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Physicochemical Properties and Solubility of Hydrocortisone Butyrate Propionate[1)]

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The physicochemical properties of the solid state of hydrocortisone butyrate propionate (HBP) were determined by thermal analysis of the solid phase. In addition, the solubility of HBP was measured in a wide variety of solvents. The physicochemical properties and solubility of HBP obtained experimentally were compared with those reported for hydrocortisone (HC).

The solid phase of HBP showed a lower melting point (122 °C) and heat of fusion (4.98 kcal/mol) than those of HC. The activity of the solid phase of HBP was significantly higher than that of HC. The solubility parameter of HBP estimated from the solubility in various solvents was 11.2 $(\text{cal/ml})^{1/2}$. This value is lower than that of HC, which was reported as 12.4 $(\text{cal/ml})^{1/2}$. Further, the solubility parameter of HBP was closer to that of skin, which was reported as 9.7—10.0 $(\text{cal/ml})^{1/2}$.

Consequently, it is considered that the high release ability from topical preparations and the high percutaneous absorption of HBP are due to the high activity of solid phase and the fact that the solubility parameter is close to that of skin.

Keywords——hydrocortisone butyrate propionate; hydrocortisone; solubility; thermodynamic activity; solubility parameter; regular solution; polar solvent

Many investigations have been reported on the correlations between the biological activity of topical corticosteroids and their physicochemical properties. The physicochemical properties of topical corticosteroids may affect the drug release from vehicles and the percutaneous absorption. Therefore, the physicochemical properties of corticosteroids have been determined with regard to the solubility, the solubility parameters, the molar attraction constants, and the partition coefficients.

Katz and Shaikh[2)] found a correlation between the activity of human skin vasoconstriction in response to topical corticosteroids and the physicochemical properties such as solubility or partition coefficients. Ostrenga and Steinmetz[3)] investigated the relationship between the molar attraction constants of fluocinolone acetonide and fluocinolide and the solubilities in various solvents. Hagen and Flynn[4)] measured the solubility parameter and the ideal solubility of hydrocortisone (HC).

However, no attempt has been reported to relate the thermodynamic activity of the solid phase and the solubility parameter of corticosteroids with percutaneous absorption. Thus, the physicochemical properties of hydrocortisone butyrate propionate (HBP) as a derivative of HC were determined and the value of the thermodynamic activity of the solid phase and the solubility parameter were compared with those reported for HC.[4)]

The differences of physicochemical properties between HBP and HC are discussed in an attempt to identify the basis of the difference in percutaneous absorption reported by Washitake *et al.*[5)]

Experimental

Material——HBP used was synthesized by Taisho Pharmaceutical Co., Ltd., and its purity was 99.7%. The other materials used were of reagent grade.

Crystalline Density Measurement——The crystalline density of HBP was measured with a Beckman densitometer (model 930) at 25 °C. The measurement was repeated three times.

Thermal Analysis——The heat of fusion (ΔH_f) of HBP crystals was determined with a differential scanning calorimeter (Du Pont 910 B thermal analysis system). A finely powdered, accurately weighed sample (1.5—2.0 mg) was sealed in an aluminium pan. An empty, sealed pan served as a reference. Samples were heated at 5 °C/min. The molar heat of fusion was calculated from the area of the melting endotherm by using a computer. The calibration coefficients were determined with accurately weighed samples of indium.

The entropy of fusion was obtained by dividing the heat of fusion by the absolute melting temperature T_f.

Solubility Measurement——An excess of HBP crystals was added to each solvent and the mixture was shaken for 24—48 h in a water bath at 25 ± 0.1 °C. The sample was filtered with a Millipore filter (0.45 μm). The HBP concentration in the filtrate was measured by high-performance liquid chromatography (HPLC) after diluting the solution to a suitable concentration with methanol.

Conditions of HPLC——The amount of HBP in each solution was determined by HPLC using a Hitachi 633 liquid chromatograph with a 15 cm × 4.0 mm i.d. stainless steel column packed with LiChrosorb RP-18, 10 μm (Merck Co., Ltd.). Other conditions were as follows: eluent, mixture of water–methanol (35 : 65); flow rate, 1.0 ml/min; detector, UV at 254 nm; sensitivity, 0.02—0.16 a.u.f.s.; injection volume, 10 μl; column temperature, 50 °C. The standard HBP solution for HPLC was prepared by using the same solvent for each sample.

Results and Discussion

Physicochemical Properties of the Solid State of HBP

HBP is a crystalline solid. When it was heated from 40 to 140 °C, it underwent only one endothermal transition at 122 °C, as shown in Fig. 1. The endotherm was confirmed to represent primarily energy consumed during melting, by the reported approach.[4]

The physicochemical properties of HBP obtained experimentally are shown in Table I. The data reported by Hagen and Flynn[4] for HC are also shown in Table I. The melting point of HBP is 122 °C, which is about 90 °C lower than that of HC, and the heat of fusion of HBP is 4.98 kcal/mol, while that of HC is 8.1 kcal/mol. The reason for the difference is thought to be that HBP molecules are not linked by hydrogen bonds in the solid phase, since the 17,21-hydroxyl groups are unavailable due to esterification.

The crystalline density of HBP is 1.20, which is slightly lower than that of HC. The molar volume of HBP is estimated from the crystalline density to be 407.2 ml/mol.

Solubility of HBP in Nonpolar Solvents

The solubility of HBP was determined in hexane, cyclohexane carbon tetrachloride, toluene, and benzene as nonpolar solvents, which had been reported to behave as regular solvents for HC.[4] The values of solubility of HBP in these solvents at 25 °C are summarized in

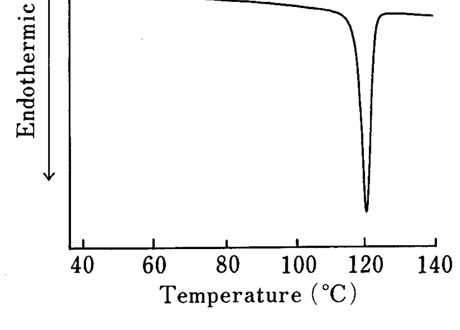
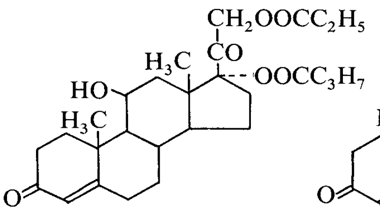
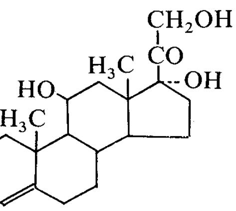


Fig. 1. Thermal Analysis of HBP by Differential Scanning Calorimetry

Table I. Physicochemical Properties of HBP and HC

	HBP	HC[a]
Molecular structure		
Molecular weight	488.6	362.5
Crystalline density	1.20	1.24
Molar volume, V_2	407.2 ml/mol	293 ml/mol
Melting temperature, T_f	122 °C	212 °C
Heat of fusion, ΔH_f	4.98 kcal/mol	8.1 kcal/mol
Entropy of fusion, ΔS_f	12.6 cal/deg/mol	16.7 cal/deg/mol
Activity of solid phase, a_2^{s}[b]	1.28×10^{-1}	5.2×10^{-3}
Solubility parameter, δ_2	11.2 (cal/ml)$^{1/2}$	12.4 (cal/ml)$^{1/2}$

a) From ref. 4. *b*) Calculated from $\ln a_2^{s} = -\frac{\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right)$.

Table II. Solubilities of HBP in Nonpolar Solvents at 25 °C

Solvent	δ_1[a] (cal/ml)$^{1/2}$	Equilibrium solubility (g/l)	Mole fractional solubility, X_2
Hexane	7.3	0.137	3.66×10^{-5}
Cyclohexane	8.2	0.172	3.81×10^{-5}
Carbon tetrachloride	8.6	2.37	4.70×10^{-4}
Toluene	8.9	24.5	5.30×10^{-3}
Benzene	9.1	41.4	7.47×10^{-3}

a) From ref. 4.

Table II as solubility (g/l) and mole fractions. Benzene, which has the largest solubility parameter among them, showed the highest solubility for HBP. The solubility of HBP increased in proportion to the solubility parameter of the solvents. The solubility of HBP in each solvent is larger by about 2 to 4 orders of magnitude than that of HC in the same solvent. In order to clarify the solubility profile of HBP, the thermodynamic activity of solid HBP (a_2^{s}) and the solubility parameter (δ_2) were estimated by using Eqs. 1 and 2, respectively.

$$\ln a_2^{s} = -\frac{\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) \tag{1}$$

$$\ln X_2 = \ln a_2^{s} - \frac{V_2 \phi_1^2}{RT}(\delta_1 - \delta_2)^2 \tag{2}$$

where T_f and T are the melting and ambient temperatures, respectively, and $\boldsymbol{R}$ is the gas constant. ΔH_f is the heat of fusion of the solid solute at the melting point. V_2 is the molar volume of solute, ϕ_1 is the volume fraction of solvent, and δ_1 and δ_2 are the solubility parameters of the solvent and solute, respectively.

With the assumptions reported by Hagen and Flynn,[4] the ideal solubility (a_2^{s}), which is equal to the thermodynamic activity of the solid phase of HBP, can be obtained by

TABLE III. Solubilities of HBP in Propylene Glycol–Water, Ethanol–Water and Dioxane–Water Mixtures at 25 °C

Solvent in water % (w/w)	Propylene glycol–water mixture			Ethanol–water mixture			Dioxane–water mixture		
	δ_{1-3}[a] (cal/ml)$^{1/2}$	Solubility (g/l)	Mole fraction[b]	δ_{1-3}[a] (cal/ml)$^{1/2}$	Solubility (g/l)	Mole fraction[b]	δ_{1-3}[a] (cal/ml)$^{1/2}$	Solubility (g/l)	Mole fraction[b]
100	15.0	35.9	5.50×10^{-3}	13.0	577	1.17×10^{-1}	10.0	422	1.09×10^{-1}
90	15.8	19.1	2.20×10^{-3}	13.8	660	1.27×10^{-1}	11.3	588	1.27×10^{-1}
80	16.6	9.04	8.91×10^{-4}	14.7	677	1.19×10^{-1}	12.7	364	4.92×10^{-2}
70	17.5	3.94	3.04×10^{-4}	15.5	280	2.71×10^{-2}	14.0	234	2.31×10^{-2}
60	18.2	1.56	1.03×10^{-4}	16.5	103	7.58×10^{-3}	15.3	44.7	3.21×10^{-3}
50	19.1	5.80×10^{-1}	3.40×10^{-5}	17.4	14.9	9.06×10^{-4}	16.6	8.27	5.01×10^{-4}
40	19.9	2.06×10^{-1}	1.09×10^{-5}	18.4	4.79	2.59×10^{-4}	17.9	2.97	1.59×10^{-4}
30	20.7	9.63×10^{-2}	4.55×10^{-6}	19.5	1.44	7.08×10^{-5}	19.2	1.13	5.42×10^{-5}
20	21.5	4.72×10^{-2}	2.04×10^{-6}	20.6	2.29×10^{-1}	1.01×10^{-5}	20.5	3.00×10^{-1}	1.31×10^{-5}
10	22.2	2.44×10^{-2}	9.69×10^{-7}	21.8	5.77×10^{-2}	2.25×10^{-6}	21.7	5.37×10^{-2}	2.15×10^{-6}
0	23.0	1.19×10^{-2}	4.40×10^{-7}	23.0	1.19×10^{-3}	4.40×10^{-7}	23.0	1.19×10^{-2}	4.40×10^{-7}

a) Calculated from Eq. 3. *b*) Calculated from Eq. 4.

substituting each parameter in Eq. 1. The value obtained was 1.28×10^{-1}.

The solubility parameter (δ_2) of HBP also estimated as follows.[4] Values of δ_2 ranging from 7 to 23 and the mole fraction of HBP (X_2) for each solvent were substituted into Eq. 2, and it was found that when the value of δ_2 is 11.2, $a_2^{\S}$ is most constant. The value of the solubility parameter of HBP is lower than that of HC which was obtained by a similar calculation.[4] Further, the value for HBP obtained by summing the molar attraction constants of the functional groups is 10.0. This value is lower than that obtained for HC in a similar manner.[4]

Solubility of HBP in Polar Solvents

The solubility of HBP was determined in propylene glycol-water, ethanol–water and dioxane–water mixtures as polar solvents. The values of solubility and mole fraction of HBP in these solvents and the solubility parameter of these mixtures are shown in Table III. The solubility parameters of these mixtures (δ_{1-3}) were estimated from the expression of Smith *et al.* as follows.[6]

$$\delta_{1-3}=\frac{\phi_1\delta_1+\phi_3\delta_3}{\phi_1+\phi_3} \tag{3}$$

where δ_1 and δ_3 are the solubility parameters of the organic solvent and water, respectively, and ϕ_1 and ϕ_3 are the corresponding volume fractions. The mole fractions (X_2) of HBP in the mixtures were calculated from Eq. 4 (see the appendix):

$$X_2=\frac{C_s/m_2}{C_s/m_2+(F/m_1+1/m_3)(1000-C_s/d_2)/(F/d_1+1/d_3)} \tag{4}$$

where m_1, m_2 and m_3 are the molecular weights of the organic solvent, HBP, and water, respectively, and d_1 and d_2 are the densities of the organic solvent and HBP, respectively. C_s is the solubility of HBP (g/l) in the mixture, and F is the weight ratio of the organic solvent and water.

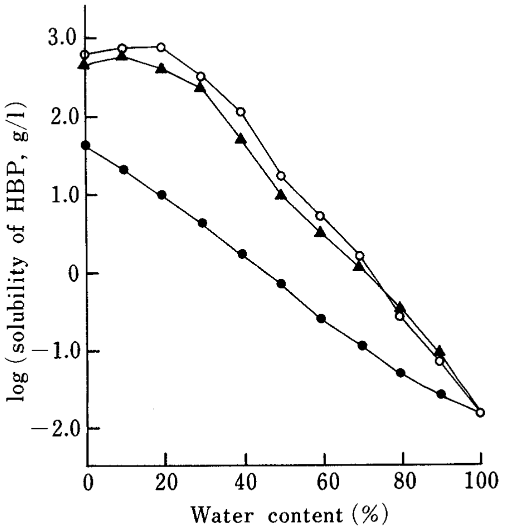


Fig. 2. Solubility of HBP in Mixed Polar Solvents at 25 °C

●, propylene glycol–water mixture; ○, ethanol–water mixture; ▲, dioxane–water mixture.

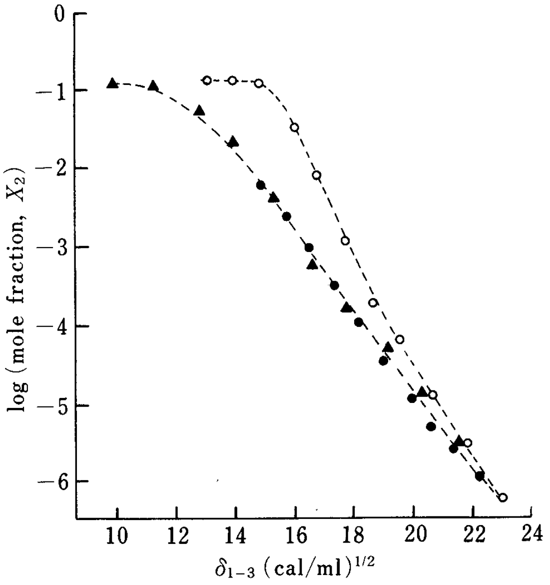


Fig. 3. Relationships between the Logarithm of Mole Fraction of HBP in Propylene Glycol–Water Mixture (●), Ethanol–Water Mixture (○), and Dioxane–Water Mixture (▲) and the Solubility Parameters at 25 °C

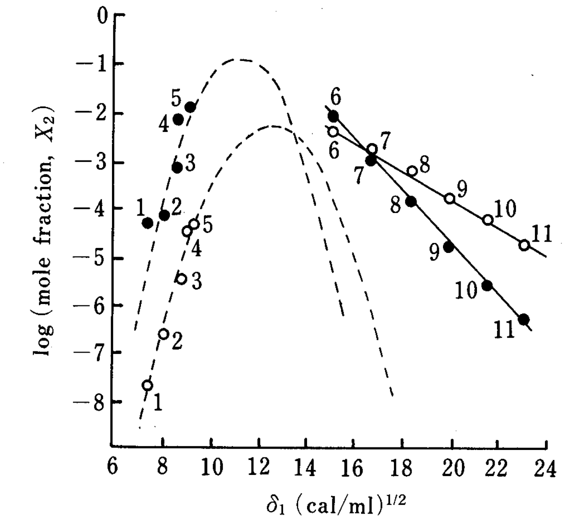


Fig. 4. Solubility Profiles of HBP (●) and HC (○) at 25 °C

1, hexane; 2, cyclohexane; 3, carbon tetrachloride; 4, toluene; 5, benzene; 6, propylene glycol; 7, 80% propylene glycol in water; 8, 60% propylene glycol in water; 9, 40% propylene glycol in water; 10, 20% propylene glycol in water; 11, water.

The relationships between the logarithmic solubility (g/l) and water content are shown in Fig. 2. The solubility of HBP in the propylene glycol–water mixture decreased logarithmically as the water content of the mixture increased. On the other hand, the solubility in the ethanol–water and dioxane–water mixtures was almost constant for water contents ranging from 0% to 30%, but then the solubility decreased logarithmically as the water content increased further.

The logarithms of the mole fractions of HBP are plotted against the solubility parameters of these mixtures in Fig. 3. These mole fractions of HBP in the propylene glycol–water and dioxane–water mixtures can be plotted on almost the same curve. However, the mole fractions of HBP in the ethanol–water mixture are shifted upwards from other plots. These results suggest a specific interaction between HBP and ethanol.

Comparison of Solubilities of HBP and HC

The solubility profiles of HBP and HC are shown in Fig. 4. The parabolic curves show the solubility in the nonpolar solvents obtained by calculation from Eq. 2 for regular solutions. The solubility in the propylene glycol–water mixtures deviates from the solubility predicted for regular solutions. The solubility of HBP in nonpolar solvents was higher than that of HC, since HBP has a higher ideal solubility and a lower solubility parameter than HC. However, the solubility of HBP in water is 25 times lower than that of HC.[4] The reason is thought to be that HBP cannot form hydrogen bonds with water because HBP lacks the 17- and 21-hydroxyl groups.

On the other hand, the percutaneous absorptions of HBP and HC have been reported by Washitake *et al.*[5] The amount of absorbed HBP is larger than that of HC at the same concentration of the drug in saline. The reason is considered to be that the chemical potency of HBP in saline is higher than that of HC, since the solubility of HBP is lower than that of HC in aqueous solution. Recently, the solubility parameter of skin has been reported to be from 9.7 to 10.0 by Liron and Cohen.[7] Therefore, the other fractors responsible for the difference of percutaneous absorption between HBP and HC are considered to be as follows.

(1) The solubility parameter of HBP is closer to that of skin, as compared with that of HC.

(2) The ideal solubility of HBP is about 20-fold higher than that of HC.

Accordingly, in order to design topical drugs which show efficient release and percutaneous absorption, it is necessary that the drugs selected should have a solubility parameter similar to that of skin, as well as high ideal solubility.

Appendix

In order to calculate the mole fraction of HBP in organic solvent–water mixtures, Eq. 4 was derived as follows. The mole fraction of HBP, X_2, is represented as;

$$X_2=\frac{w_2/m_2}{w_1/m_1+w_2/m_2+w_3/m_3} \qquad \text{A1}$$

where w_1, w_2, and w_3 are the weights of organic solvent, HBP, and water in one liter of the solution, respectively, and m_1, m_2, and m_3 are the corresponding molecular weights.

Assuming that there is no change in volume on mixing, since the change in volume on mixing is very much less than the change in the mole fraction of HBP for the various organic solvent–water mixtures, as shown in Fig. 3, the total volume, V_t, can be represented as;

$$V_t=w_1/d_1+w_2/d_2+w_3/d_3=1000\ (\text{ml}) \qquad \text{A2}$$

where d_1, d_2, and d_3 are the densities of organic solvent, HBP, and water, respectively.

The value of w_2 is equal to the solubility of HBP, C_s (g/l), and F is the weight ratio of organic solvent and water (w_1/w_3). Therefore, w_1, w_2, and w_3 are represented as;

$$w_1=F\frac{1000-C_s/d_2}{(F/d_1+1/d_3)} \qquad \text{A3}$$

$$w_2=C_s \qquad \text{A4}$$

$$w_3=\frac{1000-C_s/d_2}{(F/d_1+1/d_2)} \qquad \text{A5}$$

Then Eq. 4 can be obtained by substituting w_1, w_2, and w_3 into Eq. A1.

References and Notes

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