Massachusetts, USA). The measurement system used was searle geometry with a stationary cylindrical cup and a rotating cylindrical spindle of various geometries appropriate to the samples. The spindle was rotated at a given angular velocity, which produced a shear rate gradient through the gap between the two cylinders. The temperature of the system was controlled at 37°C.

In Vitro Release Study

The release of TCH from dental gels was determined by using a horizontal-type diffusion cell apparatus. Each cell was composed of two compartments, donor and receptor, separated by a dialysis membrane (MW cut-off 10,000–12,000). The surface area of the membrane exposed to the solution in the receiving compartment was 3.14 cm^2. The donor compartment was accurately filled with 300 mg of dental gel. The exact portion of 3-mL 200 mM phosphate buffer solution pH 7.2 was filled into the receiving compartment. Two-mL aliquots of the receiving fluid were periodically sampled at specified time intervals and replaced with the same volume of the fresh buffer solution. Suitable dilutions were made using the same buffer solution. The drug concentration was determined spectrophotometrically at 365 nm. The results were expressed as the mean±SD of three independent experiments. The experiment was controlled at 37°C. The TCH calibration curve was made by plotting the UV absorption at 355 nm against the respective drug concentration ranged from 2 mcg/ml to 10 mcg/ml.

Stability Assessment of TCH in Dental Gels

Samples of prepared dental gels were stored in closed containers at various temperatures of 4°C, 30°C, or 45°C for 90 days. An accurate weight sample equivalent to 50 mg TCH was taken at appropriate time intervals and dissolved in 30 mL cyclohexane, then transferred to the separatory funnel. The 30-mL mixture of 0.1 M ammonium oxalate solution and dimethyl formamide (7:3 volume ratio) was added to the funnel and mixed. The mixture was left until separated. The lower liquid layer was collected. This manner was done in triplicate and the lower liquid layers were collected together in a 100-mL volumetric flask and adjusted with the same solvent to volume. The solution was filtered through a 0.45-μm syringe filter. The filtrate was analyzed for TCH by UV spectrophotometry. The physical appearance of the gels after the period of storage, such as color change and phase separation, was also investigated in comparison with that of the freshly prepared gels.

Statistical Data Analysis

Statistical data analysis was performed using the t-test with $p<0.05$ as the minimal level of significance.

RESULTS AND DISCUSSIONS

The preliminary experiment for rheologic behavior of GMO alone was carried out. The result is shown in Fig. 1. The result was clear that the rheologic behavior of the pure GMO was Newtonian flow.

It has been reported that a small amount of water (less than 5%) when added to GMO yields a relatively low viscosity. The further addition of water leads to the formation of highly viscous lamellar or cubic

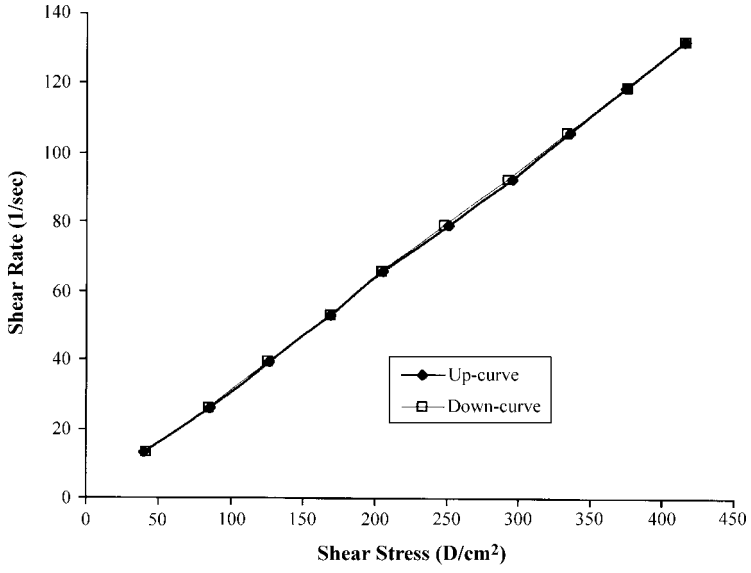

Figure 1. Rheogram of pure GMO.

Table 1. Concentrations (% w/w) of additives in GMO base formula.

	Formula				
Substances	1	2	3	4	5
GMO	60	55	40	40	40
GMS	–	–	10	10	10
MC	10	10	10	10	10
Sesame oil	–	5	10	10	10
Tween 80	–	–	–	10	–
Span 80	–	–	–	–	10
Water	30	30	30	30	30

phase.[17,18] In this study, we found that the gel base containing 30% water at 30°C gave highest viscosity, leading to the conclusion that the cubic phase of GMO was formed. However, this system was still injectable through the 22-gauge blunt needle used for in vivo administration. It is well known that methylcellulose (MC) exhibits good swelling and adhesive properties when in contact with water. Therefore, MC was added to the GMO gel formulation with the aim of promoting these properties (Table 1, formula 1). The results indicated that the rheologic behavior of MC-containing gel base was pseudoplastic with thixotropy (Fig. 2), a significant change from that of the GMO alone. The hysteresis loop with a characteristic bulge in the up-curve was considered to be due to the extreme swelling of the system caused by the added micro-particulate MC.

Sesame oil has been reported to lower the melting point of GMO.[25] When a small portion of sesame oil was added to the GMO–MC-water system (Table 1, formula 2), the rheologic behavior of the system approximated Newtonian flow (Fig. 3), similar to that of GMO alone. This result indicated that sesame oil improved the flow properties of the system.

Glycerylmonostearate (GMS) is a monoglyceride of saturated fatty acid with the same number of carbon atoms as GMO. The addition of GMS to formula 2 was done (Table 1, formula 3) with the objective of increasing the stiffness of the base. The results demonstrate that GMS affected the rheologic property of the former base as the system was changed to pseudoplastic non-Newtonian flow as shown in Fig. 4. The results also indicate that GMS decreased the swelling property of the GMO base; however, this characteristic was improved by the addition of MC. The swelling isotherm of this study is shown in Fig. 5. From the swelling isotherms, each point represented the average swelling ratio (W_t/W_o) after water uptake during 12 h. In the GMO–GMS–MC system and GMO alone, the swelling curves began to level off substantially at 1–2 h and approached the horizontal line corresponding to equilibrium swelling. At the longest swelling time, 12 h, the swelling ratios of these two systems were 2.224 and 2.207, respectively, whereas the swelling ratio of the GMO–GMS system was only 1.478.

In addition to having solubility power, surfactants have been reported to enhance the release of drug from

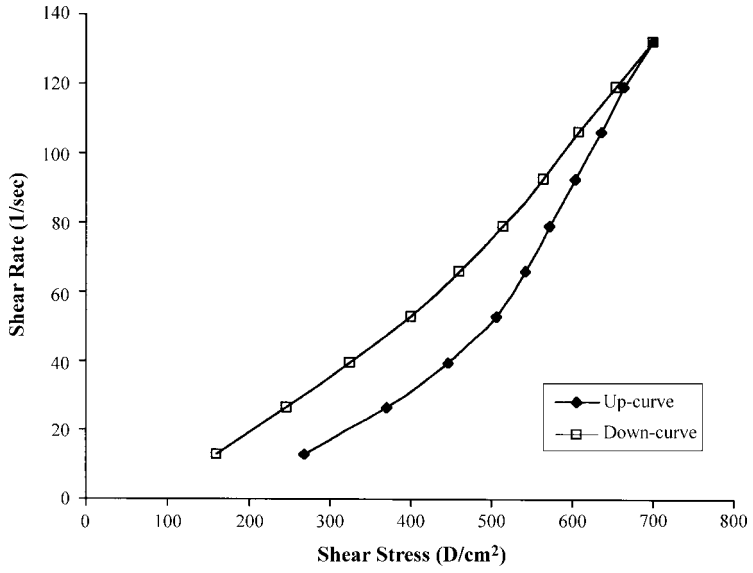

Figure 2. Rheogram of GMO base (Formula 1).

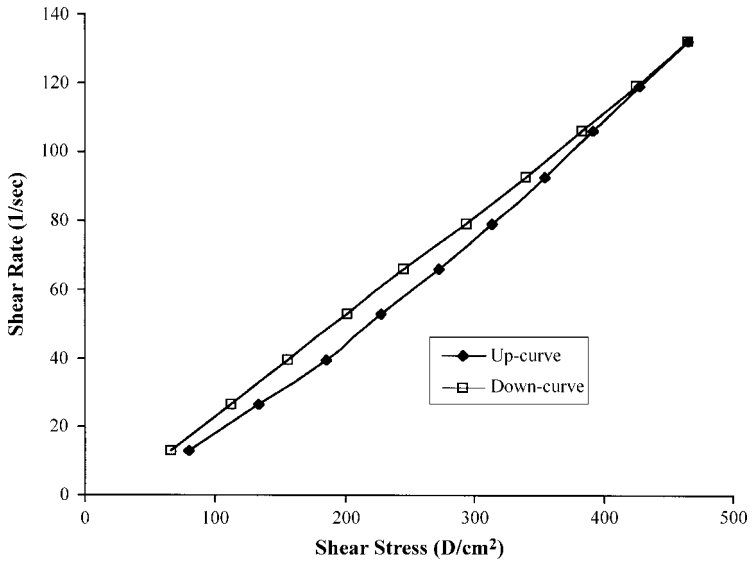

Figure 3. Rheogram of GMO base (Formula 2).

the formulations.[19,20] Hence, two different nonionic surfactants, a water-soluble Tween 80 and a lipid-soluble Span 80, were added to GMO gel base formulations (Table 1, formula 4 and formula 5, respectively) with the aim of enhancing drug release. The rheologic results show that both surfactants gave a significant change of rheologic behavior compared to that of GMO alone as shown in Fig. 6 and Fig. 7, respectively. These rheograms demonstrate pseudo-plastic flow with a huge hysteresis loop, particularly in the system that contained Tween 80, which appeared as a large bulge in the up-curve. It was considered that surfactant swelled the crystalline phase of the GMO-water system, causing the formation of a cubic ''house-of-cards structure.'' This three-dimensional network resulted in a bulged curve. The results also indicate gel-to-sol transformation and shear thinning or consistency lost through shearing. In other words, they

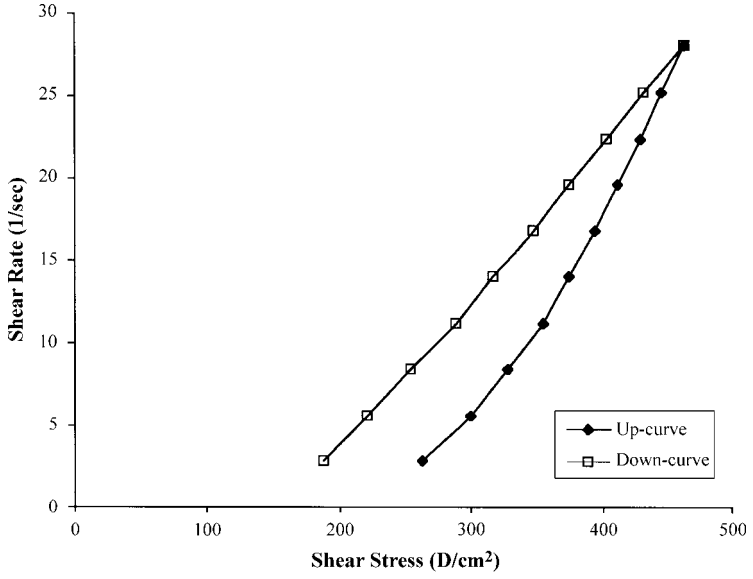

Figure 4. Rheogram of GMO base (Formula 3).

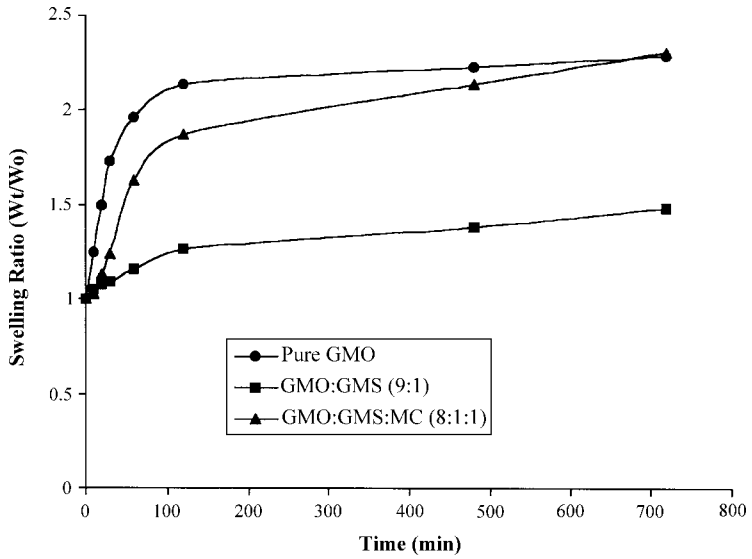

Figure 5. Effects of GMS and MC to GMO swelling isotherm.

became less viscous as the shear rate increased, which facilitated the flow of the formulations. The huge hysteresis loop indicated a breakdown of structure that did not re-form immediately when the stress was removed or released.

In pharmaceutical development of easily injectable dental gels, the rheologic behavior of the gels was nearly pseudoplastic. For this reason, suitable ingredients used in the gel base formulations in further studies were selected based on the preliminary data of rheology and swelling. Besides GMO, the selected ingredients were GMS, MC, sesame oil, and Span 80. Span 80 was selected instead of Tween 80 because of its oil soluble property, similar polarity to the other principle liquid ingredients used, and smaller area of hysteresis loop compared to that of Tween 80. Therefore, the formulated gel base system was a single liquid phase suspended with MC microparticulates.

The concentration of ingredients in the formula has been adjusted in order to express flowability through

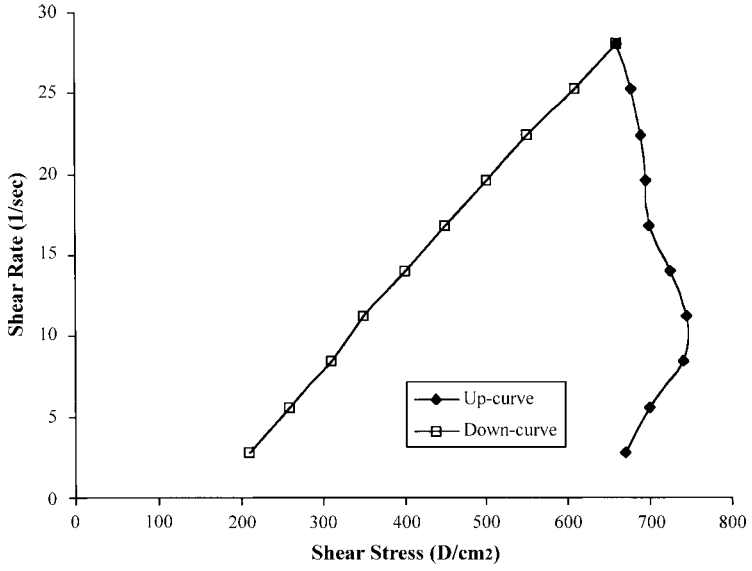

Figure 6. Rheogram of GMO base (Formula 4).

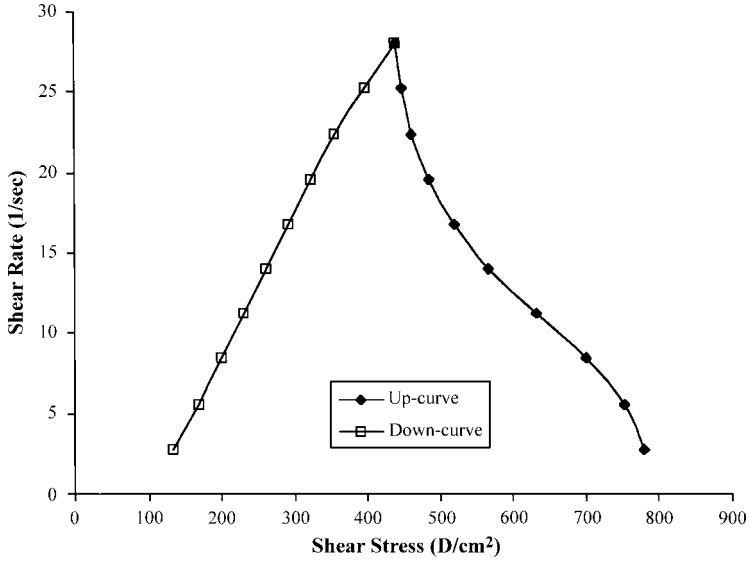

Figure 7. Rheogram of GMO base (Formula 5).

the 22-gauge blunt needle after drug incorporation. Several polyols, e.g., PG, PEG 400, and glycerol, were added to the gel base formula to be investigated for their effects on drug release. The compositions of all gel bases developed at this moment are shown in Table 2. As the drug was firstly dissolved in water before incorporation in the gel base, the complete dental gel was composed of both oily phase from the base and aqueous phase from the drug solution. Based on our previous rheologic results, it could be presumed that the liquid crystalline phase, especially the cubic one, formed easily when the GMO-water system consisted of surfactant. The highly ordered cubic liquid crystalline structure with the amphiphilic character of Span 80 gave the gel base system high ability to absorb excess water. Consequently, the aqueous solution of TCH could disperse homogeneously in the lipid gel base. All TCH dental gel formulations were subjected to the in vitro release studies, and the results were shown as drug release profiles in Fig. 8. The release of TCH from gel base formula A, which contained no polyols, was very slow, but a sufficient cumulative amount of TCH was achieved for the intended use. When the mixture of gel base and mainly GMO came into contact with water, TCH from the surface zone immediately leaked into the surrounding liquid. As the drug slowly cleared and hydration progressed, the remaining gel base turned into a condensed liquid crystalline state. This did not occur instantaneously, depending on the thickness of the gel. The drug-cleared area of the liquid crystalline gel regulated the release of TCH from the inner core, which slowly became hydrated. Furthermore, MC exhibited swelling that resulted in an increase in product viscosity. These results caused the retardation of drug release from the gel. Different polyols, e.g., propylene glycol (PG), polyethylene glycol 400 (PEG 400), and glycerol, were added to the gel base (formulation A) in order to test for their enhancing power on drug release from the base. The results indicate that the drug release from the gel bases containing each of the polyols significantly increased ($p<0.05$). It was thought that the polyols increased the hydrophilicity of the cubic liquid crystalline phase of the gel. The addition of polyols to the base also demonstrated a decrease in viscosity of the gel. Both hydrophilicity increase and viscosity decrease caused the increased rate of aqueous dissolution fluid entry into

Table 2. Compositions (% w/w) of free-water gel bases.

	Formula			
Substances	A	B	C	D
GMO	70	60	60	60
GMS	5	5	5	5
MC	5	5	5	5
Sesame oil	10	10	10	10
Span 80	10	10	10	10
PG	–	10	–	–
PEG 400	–	–	10	–
Glycerol	–	–	–	10

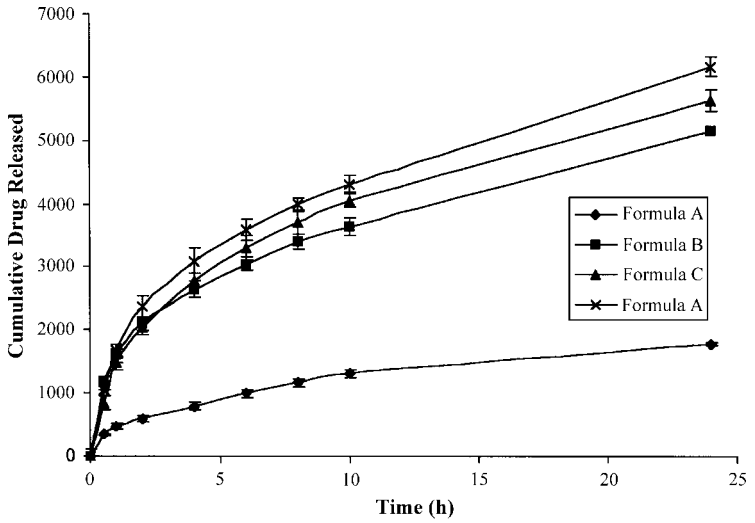

Figure 8. Release profiles of TCH dental gels (bars show the standard deviation).

the gels; hence drug release was promoted. The cumulative amount of drug release from glycerol containing gel was significantly higher than that from the other gels. Among the polyols used, glycerol was the best enhancer, as it exhibited the maximum enhancing power on TCH release from the base.

When the cumulative amount of TCH released from each formula was plotted against the square root of time, straight lines were obtained. The correlation coefficients and slopes of the lines are shown in Table 3. The results suggest that the released rate of TCH from all formulated dental gel bases was diffusion controlled, which can be described by the simplified Higuchi[21] diffusion equation:

$$Q = 2\,C_o(Dt/\pi)^{\frac{1}{2}}$$

when the drug is completely dissolved in the vehicle, Q=the cumulative amount of drug released into the receptor phase, C_o=is the initial drug concentration in the vehicle, D=the diffusion coefficient of drug in the vehicle, and t=the time elapsed since the start of drug release.

To complete the assessment of pharmaceutical formulation development, the stability of dosage form

Table 3. The correlation coefficients and slopes of straight lines of Higuchi plots.

Formula	Correlation coefficients	Slope of straight line ($\mu g \times h^{1/2}$)
A	0.99	358.54
B	0.97	979.37
C	0.93	1139.40
D	0.99	1246.20

Table 4. Physical properties of TCH dental gels after 90 days.

Formula	Storage temperatures (°C)	Physical characteristics
A	4	Change of color to yellowish
	30	Change of color to yellowish and only the surface of the gel exposed to the air, the color was changed to pale brown
	45	Change of color to brownish, phase separation, slightly more fluid
B	4	Change of color to yellowish
	30	Change of color to yellowish and only the surface of the gel exposed to the air, the color was changed to pale brown
	45	Change of color to brownish, phase separation, slightly more fluid
C	4	Change of color to yellowish
	30	Change of color to pale brown
	45	Change of color to brownish, phase separation, slightly more fluid
D	4	Change of color to yellowish
	30	Change of color to pale brown
	45	Change of color to brownish, phase separation, slightly more fluid

to obtain a long shelf life should be considered. All freshly prepared dental gels were smooth, homogeneously dispersed, and pale yellow according to the color of TCH. The physical appearance of all dental gels showed no change during 7 days of storage in all studied temperatures. After a period of 90 days, the physical properties of gels changed, as shown in Table 4. The amount of change depended on the storage temperatures; the higher the temperature, the more deterioration. Wu and Rui[22] reported that after TCH was stored for a period of time, it was converted into anhydrotetracycline, and 4-epianhydrotetracycline, and the absorbance of TCH shifted to 430 nm. Therefore, the color change that occurred after storage was considered to be due to the degradation products of TCH. The phase separation of the gel was thought to be due to the oxidation of lipids in the gel base. The percentage of drug remaining in each dental gel during 90 days is shown in Fig. 9. There is significant difference ($p>0.05$) between the stability profiles of each formula in the same temperature. However, when storage temperature increased, drug content decreased. Within 30 days, the drug concentration remaining in all dental gels stored at 4°C was above 90%, whereas the

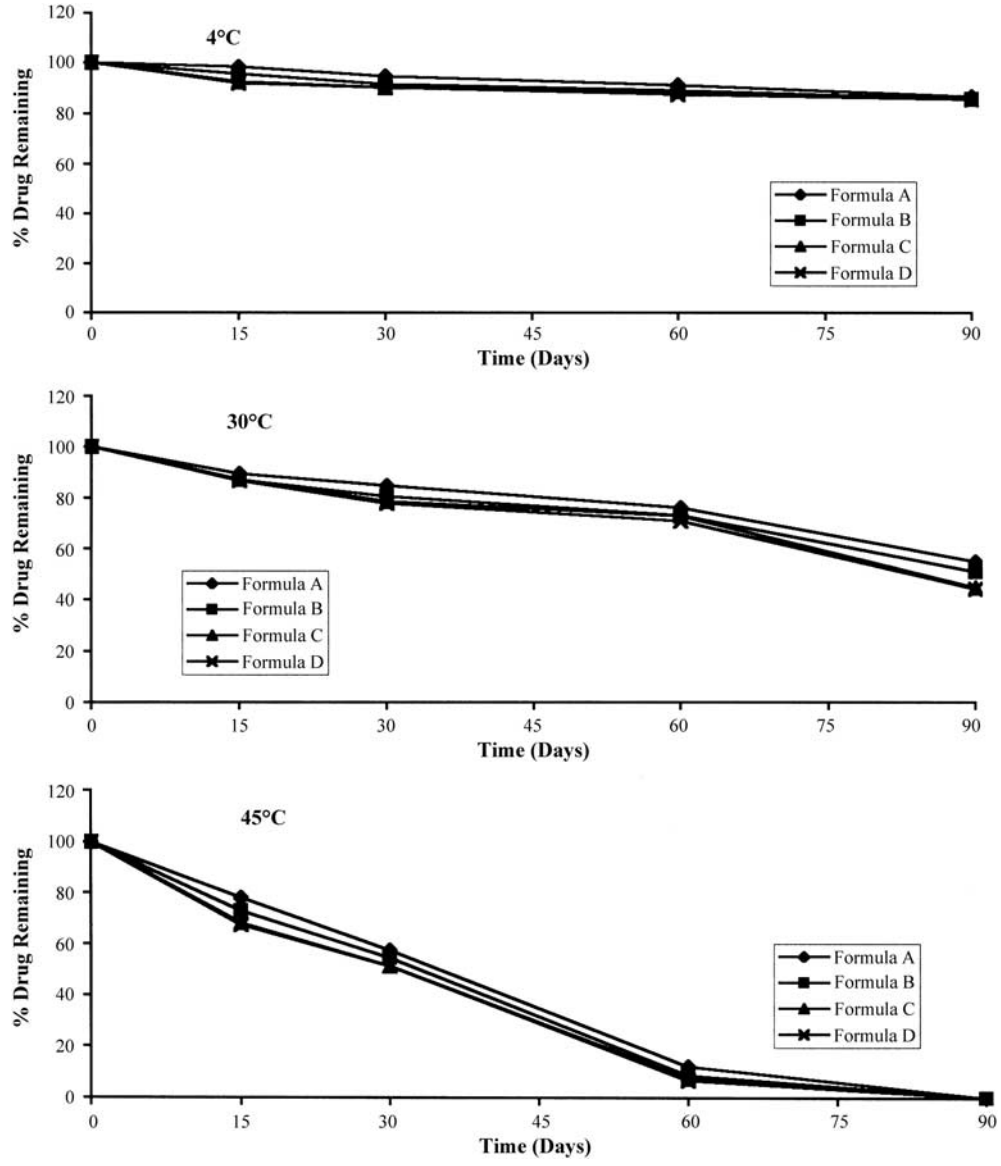

Figure 9. Stability profiles of TCH dental gels at various temperatures.

drug concentration of those kept at 30° or 45°C was below 90% within only 15 days of storage. It has been reported that TCH can be decomposed by epimerization and oxidation.[23,24] These degradation pathways were enhanced by high temperature. The loss of TCH in high storage temperatures was considered to be due to both mechanisms.

CONCLUSION

In this work, biodegradable injectable gel formulations containing mostly GMO and various additives (GMS, sesame oil, Tween 80, Span 80) were developed. The influence of such additives on physicochemical properties, such as rheology, swelling, and release characteristics of the gel formulations was studied. The rheologic property of GMO alone was Newtonian flow with certain viscosity. The addition of 30% water caused the system to increase in viscosity. The addition of MC or GMS to the GMO-water system changed the rheologic property to pseudoplastic flow. Moreover, MC enhanced the swelling property of the GMO gel formulation. The release profiles of the developed dental gels revealed that the Higuchi release model was suitable for describing the kinetics of drug release from the gel. The addition of polyols to the gel base caused an increase in the rate of drug release. The stability studies suggested that the TCH dental gel should stored in a low temperature, at least at 4°C.

ACKNOWLEDGMENT

This study was supported in part by a grant from the National Research Council of Thailand (NRCT).

REFERENCES

1. Grenier, D.; Mayrand, D. Periodontitis as an ecological imbalance. In *Oral Bacterial Ecology: The Molecular Basis*; Kuramitsu, H.K., Ellen, R., Eds.; Horizon Scientific Press: Wymondham, 2000; 275–311.
2. Genco, R.J. Antibiotics in the treatment of human periodontal disease. J. Periodontol. **1981**, *52*, 545–558.
3. Goodson, J.M.; Haffajee, A.; Socransky, S.S. Periodontal therapy by local delivery of tetracycline. J. Clin. Periodontol. **1979**, *6*, 83–92.
4. Goodson, J.M.; Holborow, D.; Dunn, R.L. Monolithic tetracycline containing fibers for controlled delivery to periodontal pockets. J. Periodontol. **1983**, *54*, 575–579.
5. Goodson, J.M.; Offenbacher, S.; Farr, D.H. Periodontal disease treatment by local drug delivery. J. Periodontol. **1985**, *56*, 265–272.
6. Addy, M.; Langeroudi, M.; Hassan, H. The development and clinical use of acrylic strips containing antimicrobial agent in the management of chronic periodontitis. Int. Dent. J. **1985**, *35*, 124–132.
7. Gobomb, G.; Friedman, M.; Soskolne, A. Sustained release device containing metronidazole for periodontal use. J. Dent. Res. **1984**, *63*, 1149–1153.
8. Ricci, E.J.; Bentley, M.V.L.B.; Farah, M.; Bretas, R.E.S.; Marchetti, J.M. Rheological characterization of poloxamer 407 lidocain hydrochloride gels. Eur. J. Pharm. Sci. **2002**, *17*, 161–167.
9. Esposito, E.; Carotta, V.; Scabbia, A.; Trombelli, L.; Antona, P.D.; Menegatti, E. Comparative analysis of tetracycline-containing dental gels: poloxamer- and monoglyceride- based formulations. Int. J. Pharm. **1996**, *142*, 9–23.
10. Bhardwaj, R.; Blomchard, J. Controlled release delivery system for the a-MSH analog melanotan-I using poloxamer 407. J. Pharm. Sci. **1996**, *85* (9), 915–919.
11. Wout, Z.G.M.; Pec, E.A.; Maggiore, J.A.; Williams, R.H.; Palicharla, P.; Johnston, T.P. Poloxamer 407—mediated change in plasma cholesterol and triglycerides following intraperitoneal injection to rats. J. Parenter. Sci. Technol. **1992**, *46* (6), 192–200.
12. Engstrom, S. Drug delivery from cubic and other liquid-water phase. Liq. Technol. **1990**, *2*, 42–45.
13. Nielsen, L.S.; Schubert, L.; Hansen, J. Bioadhesive drug delivery systems 1. Characterization of mucoadhesive properties of systems based on glyceryl mono-oleate and glyceryl monolinoleate. Eur. J. Pharm. Sci. **1998**, *6*, 231–239.
14. Engstrom, S.; Ljusbery-Wahrem, H.; Gustafsson, A. Bioadhesive properties of the monoolein water system. Pharm. Technol. Eur. **1995**, *2*, 14–17.
15. Barrett, A.J. Lysosomal enzymes. In *Lysomes : A Laboratory Handbook*; Dingle, J.T., Ed.; North-Holland Publishing Company: Amsterdam, 1972; Chapter 2.
16. Williams, B.L.; Osterbery, S.K.; Jorgensm, J. Subgingival microflora of periodontal patients in tetracycline therapy. J. Clin. Periodontol. **1979**, *6*, 210–221.
17. Sallam, A.S.; Enam, K.; Hussain, I.; Freij; Ibtisam, F. Formulation of an oral dosage form utilizing the

properties of cubic liquid crystalline phases of glyceryl monooleate. Eur. J. Pharm. Biopharm. **2002**, *53* (3), 343–352.
18. Engstrom, S.; Linlahl, L.; Wallin, R.; Engblom, J.A. Study of polar lipid drug carrier systems undergoing a thermoreversible lamellar-to-cubic phase transition. Int. J. Pharm. **1992**, *86*, 137–145.
19. Nokhodchi, A.; Shokri, J.; Dashbolaghi, A.; Hassan-Zadeh, D.; Ghafourian, T.; Barzegar-Jalali, M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. Int. J. Pharm. **2003**, *250* (2), 359–369.
20. Shokri, J.; Nokhodchi, A.; Dashbolaghi, A.; Hassan-Zadeh, D.; Ghafourian, T.; BarzegarJalali, M. The effect of surfactants on the skin penetration of diazepam. Int. J. Pharm. **2001**, *228* (1–2), 99–107.
21. Higuchi, W. Analysis of data on the medicament release from ointments. J. Pharm. Sci. **1962**, *51* (8), 802–804.
22. Wu, L.; Rui, D. Study on the stability of tetracycline hydrochloride. Kangshengsu **1982**, *7* (5), 343–345.
23. Taylor, R.B.; Durham, D.G.; Shivji, A.S.H. A kinetic study of tetracycline decomposition in acid solution. Int. J. Pharm. **1985**, *26* (3), 259–266.
24. Moore, D.E.; Fallon, M.P.; Burt, C.D. Photo-oxidation of tetracycline—a differential pulse polarographic study. Int. J. Pharm. **1983**, *14* (2–3), 133–142.
25. Norting, T.; Lading, P.; Engstrom, S.; Larsson, K.; Krog, N.; Nissen, S.S. Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides for use in the treatment of periodontal disease. J. Clin. Periodontol. **1992**, *19*, 687–692.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016