Factors Influencing the *In Vitro* Drug Release from a Liquid Droplet Dispersion System Ointment

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A study was carried out with a liquid droplet dispersion system ointment (LDDS) using mometasone furoate as the drug and ethyleneglycol salicylate as the solvent. First, drug concentrations in the bleeding liquid (C_{BL}) and in the liquid droplet (*C*s) were determined. It was suggested that a partition equilibrium is established between the two.

Next, an *in vitro* drug release test was performed. A slope obtained from plotting the cumulative amount of the drug released against the square root of time was used as an index of release. With changes in the drug concentration in ointment (*C*o) at a definite solvent concentration in ointment (*S*o), *C*o was proportional to the slope. The result predicted from C_{BL} based on the theory of thermodynamic activity corresponded with that of the actual *in vitro* drug release. On the other hand, with changes in *S*o at definite *C*o, the slope remained nearly constant, regardless of changes in *S*o. The result predicted from C_{BL} based on the theory of thermodynamic activity did not correspond with that of the actual *in vitro* drug release.

Thus, further studies from various theoretical aspects were done. It was confirmed that a proposed equation for LDDS can be put in order similar to ones either for a soluble type or a crystal dispersion type. In this process, the volume fraction of the liquid droplet phase was suggested to be an important parameter for LDDS. Further, good correlation between the found values and the proposed equation was noted. Therefore, the validity of the proposed equation was verified.

Key words ointment; *in vitro* drug release; liquid droplet dispersion system ointment; bleeding liquid

Ointments can be classified into three types according to the state of the drug.[1] A soluble type ointment is an ointment in which the drug is uniformly dissolved in the base. The crystal dispersion type ointment is an ointment in which the drug is suspended in the base. Liquid droplet dispersion system ointment (LDDS) is an ointment wherein the solvent containing the drug is finely dispersed as liquid droplets in the less compatible oily base. Schematic illustrations of the three ointments are shown in Fig. 1. Thus, LDDS consists of a continuous phase of the base and the liquid droplet (solvent) phase. Since the drug exists in a completely dissolved state, it is reported that high efficacy is expected.[2] Saitoh *et al.*[3] reported that the absorption of dexamethasone from LDDS significantly exceeded that from a conventional crystal dispersion type ointment. There are no reports which analyze the *in vitro* drug release profile from LDDS.

In a previous report,[4] the *in vitro* drug release from soluble type and crystal dispersion type ointments was clarified. Therefore, in this report, the *in vitro* drug release from LDDS has been studied.

In vitro drug release from LDDS using mometasone furoate as the drug and ethyleneglycol salicylate (EGS) as the solvent was studied. LDDS is characteristically similar to the crystal dispersion type ointment, as liquid droplets are finely dispersed in the continuous phase of the base. On the other hand, as the whole drug is dissolved therein, it is also similar to a soluble type ointment.

As to the *in vitro* drug release from ointments, when the cumulative amount of drug released against the square root of time is found to be linear, a slope of this line can be used as an index for *in vitro* drug release. W. I. Higuchi[5] reported that slope is proportional to the drug concentration in ointment for soluble type ointments. Further, T. Higuchi[6] also reported that slope is proportional to the square root of the drug concentration in ointment for crystal dispersion type ointments.

An *in vitro* drug release profile was predicted from the standpoint of thermodynamic activity.[7] Drug concentration in the bleeding liquid (BL) regarded as the continuous phase of the base,[8] was considered to be proportional to the thermodynamic activity of LDDS when the liquid droplet phase was equilibrated in concentration with the continuous phase

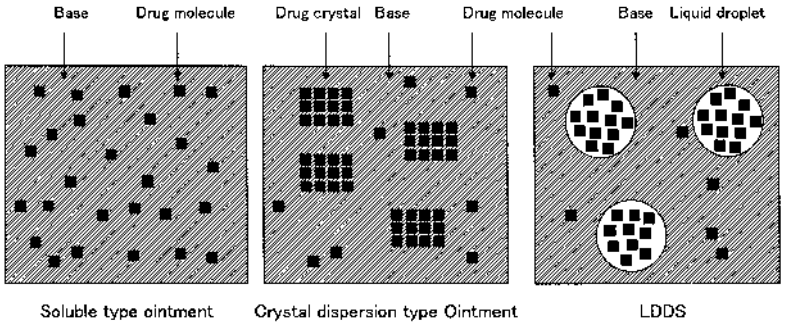

Fig. 1. Schematic Illustration of Ointment Types

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of the base. Upon application of the theory of thermodynamic activity to the *in vitro* drug release, some cases did not correspond with this theory. Thus, further theoretical studies were done. An equation for *in vitro* drug release from LDDS was proposed. The similarity of our equation to W. I. Higuchi's equation or T. Higuchi's equation was then studied. Further, the correlation between the found values and our equation was studied to verify the validity of the proposed equation.

Materials and Methods

Materials and Reagents The active ingredient, mometasone furoate, was obtained from Schering-Plough (U.S.A.). JP grade white petrolatum and liquid paraffin were used as ointment base. EGS and sorbitan sesquistearate were purchased from Tokyo Chemical Industry (Tokyo, Japan) and Nikko Chemicals (Tokyo, Japan), and used as the solvent and the dispersing agent, respectively. Betamethasone dipropionate obtained from Schering-Plough (U.S.A.) was used as the internal standard for HPLC. Other materials and reagents used were of special or HPLC grades.

Preparation of Ointment LDDS was prepared according to the method of Saitoh *et al*.[3] Compositions of the ointments are shown in Tables 1 and 2.

***In Vitro* Drug Release Test Method** According to the method reported previously,[4] an *in vitro* drug release test was carried out using a Franz type diffusion cell, a liquid phase-separating filter: 1 PS (Whatman, U.K.) as a support membrane and 70% methanol solution as the receiver solution at the experimental temperature of 37 °C. The "slope" obtained from plotting the amount of drug released against the square root of time was designated as an index for *in vitro* drug release.

Collection of BL BL was collected according to the cone mesh filtration method reported previously.[8]

Determination of Drug and Solvent Concentrations in Ointment and BL Upon the addition of *n*-hexane to the ointment or BL for dispersion, a 90% methanol solution with the internal standard was added to extract the drug. The 90% methanol phase was analyzed by HPLC.

Upon the addition of tetrahydrofuran with the internal standard to the BL in order to dissolve it, the solvent concentration was measured by HPLC under the same conditions as reported previously.[4]

Microscopic Examination Microscopic examination was performed according to the method reported previously.[8]

Measurement of Density of Ointment In order to measure the density of the ointment, 10 cm^3 of ointments were weighed.

Results and Discussion

Microscopic Examination Microscopic examination was performed on ointments (Table 1, 2) and BL from ointments (Table 1, 2). Liquid droplets in ointments were about 50 μm or less in diameter and no liquid droplet was found in BL.

Drug Concentration in BL For the purpose of studying the characteristics of LDDS, the drug concentration in BL (C_{BL}) was determined according to changes in the drug concentration in the ointment (Co) at definite solvent concentrations in ointment (So) and in changes of So at definite Co.

1) Changing Drug Concentration at Definite Solvent Concentrations: Figure 2 shows the relationship between Co and C_{BL} in the case of changing Co at definite So, as noted in Table 1. Co was proportional to C_{BL}.

2) Changing Solvent Concentration at Definite Drug Concentrations: Figure 3 shows the relationship between So and C_{BL} in the case of changing So at definite Co, as noted in Table 2. So was inversely proportional to C_{BL}. The broken curve in Fig. 3 indicates the case in which So is inversely proportional to C_{BL}.

Drug Concentrations in Liquid Droplet and Continuous Phases of the Base Further details of the relationship between Co or So and C_{BL} were studied. Figure 4 shows the relationship between So and EGS concentration in the BL (S_{BL}) in the case of changing So at a definite Co. S_{BL} was nearly constant, regardless of So; therefore, it was presumed that EGS was saturated in the continuous phase of the base. Thus, the continuous phase of the base is considered to remain the same in composition, even if the So changes. Here,

Table 1. Composition of Ointments

	Preparation (%)				
	a	b	c	d	e
Mometasone furoate	0.05	0.10	0.20	0.30	0.40
EGS	6.00	6.00	6.00	6.00	6.00
Sorbitan sesquistearate	4.00	4.00	4.00	4.00	4.00
Liquid paraffin	5.00	5.00	5.00	5.00	5.00
White petrolatum	84.95	84.90	84.80	84.70	84.60

Table 2. Composition of Ointments

	Preparation (%)				
	f	g	h	i	j
Mometasone furoate	0.10	0.10	0.10	0.10	0.10
EGS	1.50	3.00	6.00	8.00	12.00
Sorbitan sesquistearate	4.00	4.00	4.00	4.00	4.00
Liquid paraffin	5.00	5.00	5.00	5.00	5.00
White petrolatum	89.40	87.90	84.90	82.90	78.90

Composition b in Table 1 is the same as composition h in Table 2.

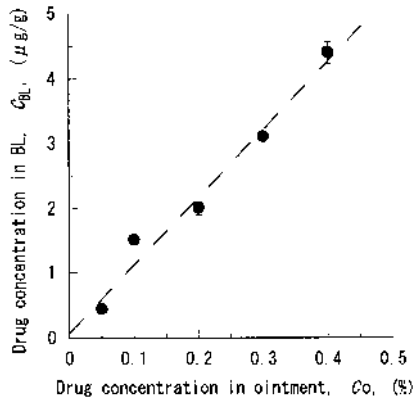

Fig. 2. Relationship between Drug Concentration in Ointment and Drug Concentration in BL

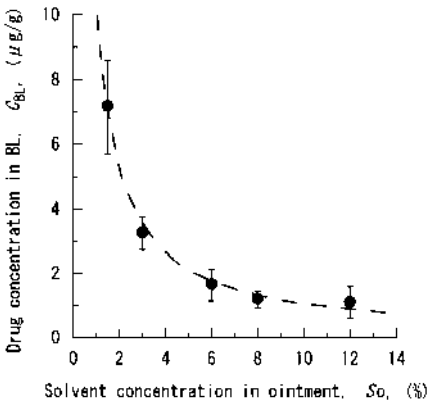

Fig. 3. Relationship between Solvent Concentration in Ointment and Drug Concentration in BL

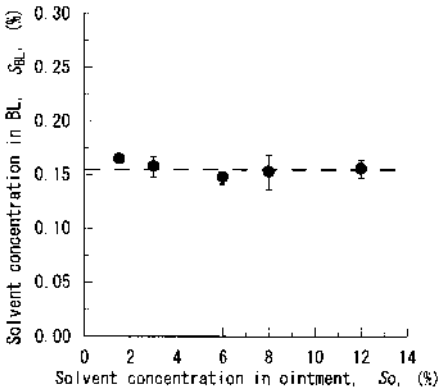

Fig. 4. Relationship between Solvent Concentration in Ointment and Solvent Concentration in BL

Table 3. Drug Concentration in BL and Drug Concentration in Liquid Droplet and Partition Coefficient

	EGS concentration in ointment (%)				
	1.5	3	6	8	12
C_{BL} (μg/g)	7.2	3.2	1.6	1.2	1.1
*C*s (mg/g)	78.1	37.0	18.0	13.4	8.9
$K=Cs/C_{BL}$	1.09×10^4	1.15×10^4	1.11×10^4	1.14×10^4	0.82×10^4

C_{BL}: Drug concentration in BL, *C*s: Drug concentration in liquid droplet.

as shown in Fig. 4 with a broken line, supposing that a definite amount of EGS is dissolved in the continuous phase of the base and dissolution of the base component to the liquid droplet is negligible, a drug concentration in the liquid droplet *C*s was calculated. The calculation method is stated under appendix 1. Table 3 shows C_{BL}, *C*s, and the partition coefficient K ($=Cs/C_{BL}$). K is nearly constant, regardless of *S*o; therefore, it is suggested that the partition law was established. Further, since K is very large, it is suggested that nearly the whole drug added in the ointment (more than 99%) exists in the liquid droplet.

Prediction of *In Vitro* Drug Release Profile Higuchi[7] reports that the thermodynamic activity of the drug in the base is proportional to percutaneous absorption of the topical drug products. Tanaka *et al.*[9] report that such thermodynamic activity of Higuchi's theory can be demonstrated by the value of the drug concentration in the base divided by the solubility of the drug to the base. As verified above, in a series of ointments used in this study, the composition of the continuous phase of the base is considered to be constant, since C_{BL} is considered to be proportional to thermodynamic activity. This is further confirmed in consideration of the suggested establishment of the partition law between the liquid droplet phase and the continuous phase of the base. C_{BL} is proportional to the thermodynamic activity of the whole ointment. The theoretical background is stated under appendix 2.

An *in vitro* drug release profile was predicted from the standpoint of thermodynamic activity. As stated above, when *C*o changes at definite *S*o, *C*o is proportional to C_{BL}, from which it can be presumed that when *C*o increases at a definite *S*o, the slope will increase in proportion to *C*o. On the other hand, when *S*o changes at definite *C*o, *S*o is inversely proportional to C_{BL}. Thus, it is presumed that when *S*o increases at a definite *C*o, the slope would decrease, being inversely proportional to *S*o.

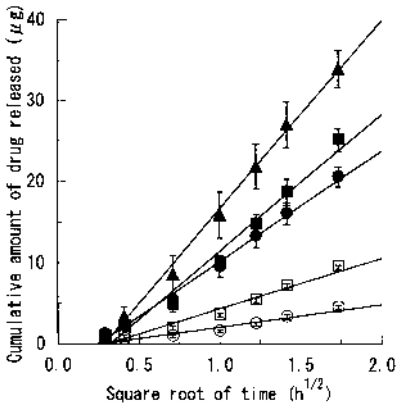

Fig. 5. Cumulative Amount of Drug Release As a Function of Square Root of Time

Drug concentration: ○,0.05%; □,0.1%; ●,0.2%; ■,0.3%; ▲,0.4%.

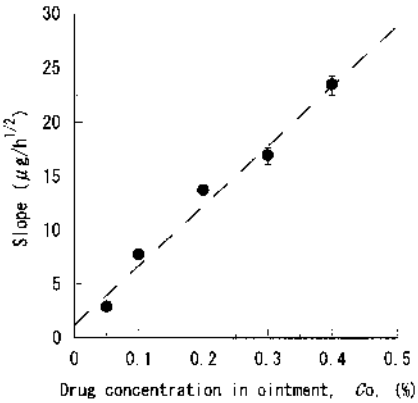

Fig. 6. Relationship between Drug Concentration in Ointment and Slope

***In vitro* Drug Release from LDDS** For the purpose of inspecting the prediction made in the previous section, the *in vitro* drug release from LDDS was studied with changes of *C*o at definite *S*o and with changes of *S*o at definite *C*o.

1) Changing Drug Concentration at Definite Solvent Concentration: Figure 5 shows the cumulative amounts of the drug released against the square root of time with the ointment composed of those noted in Table 1, *i.e.* in the case of changing *C*o at a definite *S*o of 6%. With a correlation coefficient of more than 0.97 showing good linearity, it was suggested that slope can be used as the index for *in vitro* drug release. Further, the relation between *C*o and slope is shown in Fig. 6. *C*o is proportional to slope. Thus, the presumption in the previous section was verified.

2) Changing Solvent Concentration at Definite Drug Concentration: Figure 7 shows the relationship between *S*o and slope in the case of changing *S*o at a definite *C*o of 0.1%, the ointment being composed of those elements shown in Table 2. Regardless of *S*o, the slope is nearly definite. When the *C*o is definite, *S*o is inversely proportional to C_{BL}, *i.e.*, regardless of C_{BL}, slope is definite, which is different from the presumption in the previous section.

As shown in Fig. 3, since C_{BL} is inversely proportional to *S*o, $C_{BL}\times So$ becomes constant. Thus, when *S*o changes, it is presumed that the influence of C_{BL} on slope is set off against changes of *S*o. Therefore, no apparent influence was ob-

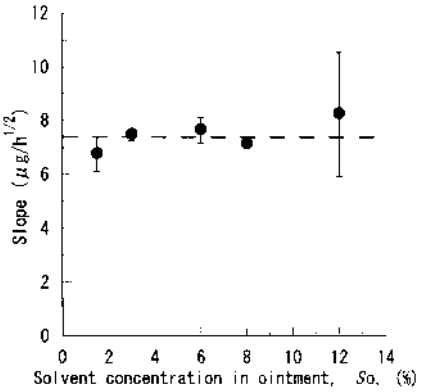

Fig. 7. Relationship between Solvent Concentration in Ointment and Slope

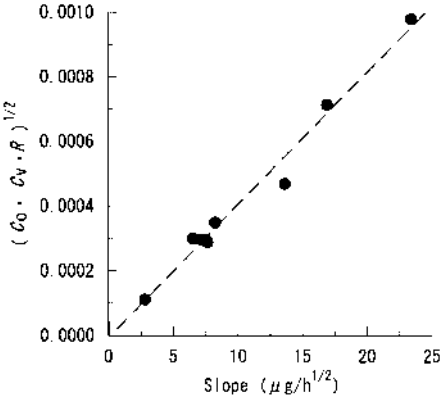

Fig. 8. Correlation between Slope and $(Co \cdot Cv \cdot R)^{1/2}$
Correlation coefficient: 0.991.

served. Meanwhile, in the case of the lower solubility of the solvent to the continuous phase of the base, *So* is considered to be nearly proportional to the volume fraction of the liquid droplet phase.

Approach from Theoretical Aspects For the purpose of studying the release profile of LDDS, the relation between *Co* and the drug concentration in the continuous phase of the base (*Cv*) was examined and obtained:

$$Co \fallingdotseq R \cdot K \cdot Cv \tag{1}$$

The method of calculation is stated under appendix 3. *Co* is approximately proportional to $R \cdot Cv$. Such a relationship is established because in LDDS the liquid droplet phase is equilibrated with the continuous phase of the base in partition, and it is markedly shifted to the liquid droplet phase; thus, nearly all of the drug is considered to be present in the liquid droplet phase.

Next, the release profile was studied. As known from Fig. 5, the cumulative amount of the drug released (Q) is in linear relation to the square root of time. When lag time is negligible, it is in relation as follows:

$$Q = \text{slope} \times t^{1/2} \tag{2}$$

In the previous section slope was known to be proportional to *Co*, thus, Eq. 2 can be expressed as follows:

$$Q = k \cdot Co \cdot t^{1/2} \quad (k \text{ is constant}) \tag{3}$$

Here, if it is supposed that even when the amount of the drug or solvent in ointment changes, the diffusion coefficient D remains unchanged; it can be $k' = k/D^{1/2}$ (k' is constant). When this relation is substituted into Eq. 3 the release of LDDS is indicated as:

$$Q = k' \cdot Co \cdot (D \cdot t)^{1/2} \tag{4}$$

This is same form as W. I. Higuchi's equation $Q = 2Co \cdot (D \cdot t/\pi)^{1/2}$, except for the constant term.

When Eq. 4 is rewritten from Eq. 1, the following equation is obtained:

$$Q = k' \cdot (K \cdot Co \cdot Cv \cdot R \cdot D \cdot t)^{1/2} \tag{5}$$

When this is compared with T. Higuchi's equation: $Q = \{(2Co - Cv) \cdot Cv \cdot D \cdot t\}^{1/2} \fallingdotseq (2Co \cdot Cv \cdot D \cdot t)^{1/2}$, it is suggested that in LDDS the volume fraction of the liquid droplet phase and the partition coefficient become important new parameters.

Further, for the purpose of verifying the validity of Eq. 5, the relationship between the found value of slope and $(Co \cdot Cv \cdot R)^{1/2}$ is shown in Fig. 8. Meanwhile, as with *Co*, *Cv* is the weight fraction and R is the volume fraction in Fig. 8, thus $(Co \cdot Cv \cdot R)^{1/2}$ is dimensionless. Good correlation was noted between them. And in cases when no explanation was available with Higuchi's thermodynamic activity, in changing *So* at definite *Co*, validity upon application of Eq. 5 thereto was verified.

Conclusion

A new equation for *in vitro* drug release from LDDS has been obtained. The equation is as follows: $Q = k' \cdot (K \cdot Co \cdot Cv \cdot R \cdot D \cdot t)^{1/2}$

A good correlation between found values and the proposed equation was noted. Therefore, the validity of the proposed equation was verified. The volume fraction of the liquid droplet, which is not present in soluble type and crystal dispersion type ointments, was suggested to be an important parameter for LDDS.

Appendix

1. Calculation of Volume Fraction and Drug Concentration in Liquid Droplet Abbreviations are defined as follows. Volume fraction of liquid droplet phase: R, density of EGS: ds, volume of ointment: Vo, volume of droplet: Vs.

$ds \cdot Vs$ is an amount of EGS after the deduction of that which dissolved into the continuous phase of the base followed by conversion to a volume.

$$Vs = \{So \cdot Vo - S_{BL} \cdot (1-R) \cdot Vo\}/ds$$

This is substituted into the equation of volume fraction:

$$R = Vs/Vo = \{So \cdot Vo - S_{BL} \cdot (1-R) \cdot Vo\}/ds/Vo$$
$$R = (So - S_{BL})/(ds - S_{BL})$$

R can be obtained by substituting the found value thereto.

On the other hand, *Cs* is the amount of the drug from which the amount dissolved into the continuous phase of the base is deducted and divided by *Vs*.

$$Cs = \{Co \cdot Vo - C_{BL} \cdot (1-R) \cdot Vo\}/Vs = ds\{Co - C_{BL} \cdot (1-R)\}/\{So - S_{BL} \cdot (1-R)\}$$

Cs can be obtained by substituting the found value thereto.

2. Thermodynamic Activity of the Whole Ointment

Abbreviations are defined as follows. Thermodynamic activity of the continuous phase of the base: a_v, solubility of the drug in the continuous phase of the base: Cv*.

Thermodynamic activity of the liquid droplet phase: a_s, solubility of the drug in the liquid droplet phase: Cs*.

To determine the thermodynamic activity of Higuchi's theory, the value of the drug concentration is divided by the solubility of the drug, and the following two equations are obtained with the continuous phase of the base and the liquid droplet phase.

$$a_v = Cv/Cv^*$$

$$a_s = Cs/Cs^*$$

When a_S was divided by a_V, the following equation was obtained.

$$a_s/a_v = (Cs/Cs^*)/(Cv/Cv^*) = (Cs/Cv)/(Cs^*/Cv^*) = K/K = 1$$

For $a_s = a_v$, a_s or a_v will be considered as the thermodynamic activity of the whole ointment.

It has already been reported that the BL is considered to represent the continuous phase of the base. The thermodynamic activity of the continuous phase of the base will be equal to the thermodynamic activity of the BL. Thus the drug concentration in BL will be proportional to the thermodynamic activity of the whole ointment.

3. The Relationship between Drug Concentration in Ointment and That in Continuous Phase of the Base Abbreviations are defined as follows. The amount of drug in the ointment: Mo, the amount of drug in the solvent: Ms, the amount of drug in the continuous phase: Mv, the volume of the continuous phase: Vv.

As the amount of drug in ointment is equal to the amount of drug in the solvent and the continuous phase of drug, $Mo = Ms + Mv$.

As the volume of ointment is equal to the volume of the solvent and the continuous phase of drug, $Vo = Vs + Vv$.

As the drug concentration in the liquid droplet is equal to value of the amount of drug in the droplet divided by the total volume of the droplet, $Cs = Ms/Vs$.

As the drug concentration in the continuous phase of the base is equal to the value of the amount of the drug in the continuous phase of the base divided by the volume of the continuous phase of the base, $Cv = Mv/Vv$.

$$\begin{aligned} Co &= Mo/Vo = (Ms + Mv)/Vo = \\ &(Cs \cdot Vs + Cv \cdot Vv)/Vo = (K \cdot Cv \cdot Vs + Cv \cdot Vv)/Vo \\ &= \{(K \cdot Cv \cdot Vs + Cv \cdot (Vo - Vs)\}/Vo = \{(K \cdot Cv \cdot Vs/Vo + Cv \cdot (Vo - Vs)/Vo\} \\ &= K \cdot Cv \cdot R + Cv \cdot (1 - R) = Cv \cdot K \cdot R\{1 + (1 - R)/(K \cdot R)\} \fallingdotseq K \cdot R \cdot Cv \end{aligned}$$

In the ointment used in this study $(1-R)$ is very small compared with $K \cdot R$, enabling us to see $\{1+(1-R)/(K \cdot R)\}$ as 1; thus, the above approximate equation is established.

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