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Physicopharmaceutical Characteristics of an Oil-in-Water Emulsion-Type Ointment Containing Diclofenac Sodium

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Abstract □ The oil-in-water (o/w) emulsion-type ointment was prepared with food additives containing diclofenac sodium. The oil phase and the emulsifier used were 1,2,3-propanetriyl trioctanoate (caprylic acid glyceryl ester) and sugar wax, and sugar ester, respectively. The emulsion stability of the o/w emulsion-type ointment as well as the diclofenac sodium release profile were investigated and compared with those from conventional ointments. The emulsion stability was evaluated in terms of the viscosity of the emulsion product, the particle size distribution of oil droplets, and the zeta potential of the droplets. It was found that sugar esters have excellent properties as emulsifiers, based on the results of viscosity and zeta potential measurements. The *in vitro* release test revealed that the amount of diclofenac sodium released from o/w emulsion-type ointment was greater than from the hydrophilic and absorptive ointments. Accordingly, it was concluded that o/w emulsion-type bases are suitable for pharmaceutical use in ointment products.

Keyphrases □ Diclofenac sodium—release from various topical ointment bases, oil-in-water emulsions, physicopharmaceutical characteristics □ Oil-in-water emulsions—use as a topical ointment base for diclofenac sodium, release rate, physicopharmaceutical characteristics □ Ointment bases—oil-in-water emulsions, topical release of diclofenac sodium, physicopharmaceutical characteristics

In developing procedures for the design of pharmaceutical products, it is necessary to consider the bioavailability and safety of both the drugs and bases. Potent steroidal agents, which have substantial anti-inflammatory properties, have been used for external application for a long time. However, these steroidal agents have side effects (1), which were found to be directly dependent on the amount of drug applied to the skin. Therefore, various nonsteroidal agents (2, 3) have been developed recently to replace the steroidal agents.

Diclofenac sodium is a potent nonsteroidal anti-inflammatory agent, which has been limited to oral (4) and rectal administrations (5). In this investigation, diclofenac sodium was selected for topical application because no toxicity or topical irritation has been reported.

Although reports on ointment application have been published (6–8), few have dealt with the selection of optimum conditions for the preparation of the ointment. Oil-in-water (o/w) emulsion-type ointment bases offer many advantages over other preparations (9): they permit incorporation of aqueous and oleaginous ingredients, they allow a greater release of many incorporated medicaments, and their rheological properties can be controlled easily. Therefore, the selection of oil base and emulsifier is one of the most important factors in the preparation of o/w emulsion-type bases.

1,2,3-Propanetriyl trioctanoate (caprylic acid glyceryl ester, I) a medium-chain triglyceride, and sugar wax were chosen as the oil phase, since the combination is very stable, solubilizes various drugs, is nontoxic, and does not irritate the human skin (10). Sugar ester is a nontoxic, tasteless, odorless, and nonirritative sucrose fatty acid ester (11). Because it is widely and safely used in food (12), cosmetic (13), and pharmaceutical fields (14), it was selected as an emulsifier in this investigation. It is available in a wide range of hydrophilic–lipophilic balances (HLB) from oil to water soluble and has excellent emulsifying and dispersing abilities. Furthermore, Nobile *et al.* conducted standard tests with the sugar ester, and they reported no irritation to the human skin (11).

Various methods have been reported for the examination of drug release from ointment (15–17); however, no unified and simplified method has yet been established. In view of the

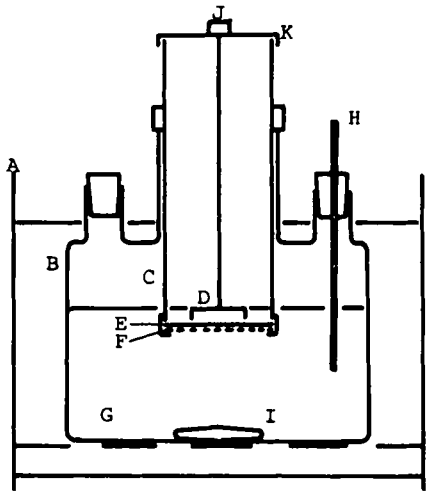

Figure 1—*Cross-sectional diagram of the drug release apparatus. Key: (A) thermostat equipment; (B) releasing fluid glass vessel; (C) inner cylindrical cell; (D) metal dish; (E) membrane; (F) metallic net; (G) releasing fluid; (H) thermometer; (I) stirring bar; (J) stopper; (K) cover.*

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Table I—The Constituents of the Hydrophilic and Absorptive Ointments

Hydrophilic Ointment		Absorptive Ointment	
White petrolatum	250.00 g	White petrolatum	400 g
Stearyl alcohol	220.00 g	Cetyl alcohol	180 g
Propylene glycol	120.00 g	Sorbitan sesquioleate	50 g
Sodium lauryl sulfate	15.00 g	Polyoxyethylene lauryl alcohol ether	5 g
Methylparaben	0.25 g	Methylparaben	1 g
Propylparaben	0.15 g	Propylparaben	1 g
Purified water	395.00 g	Purified water	363 g
Volume	1000 g	Volume	1000 g

aforementioned considerations, the o/w-type emulsion, which is a dispersion of microscopic oil droplets in a water phase, seems to be one of the most promising as an ointment base. The purpose of this work was to investigate the effects of surfactant and oil base on the physicochemical properties of ointment bases. In addition, the emulsion stability of the ointment base was evaluated in terms of (*a*) the viscosity of the emulsion product, (*b*) the particle diameter and distribution of oil droplets, and (*c*) the zeta potential of the droplets. The diclofenac sodium release profile from an o/w emulsion-type ointment was investigated and compared with those from conventional ointments.

EXPERIMENTAL

Materials—Diclofenac sodium[1] was recrystallized twice from water, with a melting range of 283–285°C. Sugar wax[2] and 1,2,3-propanetriyl trioctanoate (I, caprylic acid glyceryl ester)[3] were the dispersed phases.

Sugar wax is a sugar ester compound prepared from sucrose and palmitic acid or stearic acid. The average number of fatty acid molecules incorporated is 6.0, and its hydroxyl value and melting point are in the ranges of 80–130 and 60–66°C, respectively. Compound I is the triglyceride of caprylic acid and has the following properties: a saponification value of ~340–360, an acid value of <0.1, an iodine number of <1.0, and a hydroxyl value of <0.5.

The emulsifier used was sugar ester[4] of commercial grade, which is a nonionic surface-active agent synthesized from sucrose and palmitic acid or stearic acid. The average number of fatty acid molecules incorporated is 1.7. The content of dimethylformamide, arsenic, and heavy metals in sugar ester are very low as compared with those allowed by the Japanese Standard of Food Additives. Therefore, sugar ester is absolutely safe as a food, cosmetic, and/or pharmaceutical additive.

Preparation of o/w Emulsion-Type Ointment—The agitator used was a homomixer[5] which has two different blades: a homomixer and a paddle-mixer.

Diclofenac sodium was dissolved in the oil phase, the solution was kept at 80°C in the tank, and water preheated to 80°C was added. The concentration of diclofenac sodium in the ointment was always kept constant at 3.0% in all experiments.

The oil and water were vigorously stirred by both the homomixer and the paddlemixer at 80°C for 10 min. The speed of the homomixer was kept constant throughout the emulsification. The water-in-oil emulsion at 80°C was cooled quickly with ice water and then inverted to an o/w-type emulsion at 55°C. After this temperature was attained, the emulsion was stirred with the paddlemixer alone and gradually cooled to 20°C. The air bubbles trapped in the ointment were removed completely with a vacuum pump during the cooling process.

The conventional ointment bases used were commercial-grade hydrophilic ointment[6] and absorptive ointment[6]. The compositions of these ointments are shown in Table I.

Measurement of the Physicochemical Properties of Ointment Bases—The stability of an emulsion as an ointment base was evaluated by measuring such physicochemical properties as viscosity, particle size, and zeta potential (18). The rheological properties were measured with a rheometer[7] under a shear rate of 7.5–75 s^{-1} at 20 ± 0.1°C. The particle size distribution and the mean diameter of oil droplets were measured with a particle counter[8]. The zeta potential of oil droplets was obtained with the laser system[9]. A 0.1-g volume of o/w emulsion-type ointment was diluted with 50 mL of distilled water, and the zeta potential was measured at 20.0°C.

In addition, the o/w emulsion-type ointment was sealed in a calibrated glass tube and stored in a constant-temperature water bath at 40 ± 0.1°C. The flocculate depth and viscosity of the ointment were measured periodically to evaluate its emulsion stability. A short description of these procedures for evaluation of emulsion stability were given in a previous paper (19).

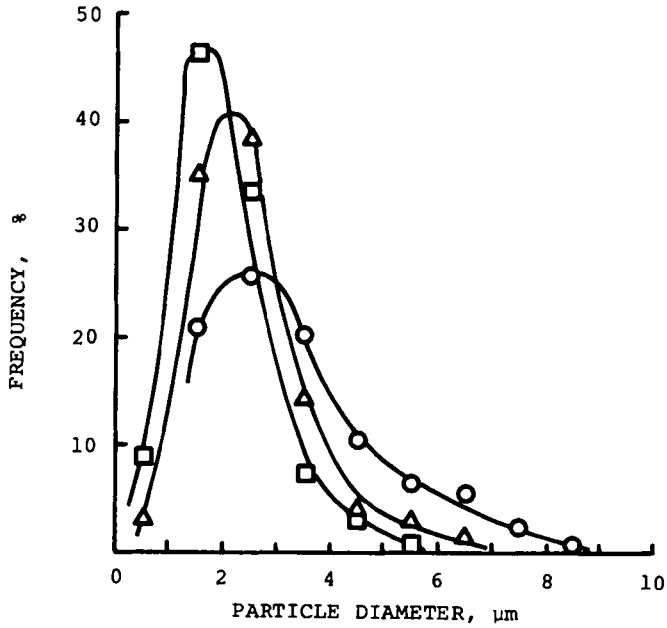

Figure 2—*Effect of rpm of the homomixer on particle diameter distribution of the o/w emulsion-type ointment. Key: (○) 3000 rpm; (△) 6000 rpm; (□) 10,000 rpm.*

Release of Diclofenac Sodium from the Ointment—The apparatus used for studying the drug released from the ointment is a modification of a common dissolution test instrument[10] (20) and is shown in Fig. 1. It consists of a metal dish (25 mm o.d., depth 6 mm), which floats on the surface of distilled water in an inner cylindrical cell. The bottom end of the inner cylindrical cell is covered with a membrane[11]. The distilled water (300 mL) was stirred at 100 rpm with a polytef-coated magnetic stirring bar placed at the bottom of the sink. The external chamber was immersed in a constant-temperature water bath maintained at 37 ± 0.1°C.

The release of the drug from various o/w emulsion-type ointment bases was examined. After reaching the required equilibrium temperature, 2.5 g of the ointment was placed on the bottom surface of the metal dish. This allowed direct contact of the donor ointment with the releasing liquid. Three-milliliter samples were withdrawn from the sink nine times over a 120-min period. The receptor phase volume was kept constant through the release run by replacing the removed sample with an equal volume of distilled water. The drug concentration was determined with a UV spectrometer[12] at a wavelength of 267 nm (21).

In the cases of the hydrophilic and absorptive ointments, diclofenac sodium powder that had been sieved through 150–200-mesh screens was mixed with molten base. The whole base was agitated at 50°C for 10 min until the solid diclofenac sodium melted completely in the base, then the ointment was cooled to 20°C. The drug release from the bases was examined in the same manner as in the case of the o/w emulsion-type ointment. The measurements were repeated five times, and the mean value of drug release concentration was calculated in all experiments.

RESULTS AND DISCUSSION

Selection of Optimum Conditions for Preparation of the o/w Emulsion-Type Ointment—The effect of impeller speed of the homomixer on the particle size distribution of the o/w emulsion-type ointment is shown in Fig. 2. In this case,

[1] Hamari Pharmaceutical Inds., Ltd., Osaka, Japan.
[2] S-10E; Dai-ichi Kogyo Seiyaku Co., Ltd., Kyoto, Japan.
[3] Panacete 800; Nippon Oil and Fats Co., Ltd., Tokoyo, Japan.
[4] S-50; Dai-ichi Kogyo Seiyaku Co., Ltd., Kyoto, Japan.
[5] Model M; Tokushu Kika Kogyo Co., Ltd., Osaka, Japan.
[6] JP X; Toho Yakuhin Co., Ltd., Tokyo, Japan.
[7] Model RM-1; Shimadzu Seisakusho Ltd., Kyoto, Japan.
[8] Model ZB; Coulter Electronics Inc, Hialeah, Fla.
[9] Lasu-Zee, Model 500; Pen Kem Inc., New York.
[10] Model TMS-103; Toyama Sangyo Co., Ltd., Osaka, Japan.
[11] SSWP 04700; Millipore Co., Milford, Mass.
[12] Model 200-20; Hitachi Ltd., Tokyo, Japan.

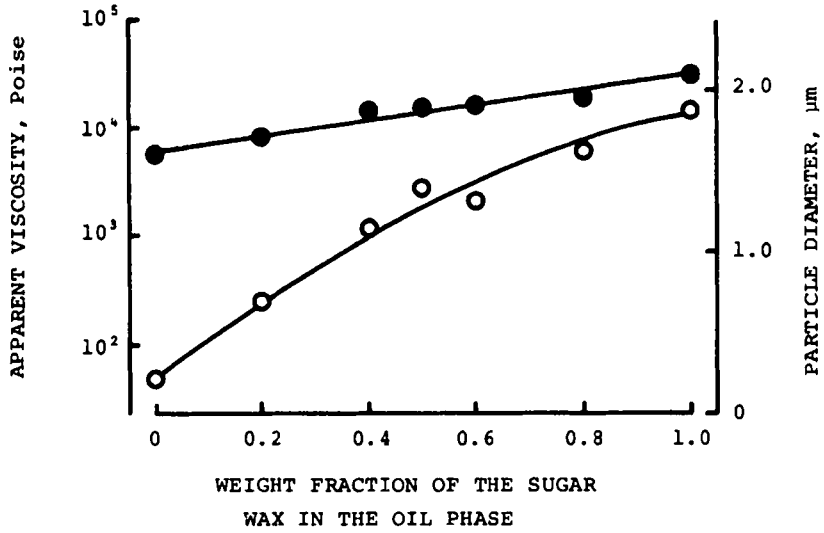

Figure 3—*Plot of viscosity and particle diameter* versus *weight fraction of sugar wax in the oil phase. Key: (○) viscosity; (●) particle diameter. Concentration of oil phase, 42%; concentration of emulsifier, 15%; revolution rate of homomixer, 10,000 rpm. The rate of shear and temperature in the measurement of viscosity were 7.5 s^{-1} and 20.0°C; the time of shear application was 30 s.*

the revolution rate of the paddlemixer was kept constant at 70 rpm. A significant effect of the difference in impeller speed was found on the size distribution curve. A narrower size distribution and a smaller standard deviation were observed with increase of the revolution rate of the homomixer. The mean diameters were 3.51 ± 1.91, 2.31 ± 1.18, and 1.93 ± 0.89 μm at 3000, 6000, and 10,000 rpm, respectively. As is evident in Fig. 2, the revolution rate of the homomixer is a very important dynamic factor in the preparation of a stable emulsion. Hence, it was kept constant at 10,000 rpm in all subsequent experiments.

Figure 3 shows the effect of the weight fraction of sugar wax in the oil phase on the viscosity and the particle size of the o/w emulsion-type ointment. The shear rate in the measurement of viscosity was 7.5 s^{-1}. It is obvious in this curve that the viscosity is remarkably increased with the increase of the weight fraction of sugar wax. This is also associated with a slight increase in the mean diameter of the droplet. This phenomenon would probably be due to complex formation between the crystallized sugar wax molecule and the emulsifier molecule on the surface of droplets during the cooling process of emulsification. Therefore, the o/w emulsion-type ointment would be sufficiently stable due to its high viscosity, which prevents flocculation and coalescence.

The zeta potential is a controlling parameter in the emulsion stability. Changes in the zeta potential with the weight fraction of sugar wax in the oil phase of the emulsion are shown in Fig. 4. The zeta potential of emulsion droplets was −38 mV when the oil phase of emulsion consisted of I alone. The value of the zeta potential gradually decreased with increase of the weight fraction of sugar wax in the oil phase of the emulsion. The minimum in this curve appears at a weight fraction of ~0.5. After the minimum, the curve increases rather rapidly with the increase in the sugar wax concentration. If the oil phase consists of equal parts of sugar wax and I, there probably exists a stable electric double layer on the surface of each droplet in the emulsion. These emulsions are semisolid at room temperature, however, and it seems that the high viscosity is a more important factor in preventing coalescence than the high zeta potential. Based on the results shown in Figs. 3 and 4, a weight fraction of 0.5 of sugar wax in the oil phase was used in all subsequent experiments.

Figure 5 shows the effect of emulsifier concentration on the viscosity of the o/w emulsion-type ointment. The shear rate in the measurement of viscosity was 7.5 s^{-1}. As the emulsifier concentration increased, the viscosity of the ointment increased linearly on a semilogarithmic plot at all concentrations of the oil phase studied. The viscosity of the ointment base was strongly affected by the concentration of sugar ester as an emulsifier. The emulsion prepared with sugar ester presumably has a stable gel structure around each droplet surface, because the globule surfaces of the oil may adsorb and consequently be stabilized by many sugar ester molecules. The viscosity of the emulsion increased remarkably with the increase of the oil concentration at all emulsifier concentrations. The reason for this result could be that as the concentration of the dispersed phase increases, the interaction between oil droplets also increases due to their closer approach in the continuous phase. This will lead to the eventual overlapping of the stream lines surrounding the individual droplets. At this stage, the overall viscosity is no longer the sum of the effects of the individual droplets. In highly concentrated emulsions, small increments in oil concentration produce large increases in relative viscosity.

When comparing the flow behavior of emulsions prepared using two or more different concentrations of emulsifier and/or oil phase, their viscosity should be measured over a wide range of shear rates. Rheograms of the ointment base prepared with four different concentrations of the emulsifier are shown in Fig.

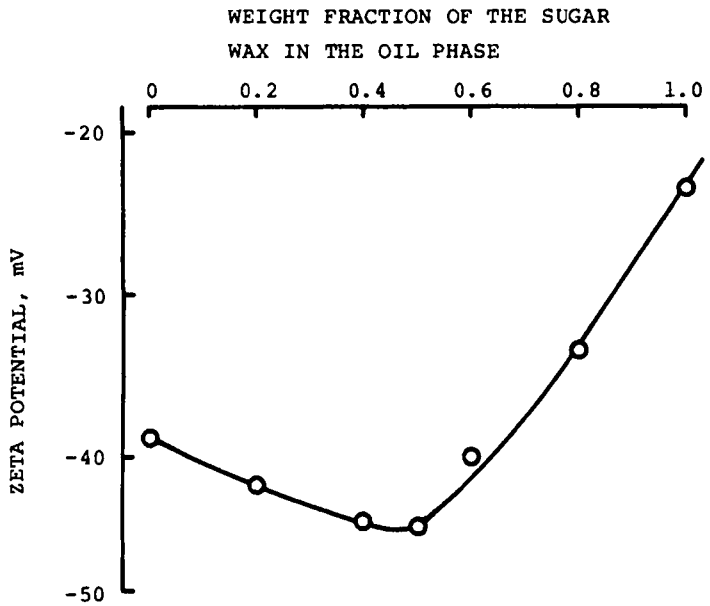

Figure 4—*Plot of zeta potential* versus *weight fraction of sugar wax in the oil phase. The temperature in the measurement of zeta potential was 20.0°C.*

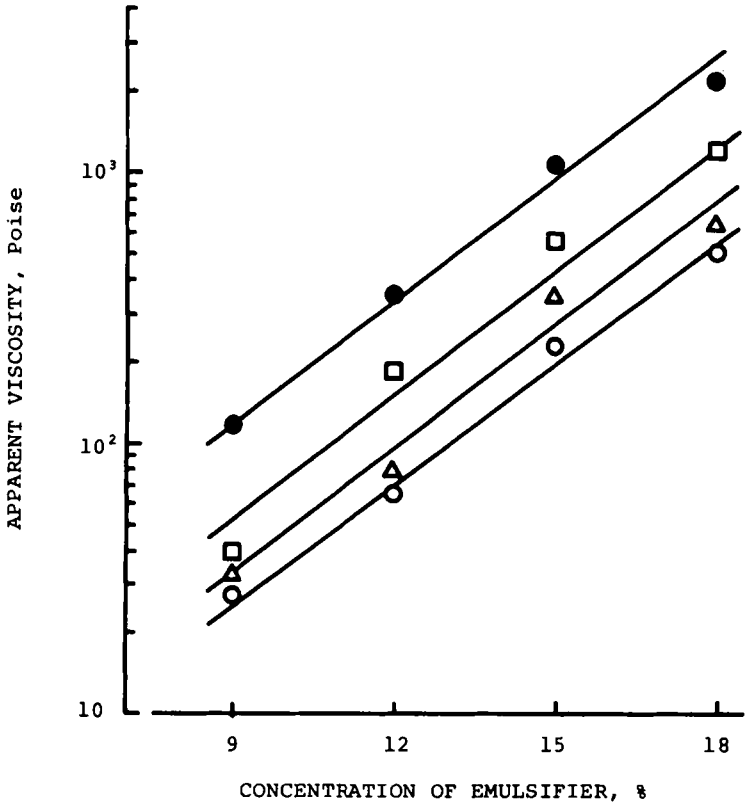

Figure 5—*Semilogarithmic plot of viscosity* versus *concentration of emulsifier. Key: concentration of oil phase (○) 30%; (△) 34%; (□) 38%; and (●) 42%. The rate of shear and temperature in the measurement of viscosity were 7.5 s^{-1} and 20.0°C; the time of shear application was 30 s.*

6. The curves show the relationship between viscosity and shear rate. As is evident in Fig. 6, it is not a horizontal relationship: the viscosity decreased markedly at first and then monotonically with an increase in shear rate. When a low steady shear was applied to the concentrated emulsion, it was often found that a steady stress did not develop instantly. This phenomenon is known as trixotropy. A hysteresis effect appears in all thixotropic ointment bases, as shown in Fig. 6.

The thixotropic behavior of an emulsion-type ointment base is of primary importance in pharmaceutical systems. Thus, it plays an important role in the mixing and flow of materials, their packaging into containers, physical stability, and even patient acceptability. Furthermore, the thixotropic property of a semisolid ointment base may affect the absorption rate of drugs through the skin as well as their biological availability. On the basis of the results shown in Figs. 5 and 6, it is possible to prepare ointments which have desirable rheological properties by controlling the amount of additives such as sugar wax, I, and sugar ester.

***In Vitro* Drug Release Profiles from the Emulsion-Type Ointment**—The equation for the release rate of drugs from an ointment base was derived by T. Higuchi (22), and subsequently, W. Higuchi (23) simplified the equation to:

$$Q = 2C_0(Dt/\pi)^{1/2} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released to the skin at time t per unit area of contact (mg/m^2), C_0 is the initial concentration of drug in the vehicle (mg/m^3), and D is the diffusion coefficient of drug in the vehicle (m^2/s), respectively. The release characteristic of diclofenac sodium from various o/w emulsion-type ointment bases over a 120-min period is illustrated in Fig. 7. The curve does not start at the origin, but has a short lag time. The experimental data were fairly well approximated by a straight line within 120 min when the amount of diclofenac sodium released was plotted against the square root of time. As shown in Fig. 7, the amount of drug released is indirectly related to the amount of oil phase in the ointment.

In general, the drug release from an emulsion base occurs in two steps: (*a*) transport of the drug dissolved in droplets of oil to the aqueous medium and (*b*) transport of the drug in the continuous aqueous phase across the membrane. In this o/w emulsion-type ointment, the amount of drug released could be controlled and the release prolonged by increasing the concentration of dispersed phase which, in turn, may affect the rate of transfer of the drug molecule from the oil droplets to the aqueous medium, the rate-limiting step for the release.

Figure 8 shows the release profiles of diclofenac sodium from o/w emulsion-type, hydrophilic, and absorptive ointments. The release rate was found to decrease in the order o/w emulsion-type ointment > absorptive ointment > hydrophilic ointment. Comparison of Fig. 7 with Fig. 8 reveals that the amounts of drug released from all o/w emulsion-type ointments are larger than from the hydrophilic ointment. This indicates that the o/w emulsion-type base prepared in this experiment has excellent properties as compared with the commercial grade hydrophilic ointment, and it appears to be very suitable

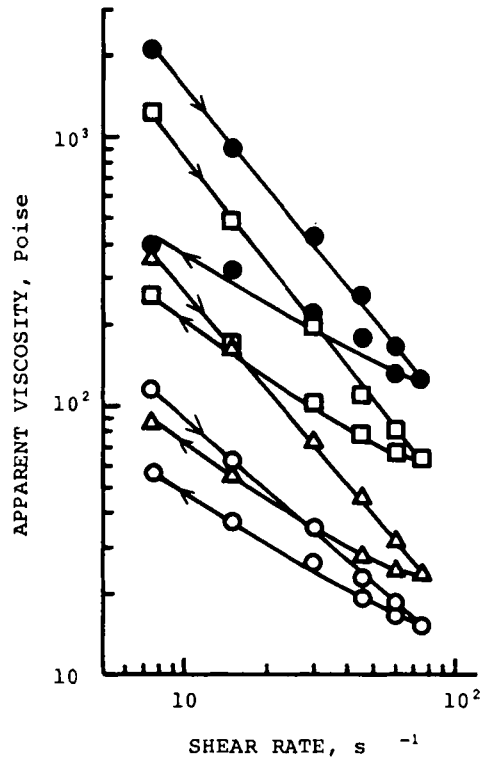

Figure 6—*Plot of viscosity against rate of shear. Key: concentration of emulsifier (○) 9%; (△) 12%; (□) 15%; and (●) 18%. Concentration of oil phase was 42%. The temperature in the measurement of viscosity was 20.0°C; the total time of shear application was 330 s.*

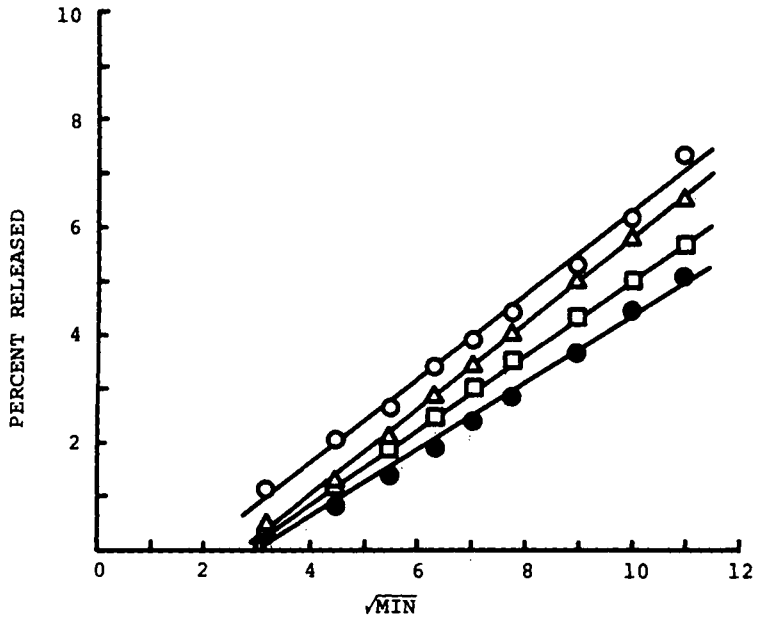

Figure 7—*Diclofenac sodium release from various o/w emulsion-type ointments. Key: concentration of oil phase (○) 30%; (△) 34%; (□) 38%; and (●) 42%.*

for use as an ointment base. In this release exeriment, dissolution of the base itself into the aqueous phase is not a serious problem within 120 min from initiation.

Evaluation of Emulsion Stability in Three Different Ointment Bases—The emulsion stability of the ointment base was evaluated in terms of visual observation and the rheology of the emulsion product. Here, 3% diclofenac sodium was admixed with each of the three different bases: hydrophilic, absorptive, and o/w emulsion-type ointments. Gross visual analysis was used to observe flocculation and creaming of the emulsions stored at a constant temperature of 40 ± 0.1°C after preparation. This analysis utilized three 15-mL calibrated glass tubes to observe each of the emulsions over a 30-d period.

In the hydrophilic ointment, a separated water phase was observed after 10 d. A flocculated oil layer appeared on the top of emulsion of absorptive ointment after 3 d only. However, no significant change was detected at all in the o/w emulsion-type ointment over a 50-d period. Accordingly, the o/w emulsion-type ointment including 3% diclofenac sodium is considered to be more stable than the other ointments, even if it is stored at room temperature for a long period.

The viscosity of each ointment stored at 40 ± 0.1°C was measured periodically with a rheometer over a 14-d period. Figure 9 illustrates the change in relative viscosity of ointment with storage time. Here, the relative viscosity, η_{rel}, was determined according to the equation:

$$\eta_{rel} = \eta/\eta_0 \qquad \text{(Eq. 2)}$$

where η is the viscosity at each storage time and η_0 at the initiation, respectively.

In the cases of the hydrophilic and absorptive ointments, the relative viscosity decreased markedly with the increase in time. The viscosity of the absorptive ointment could not be determined by this rheological method after 7 d because of the appearance of separated oil phase on the surface of the emulsion. On the other hand, no significant change was found in the viscosity of o/w emulsion-type ointment over a 50-d period. Furthermore, it was confirmed that the other physicochemical properties such as melting range, blooming, and deposition of drug crystals were almost unchanged with this base after 50 d at 40°C.

CONCLUSIONS

On the basis of physicochemical tests, it seems that the oil phase in the emulsion base consisting of 50 parts each of sugar wax and I shows excellent stability. From the results of viscosity and zeta potential measurements, sugar ester in the region of 9–18% was found to have excellent properties as an emulsifier, and it appears to be very suitable for use as an ingredient in emulsion-type ointment bases. The *in vitro* release test reveals that the amount of diclofenac sodium released from the o/w emulsion-type ointment was greater than that from the hydrophilic and absorptive ointments. The o/w emulsion-type ointment containing 3% diclofenac sodium appears to be better than conventional ointments, as indicated by visual observations and viscosity

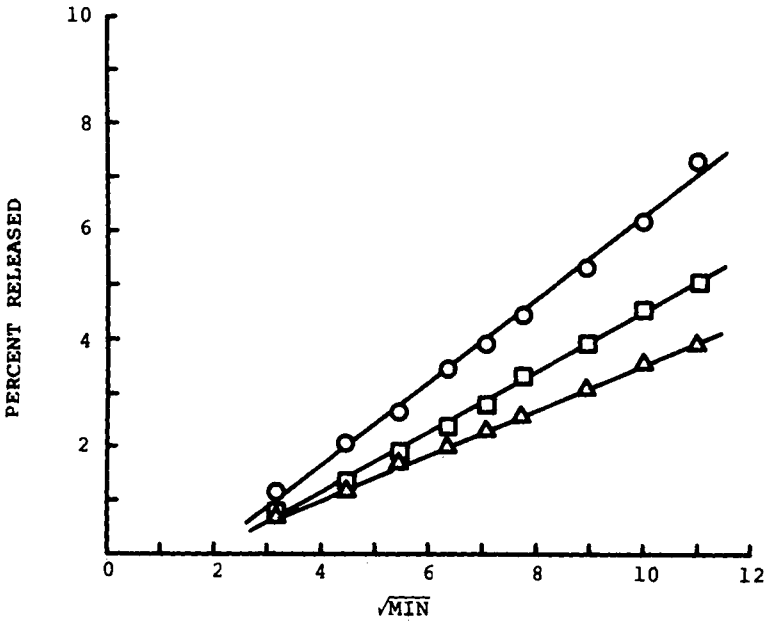

Figure 8—*Plot of diclofenac sodium released* versus *the square root of time. Key: (○) o/w emulsion-type ointment (concentration of oil phase was 30%); (△) hydrophilic ointment; (□) absorptive ointment.*

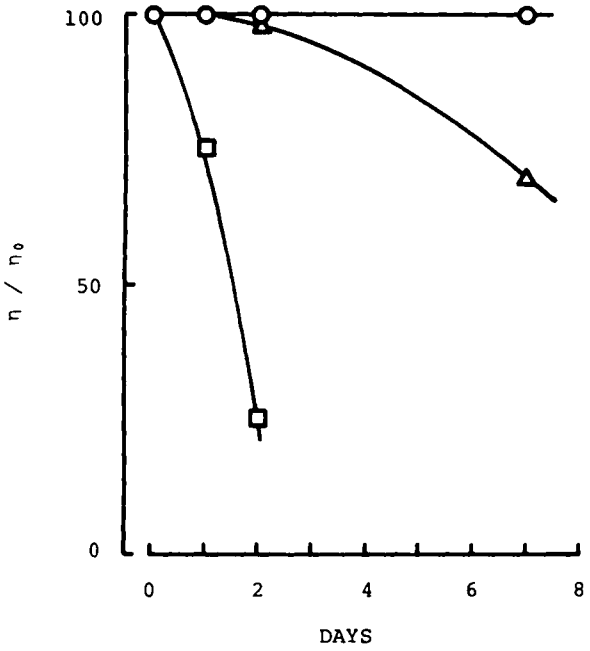

Figure 9—*Change of the viscosity of the ointment with storage time. Key: (○) o/w emulsion-type ointment; (△) hydrophilic ointment; (□) absorptive ointment. The ointments were stored at 40°C. The temperature in the measurement of viscosity was 20.0°C; the time of shear application was 30 s.*

measurements of the base over a 50-d experimental period at 40°C. Finally, the aforementioned properties suggest that these o/w-type emulsions prepared with sugar ester, I, sugar wax, and distilled water are suitable for the pharmaceutical preparation of ointments for clinical use. Future investigations will evaluate the effect of physicochemical properties of the o/w emulsion-type ointment on the indices of bioavailability through *in vivo* percutaneous absorption.

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NOTES

Determination of Calcium Gluconate by Selective Oxidation with Periodate

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Abstract □ A modified analytical method was developed which can accurately quantitate calcium gluconate and its pharmaceutical preparations in the presence of other calcium compounds or other cations able to complex with EDTA. The proposed method was based on the principle of the Malaprade reaction, according to which gluconic acid is selectively and quantitatively oxidized by sodium periodate. The content of calcium gluconate was calculated from the amount of gluconic acid found. The selective oxidation proceeded at 50°C for 10 min, yielding ~100% recovery of calcium gluconate. The proposed method was accurate, precise, and superior to the compendia EDTA-complexometric method in terms of specificity.

Keyphrases □ Calcium gluconate—determination by selective oxidation with periodate, quantitation, Malaprade reaction □ Periodate—selective oxidation, determination of calcium gluconate, quantitation, Malaprade reaction □ Malaprade reaction—determination of calcium gluconate with selective oxidation by periodate, quantitation

The EDTA-complexometric titration for the determination of calcium gluconate (I) and its pharmaceutical formulations is most commonly adopted by many current national pharmacopoeias (1–6). However, it is known that the official compendia method is only suitable for determining a sample of I which does not contain other calcium compounds or other

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