A Method for Measuring the Surface Free Energy of Topical Semi-solid Dosage Forms

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Our aim was to determine the surface free energy (SFE) of semi-solid dosage forms (SSDFs) by establishing a reproducible method for measuring the contact angle of liquids to SSDFs. Four SSDFs were used: petrolatum, an oil/water (O/W) and a water/oil (W/O) cream, and an alcohol-based gel. The SSDFs were evenly spread on a glass slide, and the change in contact angle over time was measured by dropping water, glycerol, diiodomethane and n-hexadecane as the test liquids. Depending on the combination of test liquid and SSDF, the contact angle was either constant or decreased in an exponential manner. Contact angles may have decreased in an exponential manner because the reaction between the test liquid and the SSDF altered the interfacial tension between the two phases and changed the surface tension of the test liquid and the SFE of the SSDF. The contact angle of the test liquid to the SSDF could be determined reproducibly using the initial contact angle immediately after dropping the liquid on the SSDF as the contact angle before reaction. Using the obtained contact angles and the Owens–Wendt–Rabel–Kaelble equation, we calculated the SFE and its component for the SSDFs tested and found that the results reflect the physicochemical properties of SSDFs. Furthermore, the work of adhesion (W detach) of the SSDF to Yucatan micropig skin was calculated using the SFE for the SSDFs. Interestingly, the W detach values for all SSDFs tested were comparable.

Key words surface free energy; contact angle; semi-solid dosage form; Owens–Wendt–Rabel–Kaelble method; Yucatan micropig

Introduction

Topical medicines such as liquids, creams, ointments, and gels are applied directly to treat the affected area. The base of a topical medication helps the formulation adhere to the skin and keep the active ingredients on the affected area for a long time. However, differences in the base and active ingredients change the wettability and adherence of the formulation when applied to the skin. Therefore, the ability to predict the wettability and adherence of topical medications on the skin based on their physicochemical properties would aid in the evaluation of bases and the rational development of formulations.

Surfaces exhibit excess energy due to intermolecular forces. This energy is called surface tension in the case of liquids and surface free energy (SFE) in the case of solids. Surface tension and SFE can be divided into many components, such as disperse, polar, and hydrogen bond components. In general, the wettability and adhesion of a liquid to a solid is determined by the surface tension of the liquid and the SFE of the solid. The surface tension of a liquid can be measured by the Wilhelmy, du Noý, or pendant drop methods. In contrast, the SFE of a solid cannot be measured directly and is generally calculated from a theoretical formula using the contact angle of the test liquids to the solid. There are many methods for determining SFE, such as the Owens–Wendt–Rabel–Kaelble (OWRK),1,2 Kitazaki–Hatá,3 Wu,4 and acid-base theories.5

We previously reported that the wettability and adhesion of lotions to the skin can be accurately predicted using an analytical method based on the OWRK method.6) This prediction requires knowledge of each component of the surface tension of the lotion. The surface tension of the liquid formulation can be measured in a relatively simple manner. On the other hand, to determine the SFE of semi-solid dosage forms (SSDFs) such as ointments, creams, and gels, it is necessary to measure the contact angle using several test liquids, as in the case of solids. However, because of differences in the compatibilities of some combinations of test liquid and the SSDF, when the test liquid is dropped onto the SSDF, the interface becomes very unstable due to the dissolution of the SSDF into the liquid and the penetration of the liquid into the SSDF. There are several reports of contact angle measurements of SSDF for paraffin wax2–10 but none for other SSDFs, and there is no general test method for determining the contact angle of a test liquid to a SSDF. There is therefore need to establish a rational method for measuring the contact angle of a test liquid to a SSDF.

The aim of this study was to determine the SFE of a SSDF by establishing a reproducible method for measuring the contact angles of liquids to SSDFs. In this paper, we also attempted to calculate the work of adhesion of the SSDFs to Yucatan micropig skin using the obtained SFE for the SSDFs.

Experimental

Materials Polystyrene sheet (PS, size 200 × 300 mm, thickness 1 mm) was purchased from Hikari Co., Ltd. (Osaka, Japan). Vaseline (VA, Sun White® P-1) was a gift from Nikko Rica Corporation (Tokyo, Japan), Hirudoid® Soft Ointment 0.3% (HSO), Hirudoid® Cream 0.3% (HC), and Hirudoid® Gel 0.3% (HG) were purchased from Maruhou Co., Ltd. (Osaka, Japan). The list of additive agents contained in these SSDFs is shown in Table 1.11–13 Water (distilled water for injection) was purchased from Otsuka Co., Ltd. (Tokushima, Japan).
Glycerol (GLY), diiodomethane (DIM), and n-hexadecane (C-16) were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). All test liquids were of the highest commercial quality available and were used without further purification. The surface tension ($\gamma_S$) and its disperse ($\gamma_S^d$) and polar ($\gamma_S^p$) components of the liquids reported by Rabel, Kitazaki and Hata and Jasper are shown in Table 2.

Contact Angle Measurement The contact angles of the test liquids on the SSDFs were measured by the sessile drop method using an optical contact-angle measuring instrument (OCA20, DataPhysics Instruments GmbH, Filderstadt, Germany) at 25°C. A film applicator (4AP, Taiyu Kizai Co., Ltd., Osaka, Japan) was used to spread the SSDF on a glass slide (Matsunami Glass Ind., Ltd., Osaka, Japan) to a thickness of 50 µm. Each test liquid (2 µL) was dropped on the slide and a movie sequence of the droplet shape was immediately recorded at 60 frames per second. The contact angle of each drop was determined using circle- or ellipse-fitting methods. Note that the starting time of the measurement (0 s) was set to when the droplet left the needle tip. The data represent the mean and standard deviation values of 5 independent measurements.

Determination of SFE Using the OWRK Method Although there are many theoretical formulas for measuring SFE, the OWRK method is the most commonly used. When a droplet on a solid surface is in equilibrium, Young’s equation (Eq. (1)) is established:

$$\gamma_S = \gamma_{SL} + \gamma_{L} \cdot \cos \theta$$

where $\gamma_S$ is the SFE of the solid, $\gamma_{SL}$ is the interfacial tension between the solid and the liquid, $\gamma_L$ is the surface tension of the liquid, and $\theta$ is the contact angle. However, it is not possible to obtain $\gamma_S$ from Young’s equation just by measuring $\theta$ because $\gamma_{SL}$ cannot be measured directly. On the other hand, according to the Owens–Wendt equation (Eq. (2)), $\gamma_{SL}$ is calculated from $\gamma_S$ and $\gamma_L$ and their disperse component ($\gamma_S^d$, $\gamma_L^d$) and polar component ($\gamma_S^p$, $\gamma_L^p$).

$$\gamma_{SL} = \gamma_S + \gamma_L - 2 \sqrt{\gamma_S^d \cdot \gamma_L^d + \gamma_S^p \cdot \gamma_L^p}$$

From these two equations, the OWRK equation (Eq. (3)) can be obtained.

$$\gamma_L (1 + \cos \theta) = 2 \sqrt{\gamma_S^d \cdot \gamma_L^d} + 2 \sqrt{\gamma_S^p \cdot \gamma_L^p}$$

Deconstructing this equation provides a linear equation in the form $y = mx + c$ (Eq. (4)).

Results and Discussion Contact Angles of Liquids on SSDFs Figure 1 shows the change in droplet shape over time when water and DIM are dropped on PS and HSO. When either test liquid is dropped on PS, which is a solid, the droplet shape of the test liquid remains essentially unchanged, indicating that the test liquid quickly reached an equilibrium state on PS. In contrast, for the SSDF HSO, the droplet shape changed immediately after the test liquid was dropped onto it, indicating a reaction at the interface between the test liquid and HSO.

Figure 2 shows the change in contact angle over time for PS and four SSDFs (VA, HSO, HC, and HG) after dropping test liquids (water, GLY, DIM, and C-16). When any of these test liquids was dropped on PS, the contact angle hardly changed. This indicates that PS does not react with these test liquids, and that the three forces (the surface free energy of PS, the interfacial tension between PS and the test liquid, and the surface tension of the test liquid) are balanced at the triple-phase point (where the solid, the liquid droplet, and the surrounding gas are all in contact). In this case, the equilibrium contact angle can be determined from the measurement.

The change in contact angle for a combination of SSDF and test liquid can be classified into two patterns: 1, the contact angle hardly changes, and 2, the contact angle decreases in

| Brand name                        | Abbreviation | Manufacturer            | Dosage form                       | Additive agents                                  | Ref. |
|-----------------------------------|--------------|-------------------------|-----------------------------------|--------------------------------------------------|------|
| Sun White® P-1                    | VA           | Nikko Rica Corporation  | Oleanious base                    | Glyceryl, squalene, light liquid paraffin, paraffin, ceresin, white petrolatum, white beeswax, glycerin fatty acid ester, dibutylhydroxytoluene, edetate sodium hydrate, methyl parahydroxybenzoate, propyl parahydroxybenzoate | 11   |
| Hirudoid® Soft Ointment 0.3%      | HSO          | Maruho Co., Ltd.        | Water-in-oil emulsion base        | Glyceryl, stearic acid, potassium hydroxide, white petrolatum, lanolin alcohol, cetostearyl alcohol·sodium cetostearyl sulfate mixture, myristyl alcohol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, isopropyl, propylene glycol, trisopropanamline, carbouxyvinyl polymer, perfume oil | 12   |
| Hirudoid® Cream 0.3%              | HC           | Maruho Co., Ltd.        | Oil-in-water emulsion base        | Isopropanol, propylene glycol, trisopropanamline, carbouxyvinyl polymer, perfume oil | 13   |
| Hirudoid® Gel 0.3%                | HG           | Maruho Co., Ltd.        | Alcohol-based gel                 | Isopropanol, propylene glycol, trisopropanamline, carbouxyvinyl polymer, perfume oil | 13   |

Table 2. Surface Tension and Its Components for the Test Liquids Used in This Study

| Test liquid | $\gamma_L^d$ (mN/m) | $\gamma_L^p$ (mN/m) | $\gamma_L$ (mN/m) |
|-------------|---------------------|---------------------|------------------|
| Water       | 72.30               | 18.70               | 53.60            |
| GLY         | 65.20               | 28.30               | 36.90            |
| DIM         | 50.80               | 46.80               | 4.00             |
| C-16        | 27.47               | 27.47               | 0.00             |

$$\frac{\gamma_L (1 + \cos \theta)}{2\sqrt{\gamma_L^d}} = \sqrt{\gamma_S^d \cdot \gamma_L^d} + \sqrt{\gamma_S^p \cdot \gamma_L^p}$$

(4)

Here, the disperse component ($\gamma_L^d$) and the polar component ($\gamma_L^p$) of the SFE of the solid are included in the intercept c and the slope m, respectively. To determine $\gamma_S$ using Eq. (4), it is necessary to measure the contact angle using two or more test liquids whose $\gamma_L^d$ and $\gamma_L^p$ are already known (Table 2). Note that $\gamma_S$ is the sum of each component and is given by Eq. (5).

$$\gamma_S = \gamma_S^d + \gamma_S^p$$

(5)
an exponential manner. These outcomes are likely due to the reactivity between the SSDF and the dropped test liquid. For example, in combinations of different external phases, such as VA (an oleaginous base) and water or HC (an oil/water (O/W) emulsion base) and C-16, the contact angle remained almost constant because the reactivity between the two phases was low. On the other hand, in combinations of similar external phases, such as HG (an alcohol-based gel) and GLY or VA (an oleaginous base) and C-16, the contact angle decreased exponentially due to the high reactivity between the two phases. We anticipated that HSO (a W/O emulsion base) would have low reactivity with water and GLY, but observed the opposite, perhaps because the inner phase of HSO directly interacted with water and GLY, or the glycerol fatty acid ester (a surfactant contained in the outer phase) aided the reaction. These results suggest that when a test liquid and SSDF are compatible,
the additive agents in the SSDF dissolve into and/or adsorb onto the test liquid and change the surface tension of the test liquid and the interfacial tension between the SSDF and test liquid. At the same time, penetration of the test liquid into the SSDF would also change the SFE of the SSDF. These results indicated that the equilibrium contact angle often cannot be measured. Therefore, in this study, we decided to evaluate the initial contact angle immediately after dropping the test liquid onto the SSDF and regarding this value as the contact angle prior to the reaction between the test liquid and the SSDF.

**Contact Angle and SFE of the SSDFs** Table 3 shows the average values of the initial contact angles and their standard deviations obtained from 5 individual measurements for various combinations of test liquid and SSDF. The standard deviations were all relatively small, and the contact angles could be obtained with good reproducibility in all measurements. If the properties of the test liquid and SSDF were similar, the contact angle was small, and if the properties of the two were different, the contact angle was large.

Figure 3 shows a plot based on the OWRK equation (Eq. (4)). The coefficient of determination ($R^2$) for both regression lines ranged from 0.794 to 0.984, indicating a good linear relationship. $\gamma_p$ and $\gamma_d$ were calculated from the intercept and the slope of these regression lines (Fig. 4). As shown in Fig. 4, VA has the lowest SFE of the four SSDFs tested because it contains alcohols such as isopropanol and propylene glycol as additive agents. Note that, if the contact angle after a certain time is used instead of the initial contact angle, the SFE is estimated to be larger because the contact angle becomes smaller due to the reaction between the test liquid and SSDF. From the above results, it can be concluded that the SFE and its components obtained by our method were reasonable values.

**Work of Adhesion of SSDF to Yucatan Micropig Skin** The equation for the work of adhesion ($W_A$, Eq. (7)) can be derived from the Owens–Wendt equation (Eq. (2)) and the Dupré equation (Eq. (6)).

$$W_A = (\gamma_s + \gamma_d) - \gamma_{SL}$$  \hspace{1cm} (6)

$$W_A = 2\sqrt{\gamma_p \cdot \gamma_d ^{p}} + \sqrt{\gamma_p ^{S} \cdot \gamma_d ^{S}}$$  \hspace{1cm} (7)

This equation was originally intended to calculate the work of adhesion between a liquid and a solid. The work of adhesion for SSDF to Yucatan micropig (YMP) skin can be determined by regarding $\gamma_p$ and $\gamma_d$ in Eq. (7) as the SFE of the SSDF and YMP skin, respectively. We calculated $W_A$ using the results for the dorsal area of YMP skin reported by Fujii et al.[$^{10}$] [$\gamma_p = 39.05 \text{ mN/m}$ (\gamma_p^S = 37.04 \text{ mN/m}, \gamma_p^S = 2.01 \text{ mN/m})]. Interestingly, as shown in Fig. 5, the $W_A$ values of all SSDFs tested were comparable. From Eq. 7, it can be seen that the $W_A$ between the SSDF and YMP skin depends on the geometric mean of the same components of the individual SFEs. The SFE for YMP skin is dominated by the disperse component and has a slight polar component. The SFE for VA and HSO is small, but the disperse component accounts for a large proportion of the SFE, suggesting that they have a large $W_A$, mainly due to the interaction with the disperse component of YMP skin. On the other hand, HC and HG have a very large polar component, indicating that they have a large $W_A$ even if the

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**Table 3. Initial Contact Angles of Each Test Liquid on the SSDFs ($\sigma = 5$)**

|        | VA          | HSO         | HC          | HG          |
|--------|-------------|-------------|-------------|-------------|
| Water  | 121.85° ± 1.40 | 87.04° ± 1.13 | 27.29° ± 1.65 | 57.88° ± 2.50 |
| GLY    | 110.39° ± 1.65 | 72.94° ± 2.05 | 51.49° ± 2.38 | 58.31° ± 1.90 |
| DIM    | 78.34° ± 2.34 | 73.99° ± 1.22 | 94.15° ± 0.89 | 72.85° ± 1.41 |
| C-16   | 28.17° ± 0.60 | 26.07° ± 1.91 | 46.61° ± 1.74 | 50.46° ± 0.89 |

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**Fig. 3.** OWRK Plots for Various Test Liquids against the SSDFs Tested
Conclusion

In this study, we established a method to measure the contact angle of liquids to SSDFs. Depending on the combination of test liquid and SSDF, the contact angle decreased in an exponential manner with time. For these cases, the contact angle of the test liquid to the SSDF can be determined reproducibly by adopting the initial contact angle immediately after the test liquid is dropped on the SSDF. Also, using the OWRK equation, the surface free energy of the SSDF and the work of adhesion to YMP skin were successfully determined. This study used four types of test liquids: water, glycerol, diiodomethane, and \( n \)-hexadecane. However, other liquids can be selected if the surface tension and their components are already known, and theoretically it is possible to use only two test liquids.

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Conflict of Interest

The authors declare no conflict of interest.

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