Chem. Pharm. Bull.
30(8)2906—2911(1982)

Studies on Pharmaceutical Drug Design for Suppositories. II. Rheological Properties of Emulsion-Type Suppository Bases

SHUN'ICHI NORO,* YOSHIHITO KOMATSU, and TAKASHI UESUGI

Meiji College of Pharmacy, Yato-cho 1-22-1, Tanashi, Tokyo 188, Japan

(Received November 13, 1981)

The rheological characteristics of emulsion bases must be chosen so as to produce a suppository having optimum physical, chemical and pharmacological properties. In this study, we measured some rheological characteristics of the emulsion in order to find favorable physicochemical conditions for the preparation of emulsion-type bases.

The suppository consisted of Witepsol S-55, aqueous polymer, Amisoft surfactant and water. The preparation procedure was that described in our previous paper. The vicosity and visco-elasticity of suppository bases were measured with a Vismetron and an RM-1 or RV-12 type rheometer.

Amisofts had excellent rheological properties as surfactants for emulsion-type suppository bases, as compared with sodium dodecyl sulfate or Tween 80. The activation energy of viscosity increased gradually at first and then sharply with increasing volume concentration of the dispersed phase after passing through the 50% point. The change in the activation energy was substantial when the volume concentration rose over 60%.

Keywords——activation energy; Casson equation; emulsion; pseudoplastic; rheogram; rheology; suppository; thixotropy; yield value

In general, emulsions are useful in many areas of the pharmaceutical industry. For example, emulsion-type bases for use in suppositories possess many outstanding characteristics as compared with hydrophilic or hydrophobic bases.[1] From the physicochemical point of view, there are many factors which affect suppository formation. They include viscosity,[2] elasticity,[3] consistency,[4] particle size,[5] melting point,[6] liquefaction time,[7] and so on. Rheological properties are considered to be extremely important in the pharmaceutical formulary planning of suppository bases, and furthermore, they greatly affect the stability and safety of products.[8]

The rheological characteristics of emulsion bases must be chosen so as to produce a suppository having optimum physical, chemical and pharmacological properties. For example, when insoluble drugs are dispersed in suppository bases, it is desirable to use highly viscous bases in order to prevent the sedimentation of suspended particles.[9] On the other hand, if the suppository bases contain high concentrations of insoluble drugs which have small particle diameters, the viscosity of bases may be greatly increased.[10] In this case, the viscosity of the base should be reduced by the addition of a suitable substance.

When the drug is to be given by rectal administration, the suppository bases must be designed to be fluid enough to spread quickly and easily over the affected area of rectal membrane.[11]

Finally, it is considered that the ideal suppository bases should have a high viscosity at negligible shear, *i.e.*, during shelf storage, and they should have a low viscosity at high shearing rate, *i.e.*, during agitation, pouring, and spreading.[12] In addition, suppository bases which are thixotropic as well as pseudoplastic should be useful[13] since they form a gel on standing and become fluid when disturbed.

In this study, we measured some rheological characteristics of suppository bases to study favorable physicochemical conditions for the preparation of emulsion-type bases. Among many factors affecting the rheological properties of emulsion bases, the kind and concentration of surfactants or polymers, and the volume ratio of water phase to oil phase are important factors.

Experimental

1. **Preparation of Emulsion-Type Suppository**——As a dispersed phase, Witepsol S-55 (WS-55) was selected. Witepsol S-55 is a mixture of mono-, di-, and triglycerides of naturally occurring saturated fatty acids (C_{12}—C_{18}), with a melting range of 32—35°C. The specific gravity of Witepsol S-55 at 20°C ranges from 0.950 to 0.988; it has an iodine number of less than 3, a saponification value of 230 to 240 and a hydroxyl value of less than 15. Its melting behavior both *in vitro* and *in vivo* is such that a suppository of Witepsol S-55 without any drug melts almost completely in the human rectum within 10 min.[14] Furthermore, Witepsol has excellent properties in both emulsification and dispersion as an emulsion-type base, as compared with other glycerin ester derivatives.[15] Witepsol S-55 used in this experiment was an extra-pure grade material.

The emulsifiers used were commercial grade Amisofts; CS-11, GS-11, and HS-21 (Ajinomoto Co., Tokyo). Amisofts are synthesized from L-glutamate and natural fatty acids, and their chemical structure is represented as follows $^{-}OOC-CH_2CH_2CH\ (NH-OCR)COO^{-}$. CS-11 is *N*-palm oil fatty acyl-*l*-mono sodium glutamate and its molecular weight is 359. GS-11 is *N*-fatty acyl-*l*-mono sodium glutamate, and its molecular weight is 420. HS-21 is *N*-stearoyl-*l*-di sodium glutamate, and its molecular weight is 452.

The polymers used were sodium alginate (Alg–Na, M.N. = 1.4×10^5), sodium carboxymethylcellulose (CMC–Na, M.N. = 8.0×10^4), and sodium polyacrylate (PAA–Na, M.N. = 8.0×10^4).

Detailed descriptions for the preparation procedure for emulsion-type suppositories from the abovementioned substances were given in our previous paper.[16]

2. **Measurement of Rheological Properties of Suppository Bases**——Rheological properties of suppository bases (viscosity or visco-elasticity) were measured with a Vismetron (Shibaura system Co., Tokyo), a rheometer type RM-1 (Shimadzu Seisakusho Co., Kyoto), and a rheometer RV-12 (Haake Co., West Germany). These procedures were carried out at 37±0.1°C.

Results and Discussion

First, the effects of the kind of surfactant and polymer on the rheological properties of the resultant emulsion were studied.

When comparing the flow behavior of emulsions prepared using two or more different surfactants, their viscosity should be measured over a wide range of shear rates. Rheograms of the suppository base prepared with four different surfactants are shown in Fig. 1. The volume ratio of water phase to oil phase was 1 : 1, and the concentration of sodium alginate (Alg–Na) as an additive was 1.0%. The curves showing the relationship between viscosity and shear rate were not horizontal, showing that the viscosity decreased markedly at first and then monotonically with increase of shear rate. When a low steady shear was applied to the concentrated emulsions, it was often found that a steady stress did not develop instantly. This phenomenon is known as thixotropy. A hysteresis effect appears in all thixotropic suppository bases,[17] as shown in Fig. 1. For the emulsion-type bases, the viscosity decreased in the order HS-21, GS-11, CS-11, and SDS. Since higher viscosities were observed for the emulsions prepared with the three Amisofts than for the emulsion with SDS, the surface activity of Amisofts is considered to be higher than that of SDS. Accordingly, the use of Amisofts as surfactants should give excellent rheological properties to emulsion-type suppository bases, as compared with the use of SDS.

Figure 2 shows the effect of polymers (1.0%) on the rheogram of the emulsion-type suppository. When PAA–Na was used as a polymer, the viscosity of the suppository base had the highest values. The effectiveness was found to decrease in the order PAA–Na, CMC–Na, and Alg–Na. This result can be explained as follows; PAA–Na as a polymer has higher molecular weight and is associated through stronger van der Waals forces or hydrogen bonds around individual droplets, as compared with CMC–Na and Alg–Na.

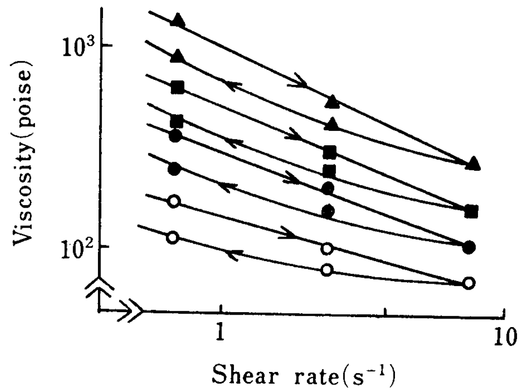

Fig. 1. Effect of Emulsifying Agents on the Viscosity of Suppository Bases

▲: HS, ■: GS, ●: CS, ○: SDS.
Polymer, Alg-Na 1.0%.
Volume ratio of water phase to oil phase, 1: 1.

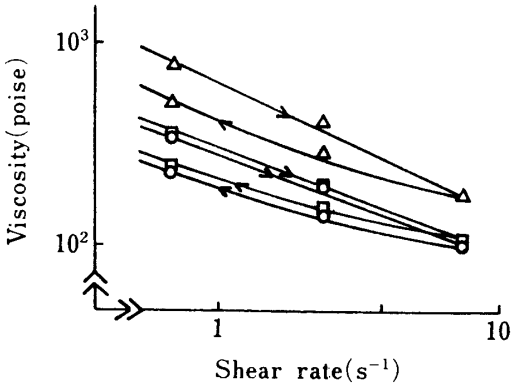

Fig. 2. Effect of Polymers on the Viscosity of Suppository Bases

△: PAA-Na, □: CMC-Na, ○: Alg-Na.
Polymer concentration, 1.0%.
Emulsifier, Amisoft CS-11 1.0%.
Volume ratio of water phase to oil phase, 1: 1.

Figure 3 illustrates the changes of rheograms for the base containing 50% Witepsol S-55 caused by repeated application of shear at a varying from 7.5 to 75 s^{-1}. The number of times of shear application had a large influence on the rheogram. In the first application, the down-curve was markedly displaced to a lower position than the up-curve, showing that the emulsion had a lower consistency at any rate of shear on the down-curve than it had on the up-curve. This phenomenon indicates that a breakdown of gel-structure occurs with increasing stress (the up-curve) and that this is not reversed immediately on the down-curve, even though the stress is removed or reduced. On the other hand, only a slight difference was observed between up- and down-curves of the rheogram for the emulsion at the fifth application. This result suggests that the stable gel-structure of the emulsion completely breaks down, probably due to the formation of aligned droplets.

Schematic models for the two types of rheogram, which were obtained by increasing the shear rate from zero to 75 s^{-1} (right side) and decreasing it from 75 to zero s^{-1} (left side), are shown in Fig. 4. Experimental points such as those at the start, top, and end of shear appli-

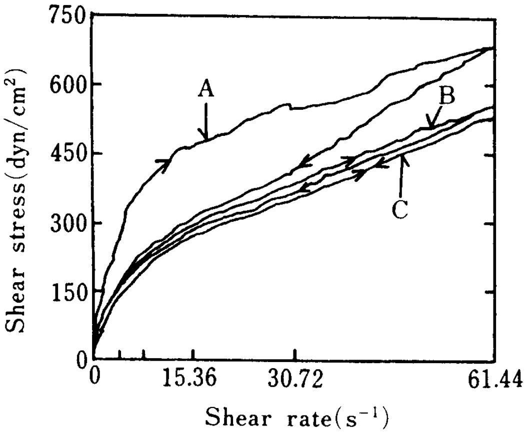

Fig. 3. Changes of the Rheogram as a Function of the Number of Times of Shear Application at 37 ± 0.1°C

A: once, B: three times, C: five times.
Emulsifier, Amisoft CS-11 1.0%.
Polymer, Alg-Na 1.0%.
Volume ratio of water phase to oil phase, 1: 1.

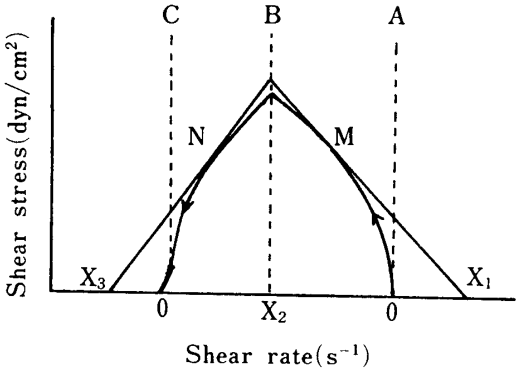

Fig. 4. Schematic Diagram for Analyzing Rheograms

Slope of line $\overline{X_1B}$ --- a.
Slope of line $\overline{BX_3}$ --- b.

cation given in Fig. 4 are indicated by A, B, and C, respectively. The midpoints of the curves AB and BC are represented by M and N. The tangents were drawn at the points M and N, and the slopes of the lines were calculated. The ratio of the slope of line $\overline{X_1B}$ to the slope of line $\overline{BX_3}$ was evaluated (designated as a/b). The observed value of a/b represents the magnitude of thixotropy, *i.e.*, the extent to which the structure of the material is broken down with increasing shear rate. That is to say, the extent of breakdown of gel structure increases with decrease of a/b from unity.

Next, in order to characterize the thixotropic property, the exponent of structural viscosity, N, was calculated by the commonly used logarithmic formula,[18]

$$\log D = \log C + N \log S \qquad (1)$$

where D is the shear rate, S is the shear stress and C is a constant.

The values of a/b and N are summarized in Table I and the effect of both surfactants and polymers on the values were examined. From the data of Table I, it is clear that the value of a/b decreases as the value of N becomes higher. For emulsions prepared with different surfactants, the value of N increases in the order HS-21, CS-11, and GS-11. Similarly, the value of a/b decreases in the order Alg–Na, CMC–Na, and PAA–Na for the three polymers.

TABLE I. Effect of Surfactants and Polymers on a/b and the Exponent of Structural Viscosity N

Surfactant	HS-21	GS-11	CS-11	SDS
N	5.5	5.2	5.2	4.2
a/b	0.70	0.80	0.79	0.85

Polymer: 1% Alg-Na.

Polymer	PAA	CMC	ALG
N	6.9	5.9	5.5
a/b	0.62	0.65	0.70

Surfactant: 1% HS-21.

The thixotropic behavior of an emulsion-type suppository base is of primary importance in pharmaceutical systems. Thus, it plays an important role in mixing and flow of materials, their packaging into containers, physical stability, and even patient acceptability. Furthermore, the thixotropic property of a semisolid suppository base may be considered to affect the absorption rate of drugs through the rectal membrane and their biological availability. The square root of shear rate, $\sqrt{D}$, was plotted against the square root of shear stress, $\sqrt{S}$, for the emulsions prepared with four different surfactants, and an approximately linear relation was obtained in each case, as shown in Fig. 5. Accordingly, the relation between $\sqrt{D}$ and $\sqrt{S}$ fits the equation of Casson:[19]

$$\sqrt{S} = k + k' \sqrt{D} \qquad (2)$$

where k is the intercept at $\sqrt{D}=0$ and k' is the slope of the line. The plots of $\sqrt{D}$ against $\sqrt{S}$ for the emulsions prepared with three different polymers are shown in Fig. 6, in which a similar tendency to that shown in Fig. 5 can be observed. The results in Figs. 5 and 6 indicate that the emulsion-type suppository bases exhibit pseudo-plastic flow. If the straight line is extrapolated to the shear stress axis, the yield value, which is equal to k in Eq. (2), can be obtained. At stresses below the yield value, the suppository bases act as an elastic material, and their viscosity decreases with increasing shear rate at stresses over the yield value. Conse-

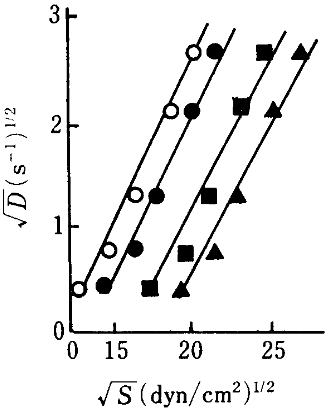

Fig. 5. Plots of Square Root of Shear Rate against Square Root of Shear Stress: Effect of Surfactants on the Flow Curve

▲: HS, ■: GS, ●: CS, ○: SDS.
Polymer, Alg-Na 1.0%.
Volume ratio of water phase to oil phase, 1: 1.

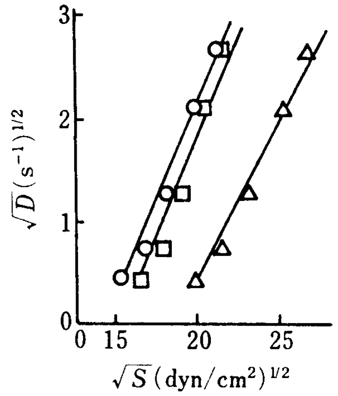

Fig. 6. Plots of Square Root of Shear Rate against Square Root of Shear Stress: Effect of Polymers on the Flow Curve

△: PAA-Na, □: CMC-Na, ○: Alg-Na.
Emulsifier, Amisoft CS-11 1.0%.
Volume ratio of water phase to oil phase, 1: 1.

quently, the yield value is an important rheological parameter in formulating an effective suppository.

In general, the viscosity of a liquid or semisolid decreases as the temperature is raised. The temperature dependence can be expressed approximately for many pharmaceutical products by means of the Andrade equation for chemical reactions.

$$\eta = A\exp(\varDelta E/\boldsymbol{R}T) \qquad (3)$$

or

$$\log\eta = \log A + \frac{\varDelta E}{2.303\,\boldsymbol{R}}\cdot\frac{1}{T} \qquad (4)$$

where A is a constant depending on the molecular weight and molar volume of the substance, $\varDelta E$ is an activation energy required to initiate flow between the molecules, $\boldsymbol{R}$ is the gas constant, and T is the absolute temperature.

The viscosity data, obtained for the emulsions with four different volume ratios of water phase to oil phase at temperature between 30 and 50°C in the presence of 1.0% Amisoft CS-11 and 1.0% sodium alginate, are shown in Fig. 7. Here, the horizontal axis corresponds to the reciprocal of the absolute temperature and the vertical axis to the logarithmic viscosity. It is clear from Fig. 7 that the relation between log η and $1/T$ is linear at every volume ratio. Accordingly, the activation energy of viscosity of suppository bases can be calculated from the slope of the line in Fig. 7.

Figure 8 shows the relation between the volume percentage of dispersed phase and the activation energy of viscosity. The activation energy, E, increased gradually at first and then sharply (after passing through the 50% point) with increasing volume percentage of dispersed phase. Thus, the change in the activation energy was particularly great when the volume percentage was high. The reason for this results is considered to be as follows: as the concentration of dispersed phase increases, the interaction between droplets increases due to their closer approach in the continuous phase, which will lead to eventual overlapping of the streamlines surrounding individual droplets. At this stage, the overall viscosity is no longer the sum of the effects due to the individual droplets. In highly concentrated emulsions, the flow becomes pseudoplastic, and small increments in Witepsol S-55 concentration produce large increases in relative viscosity. Consequently, it is apparent that more energy is required

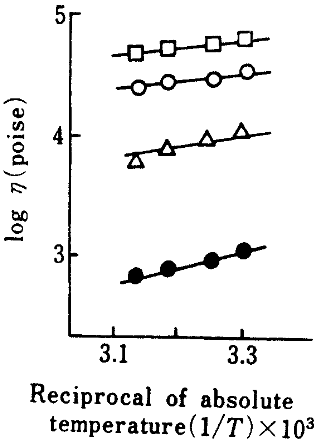

Fig. 7. Relation between the Logarithmic Viscosity of Suppository Bases and the Reciprocal of Absolute Temperature

□; 4:6, ○; 5:5, △; 6:4, ●; 7:3.
Emulsifier, Amisoft CS-11 1.0%.
Polymer, Alg-Na 1.0%.

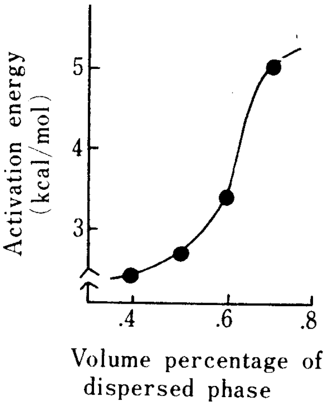

Fig. 8. Relation between the Volume Percentage of Dispersed Phase and the Activation Energy of Viscosity

Emulsifier, Amisoft CS-11 1.0%.
Polymer, Alg-Na 1.0%.

to break bonds or permit flow suppository bases composed of many particles which are associated through van der Waals forces or hydrogen bonds with increasing volume of dispersed phase.

Conclusion

On the basis of the rheological properties of the bases studied so far, these o/w type emulsions consisting of Witepsol S-55, surfactant, polymer, and water seem to have excellent properties for pharmaceutical application as suppositories.

References

1) J.H. Fincher, D.N. Entrekin, and C.W. Hartman, *J. Pharm. Sci.*, **55**, 23 (1966).
2) S.S. Davis, *J. Pharm. Sci.*, **58**, 412 (1969).
3) G.B. Thurston and A. Martin, *J. Pharm. Sci.*, **67**, 1499 (1978).
4) E. Nour El-Din, N.M. Mursi, A. Abdelbary, and N. Fods, *Pharmazie*, **32**, 819 (1977).
5) Aly A. Kassem, E. Nour El-Din, A. Abdelbary, and H. Fadel, *Pharmazie*, **30**, 475 (1975).
6) I. Setnikar and S. Fantelli, *J. Pharm. Sci.*, **51**, 566 (1962).
7) I. Setnikar and S. Fantelli, *J. Pharm. Sci.*, **52**, 38 (1963).
8) O.F. Weiss, *Arch. Pharm. Chem.*, **68**, 835 (1961).
9) J.J. Rutten, C.J. Blaey and J. Polderman, *Inter. J. Pharm.*, **3**, 179 (1979).
10) E. Din, N.M. Marsi, A.A. Bary, and N. Foda, *Pharmazie*, **32**, 515 (1977).
11) E.L. Parrott, *J. Pharm. Sci.*, **64**, 878 (1975).
12) R.L. Goldemberg and C.P. De la Rosa, *J. Soc. Cosmet. Chem.*, **22**, 635 (1971).
13) H.R. Moskowitz and D. Fishken, *Cosmetics and Toiletries*, **93**, 31 (1978).
14) W.A. Ritchel, "Angewandte Biopharmazie," Wissenschaftliche Verlagsgesellshaft, Stuttgart, 1973, pp. 465—487.
15) S.A. Ibrahim, A. Abdelbary, H. Elsorady, and H. Abdelmonem, *Pharmazie*, **35**, 170 (1980).
16) S. Noro, Y. Komatsu, and T. Uesugi, *Chem. Pharm. Bull.*, **30**, 2900 (1982).
17) B.D. Marsh, *Trans. Soc. Rheo.*, **12**, 479 (1968).
18) I. Bernard, *Cosmetics and Toiletries*, **93**, 23 (1978).
19) N. Casson, "Rheology of Disperse Systems," ed. by C.C. Mill, Pergamon Press, London, 1959, pp. 84—104.