Physicochemical Studies on Decoctions of Kampo Prescriptions. II.[1] Relationship between the Hydrophobic Parameter of the Crude Drug Components and Their Transfer Ratio into the Decoctions

Kaoru NAKAJIMA,* Yoshiko TAKEUCHI, Heihachiro TAGUCHI, Koji HAYASHI, Minoru OKADA, and Masao MARUNO

Tsumura Central Research Laboratories, Tsumura & Co., 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-11, Japan. Received March 3, 1994; accepted June 16, 1994

Assuming that the general partition of crude drug components between oil and water can be replaced by that between the crude drug residue and the decoction solution, the following equation can be derived linking the transfer ratio (r_T) of the components and the capacity factor (k') on reverse-phase HPLC:

$$\log (100/r_T - 1) = a \log k' + b$$

In this equation, a and b are constants when the method of preparation of decoctions and the HPLC conditions are kept constant. In order to verify this relationship, some model decoctions were prepared using small size preparations (0.5—1.0 mm) of crude drugs, and the correlation between $\log (100/r_T - 1)$ and $\log k'$ of the components was examined. Since the correlation coefficient of the equation was calculated to be 0.9 or higher in these model decoctions, the assumption was useful for investigating this relationship between the transfer ratio and the hydrophobic or related parameters. Thus, the transfer ratios of all components in a decoction could be evaluated as a single continuous line rather than an aggregation of single points for the transfer ratios, and most of the highly hydrophobic components could be transferred to the decoctions without dissolution in water.

Keywords transfer ratio; crude drug component; kampo decoction; hydrophobic parameter; HPLC; capacity factor

In the previous paper,[1] we described how the transfer ratio (r_T, %) of organic crude drug components into a kampo decoction is regulated primarily by their hydrophobicity. In addition, the transfer ratio of the crude drug components and their extrapolated $\log k'$, a substitute for the hydrophobic parameter, did not exhibit a simple linear relationship. In the present study, some experiments were carried out for a theoretical investigation of this relationship and its validity to clarify how the transfer ratio is related to the extrapolated $\log k'$.

Firstly, the following factors are considered to affect the transfer ratio involving the transfer of crude drug components to the decoction.

i) Solubility of the crude drug components in water (concentration, temperature, pH and the promotion or inhibition of dissolution by coexisting materials)

ii) Transfer without dissolution in water (formation of suspensions and/or emulsions)

iii) Proportion of the extractant (water) to the crude drug

iv) Form of the crude drug (size, portion where the components are contained)

v) Amounts of the components in the crude drug

vi) Kinds of crude drugs compounded

vii) Decoction time

viii) Recovery ratio of the decoction

ix) Chemical reactions (compound degradation or formation, complex formation, *etc.*)

x) Other physical factors (such as evaporation, adsorption and attachment)

Since the transfer of crude drug components to a decoction is considered to be affected by complex interactions among these factors, the phenomenon itself is expected to be very complicated. However, factors iii—viii can be controlled under certain conditions, and factors ix and x can be ignored by selecting stable crude drug components for evaluation. Therefore, the careful selection of the components to be evaluated and the standardization of decoction conditions will allow an analysis of factors i and ii to be carried out; those two factors are considered to be directly related to the physicochemical properties of the components.

In this study, we prepared weak model decoctions of 13 individual crude drugs (Gardeniae Fructus, Paeoniae Radix, Puerariae Radix, Astragali Radix, Saposhnikoviae Radix, Forsythiae Fructus, Artemisiae Capillaris Spica, Alpiniae Officinarum Rhizoma, Zingiberis Rhizoma, Schisandrae Fructus, Alismatis Rhizoma, Magnoliae Cortex and Trichosanthis Semen) cut for ordinary dispensing (large size preparations) and, in order to minimize the effect of variations in the proportions of the contents of the components, they were cut into smaller fragments of a fixed size (small size preparations) under the same conditions and then the transfer ratios of the various crude drug components were examined. In addition, we prepared decoctions of a model prescription consisting of 9 crude drugs (Gardeniae Fructus, Paeoniae Radix, Artemisiae Capillaris Spica, Zingiberis Rhizoma, Schisandrae Fructus, Alismatis Rhizoma, Magnoliae Cortex, Trichosanthis Semen and Bupleuri Radix) using large and small size preparations and determined the transfer ratios of various drug components, except Bupleuri Radix. We then studied the relationship between the transfer ratios to these model and kampo decoctions with the extrapolated $\log k'$ values, reported previously as a substitute parameter for the hydrophobicity, based on our hypothesis relating to the transfer ratio described in the preceding paper.

Experimental

Determination of the Transfer Ratios of Crude Drug Components to Model Decoctions. Crude Drugs Crude Drugs: Gardeniae Fructus, Paeoniae Radix, Puerariae Radix, Astragali Radix, Saposhnikoviae Radix, Forsythiae Fructus, Artemisiae Capillaris Spica, Alpiniae Officinarum Rhizoma, Zingiberis Rhizoma, Schisandrae Fructus, Alismatis Rhizoma, Magnoliae Cortex, Trichosanthis Semen and Bupleuri Radix, cut for dispensing were purchased from Uchida Wakanyaku, Co., Ltd. Schisandrae Fructus was crushed in an iron mortar to break the seeds.

Preparation of Crude Drugs Large Size Preparations: Ordinary cut preparations for dispensing were sifted and fragments of 2.5 mm or over were used for the large size preparation. Artemisiae Capillaris Spica was used without sifting.

Small size preparations: Large size preparations were cut up with a knife and sifted fragments of 0.5—1.0 mm were used for the small size preparation.

Standard Compounds The following compounds, except for **18** which was synthesized, were isolated from each crude drug and identified or determined when the structures were unknown (Chart 1): Geniposide (**3**, Gardeniae Fructus), paeoniflorin (**4**, Paeoniae Radix), puerarin (**5**, Puerariae Radix), 7-glucosyloxy-3′-hydroxy-4′-methoxyisoflavone (**7**, Astragali Radix), *prim*-*O*-glucosylcimifugin (**9**, Saposhnikoviae Radix), 4′-*O*-*β*-D-glucosyl-5-*O*-methylvisamminol (**10**, Saposhnikoviae Radix), phillyrin (**11**, Forsythiae Fructus), astragaloside I (**15**, Astragali Radix), 6,7-dimethylesculetin (**18**, Artemisiae Capillaris Spica), cimifugin (**19**, Saposhnikoviae Radix), 5-*O*-methylvisamminol (**20**, Saposhnikoviae Radix), 5-hydroxy-7-(4″-hydroxy-3″-methoxyphenyl)-1-phenylhept-3-one (**21**, Alpiniae Officinarum Rhizoma), [6]-gingerol (**22**, Zingiberis Rhizoma), schizandrin (**23**, Schisandrae Fructus), alisol C monoacetate (**24**, Alismatis Rhizoma), [6]-shogaol (**25**, Zingiberis Rhizoma), honokiol (**26**, Magnoliae Cortex), magnolol (**27**, Magnoliae Cortex), gomisin N (**28**, Schisandrae Fructus), and 1,3-ditrichosanoyl-2-linoleoylglycerol (**29**, Trichosanthis Semen).

Preparation of Model Decoctions Single-Drug Decoctions: 1.00 g of the large or small size preparation of each single-drug was decocted using a standardized method with the following mixed-drug decoctions.

Mixed-Drug Decoctions: Each 1.00 g sample of large or small size preparations of 9 drugs (Gardeniae Fructus, Paeoniae Radix, Artemisiae Capillaris Spica, Zingiberis Rhizoma, Schisandrae Fructus, Alismatis Rhizoma, Magnoliae Cortex, Trichosanthis Semen and Bupleuri Radix) was compounded and decocted by the following method.

A mixture of crude drugs compounded according to each model decoction was placed in a 1-liter beaker and decocted with 600 ml water on an electric heater (National NK-685SG; 300—600 W) for about one hour until the volume was reduced to about 300 ml. The decoction was filtered through 2 layers of gauze while hot, the volume adjusted to 300 ml with water after cooling and then used for analysis.

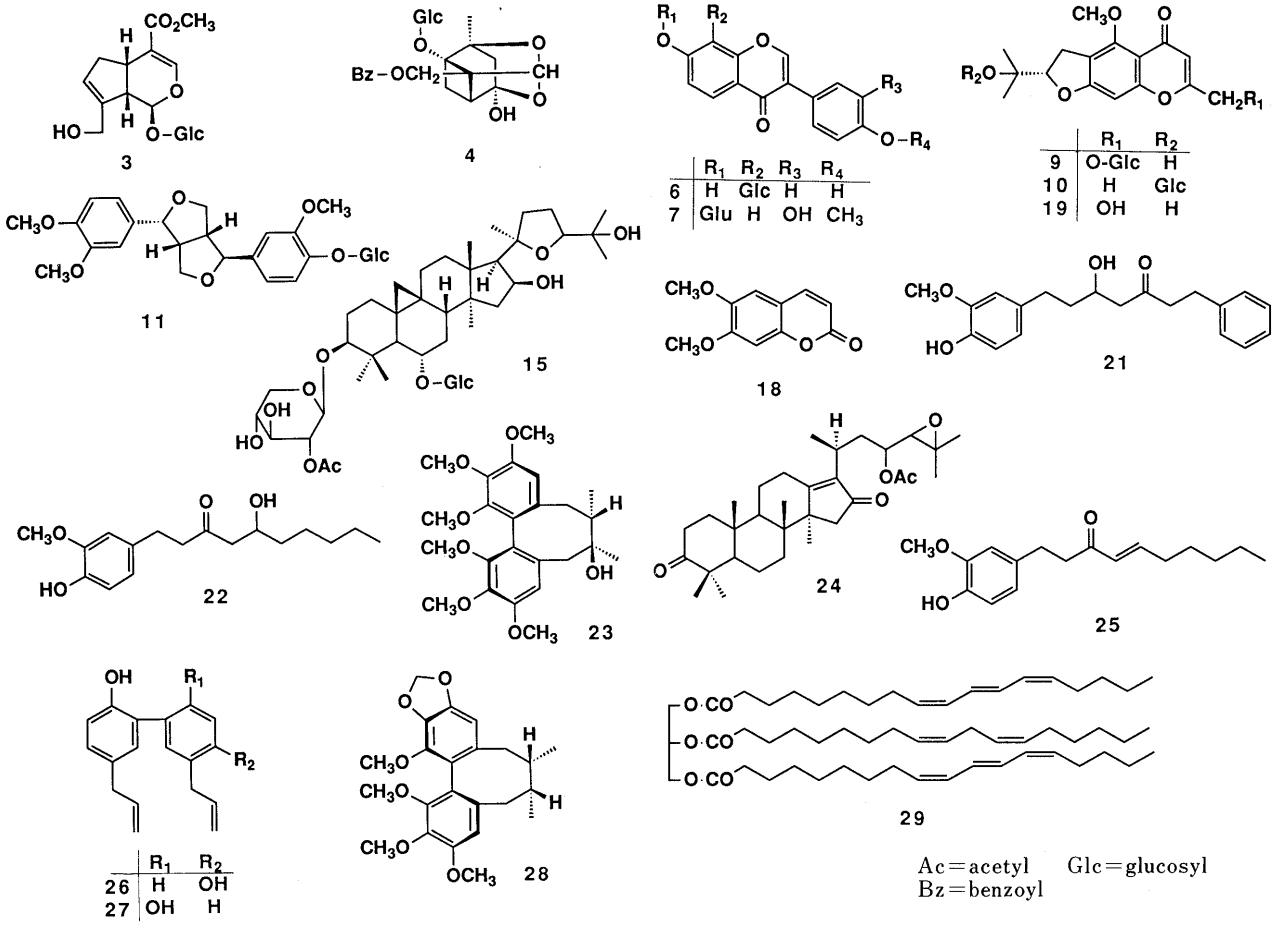
Preparation of Sample Solutions for HPLC Samples for the determination of components transferred with dissolution: The mixed-drug decoctions were passed through a filter (pore size 0.45 μm) at room temperature.

Samples for the determination of total components transferred: An aliquot (50—100 ml) of the model decoctions was mixed with 50 ml butanol, and the mixture concentrated under reduced pressure. The residue was extracted with 50 ml methanol by refluxing for 30 min. The residue was treated again with 50 ml methanol. The extracts were combined, concentrated under reduced pressure and then adjusted to a fixed volume with methanol.

Only **29** was extracted with a mixture of chloroform and methanol (1 : 1) and diluted to a fixed volume with the same mixed solvent.

Preparation of Standard Solutions for HPLC Each crude drug was pulverized, accurately weighed, and extracted by refluxing with 50 ml methanol for 30 min. After filtration, the residue was treated similarly again with 50 ml of methanol. The extracts were combined, concentrated under reduced pressure, and adjusted to a fixed volume with methanol.

For the analysis of **29**, extraction was carried out using a mixture of chloroform and methanol (1 : 1), and the volume was adjusted with the



	R_1	R_2	R_3	R_4
6	H	Glc	H	H
7	Glu	H	OH	CH_3

	R_1	R_2
9	O-Glc	H
10	H	Glc
19	OH	H

	R_1	R_2
26	H	OH
27	OH	H

Chart 1

TABLE I. HPLC Conditions for the Quantitative Analysis of Crude Drug Components in Model Decoctions

Component	Mobile phase	Detection
3	CH_3CN–CH_3OH–H_2O (1:1:9)	UV 254 nm
4	CH_3OH–H_2O (3:7)	UV 240 nm[a)]
6	CH_3CN–H_2O (3:17)	UV 254 nm
7	THF–CH_3CN–CH_3OH–H_2O (1:1:1:30)	UV 254 nm[a,b)]
9, 10, 19	CH_3CN–CH_3OH–1%CH_3CO_3H (1:1:7)	UV 254 nm[a)]
11	CH_3CN–CH_3OH–H_2O (2:1:10)	UV 254 nm[c)]
15	CH_3CN–CH_3OH–H_2O (13:13:14)	RI[d)]
18	THF–CH_3CN–H_2O (1:1:10)	UV 254 nm
21	CH_3CN–1%CH_3CO_2H (1:2)	UV 280 nm[a)]
22, 25	CH_3CN–CH_3OH–H_2O (1:1:2)	UV 280 nm[a)]
23, 28	CH_3CN–CH_3OH–H_2O (11:11:18) 8 min→(10:10:10)	UV 254 nm
24	THF–CH_3CN–CH_3OH–H_2O (1:1:1:4)	UV 254 nm
26, 27	CH_3CN–CH_3OH–H_2O (2:4:3)	UV 254 nm
29	THF–CH_3CN–H_2O (5:5:1)	UV 254 nm

Equipment, ALC/GPC 244 (Waters); column, μ Bondapak C_{18} (10 μm, 3.9 mm i.d. × 30 cm, Waters); flow rate, 1 ml/min. *a*) Equipment, Trirotar III (JASCO). *b*) Column, Nucleosil $5C_{18}$ (5 μm, 4 mm i.d. × 15 cm, Sumitomo Chemicals). *c*) Column, Nova pak C_{18} (4 μm, 3.9 mm i.d. × 15 cm, Waters). *d*) Detector, differential refractometer.

same mixed solvent.

HPLC Assay Each sample and standard solution for HPLC was passed through a 0.45 μm filter and a fixed volume was subjected to HPLC. Table I shows the composition of the mobile phases and the HPLC detection wavelengths. The transfer ratio (%) was determined by comparison of the peak area with that of the corresponding standard solution for HPLC. Also, the difference between the transfer ratio with dissolution and the total transfer ratio, which were determined sparately, was defined as a transfer ratio without dissolution.

Results and Discussion

Relationship between the Transfer Ratio and the Hydrophobic Parameter. Transfer Ratios of Crude Drug Components Structure–activity correlation studies have shown that the biomembrane is more permeable to highly lipophilic compounds. Collander examined the permeability of plant membranes to alcohols, esters, and ethers using *Chara ceratophylla* and observed a linear relationship between the membrane permeability and the ether/water partition coefficient.[2] A similar relationship was also observed for animal biomembranes. In connection with the poisoning of aquatic animals by pollutants such as agricultural chemicals, the octanol/water partition coefficient has been used to estimate the biological concentration coefficient.[3] Many studies on drug absorption have been conducted to date. Concerning the transfer of crude drug components to decoctions, the following hypothesis ivolves defining the residue of the crude drug as the organic phase and the decoction as the water phase and assumes that the transfer ratio of a given component is regulated by the oil/water distribution between the residue of the crude drug and the decoction. Since actual kampo decoctions are turbid water solutions, this hypothesis is not valid. However, we carried out this study on the assumption that weak decoctions, in which water is the dominant component, are water solutions of crude drug components. Actual kampo decoctions will be evaluated later.

In Eq. 1 involving the transfer ratio (r_T), the percentage of the content of the crude drug components in the decoction compared with the content in the bulk drug, is given as:

$$r_T = \frac{100 n_W}{n_B} \tag{1}$$

where n_B is the mole number of the component in the bulk drug, and n_W in the decoction. Since n_B is sum of the moles of the components in the residue of the crude drug (n_C) and in the decoction (n_W), Eq. 1 may be converted to Eq. 2:

$$r_T = \frac{100 n_W}{n_C + n_W} \tag{2}$$

Because the mole number is a product of the concentration (c) and the volume (v), Eq. 2 can be expressed as:

$$r_T = \frac{100 c_W v_W}{c_C v_C + c_W v_W} \tag{3}$$

which can be converted to:

$$\frac{c_C}{c_W} = \frac{v_W}{v_C}\left(\frac{100}{r_T} - 1\right) \tag{4}$$

The left term c_C/c_W is the ratio of the concentration of the component in the residue of the crude drug to that in the decoction which in this system means the partition coefficient ($P_{Dec.}$). The term of $100/r_T - 1$ corresponds to the molar ratio of the component in the drug residue to the decoction (n_C/n_W).

Relationship between the Transfer Ratio and the Hydrophobic Parameter For a given compound, the relationship of the partition coefficient between an organic solvent and water (P_1) with that between an other organic solvent and water (P_2) can be expressed as:

$$\log P_2 = A \log P_1 + B \tag{5}$$

where A and B are constants.[4] In reverse-phase HPLC, the proportion of the solute retained by the organic stationary phase is represented by the capacity factor (k'),[5] which is expressed as:

$$\frac{c_s}{c_m} = \frac{v_m}{v_s} k' \tag{6}$$

where c_s is the concentration of a given solute in the stationary phase, c_m the concentration of the solute in the mobile phase, and v_s and v_m the volumes of both phases, respectively. The term c_s/c_m on the left corresponds to the partition coefficient (P_{HPLC}) in HPLC. Therefore, the following Eq. 7 is obtained by substituting Eqs. 4 and 6 for Eq. 5.

$$\log\left(\frac{100}{r_T} - 1\right) + \log\left(\frac{v_W}{v_C}\right) = A \log k' + A \log\left(\frac{v_m}{v_s}\right) + B \tag{7}$$

Here, $\log(v_W/v_C)$ is a constant when the conditions of decoction, *e.g.*, the volumes of drug residue and decoction, are constant. Also, $\log(v_m/v_s)$ is a constant when the HPLC conditions, *e.g.*, column, composition of the mobile phase, equipment, flow rate of the mobile phase and so on are the same. Hence, the following, Eq. 8, can be obtained,

$$\log\left(\frac{100}{r_T} - 1\right) = a \log k' + b \tag{8}$$

where a and b are constants. When k' is defined as the capacity factor in HPLC using a reverse-phase partition

gel column and water as the mobile phase, it may be substituted for the hydrophobic parameter. Equation 9 is obtained as described previously.

$$\log\left(\frac{100}{r_T}-1\right)=a'\log P+b' \quad (9)$$

where a' and b' are constants, and P is the partition coefficient between octanol and water. Equation 9 expresses the relationship between the partition coefficient and the transfer ratio. However, since the P value of very highly hydrophobic substances is difficult to determine experimentally, Eq. 8 is much more practical than Eq. 9 for the actual experimental investigations.

Equation 5 is not necessarily applicable to all organic compounds, and the correlation between P_1 and P_2 is known to be altered by solvent interactions and the H-tolerance of the solutes, *i.e.* their capacity for hydrogen bonding.[6] Therefore, in this study, components of crude drugs are separately evaluated as glycosides and non-glycosides as in the previous study.

Generally, the partition equilibrium is discussed for one solute between water and an immiscible organic solvent. However, a kampo decoction contains a large number of components. Since the other components in the decoction compose part of the solvent to a certain component as solute, the theory of partition equilibrium is considered to be directly applicable to individual solutes in the decoction. If the hydrophobicity of all the crude drug components in a decoction could be altered continuously, the character of the decoction solution would also change as a solvent for each component. Furtherfore, if all crude drug components in a decoction could be regarded as a series of components with continuously changing affinity for water, the properties as the whole solvent would also continuously change for each solute. Therefore, the relationship between the transfer ratios of these components and their hydrophobic parameters can be regarded as a continuous line rather than aggregation of separate points. It is considered that all the components, ranging from hydrophilic to lipophilic, in the decoction are simultaneously exerting promotive and/or inhibitory effects on the dissolution of a given component.

Transfer Ratios to Model Decoctions Figure 1 shows the transfer ratios of various components of crude drugs to model decoctions from large (>2.5 mm) and small size (0.5—1.0 mm) preparations of a single or mixed-drugs in the order of the extrapolated $\log k'$ (a substitute for the hydrophobic parameter). Hydrophobic components in

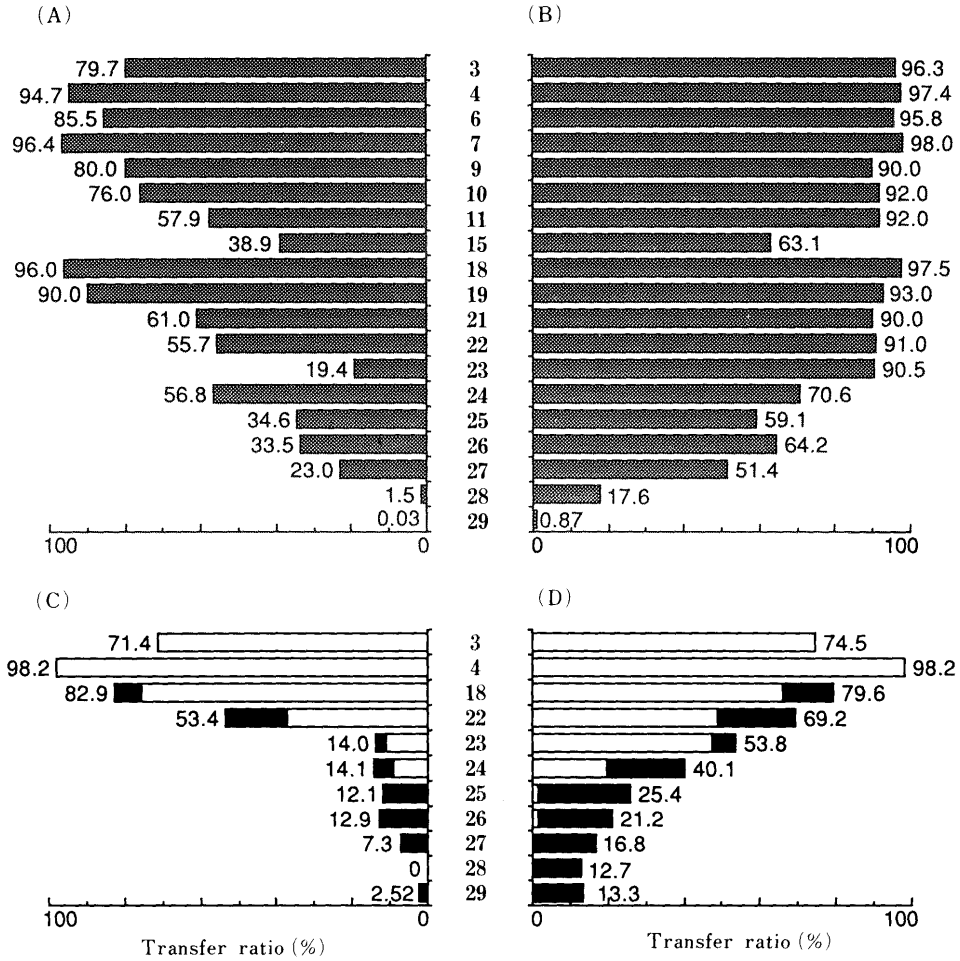


Fig. 1. Transfer Ratios of Crude Drug Components into Single- (Upper) or Mixed-Drug (Lower) Decoctions Using Large (Left) or Small (Right) Size Preparations

(A), large size preparation (>2.5 mm), single-drug decoction; (B), small size preparation (0.5—1.0 mm), single-drug decoction; (C), large size preparation (>2.5 mm), mixed-drug decoction; (D), small size preparation (0.5—1.0 mm), mixed-drug decoction. ▨, (total) transfer ratio; □, transfer ratio with dissolution; ■, transfer ratio without dissolution.

model decoctions from mixed-drugs were adsorbed to the filter material (0.45 μm, filter for aqueous solvent) during sample preparation for HPLC analysis so that their transfer ratio with dissolution could not be accurately determined. Therefore, the transfer ratios of components with and without dissolution in model decoctions using mixed-drugs are shown as reference values and there is a suggestion of a trend. Moreover, saikosaponins a, d and b groups were excluded from the analysis because they undergo chemical reactions during the decoction process[7] and their concentrations in the standard solutions could not be accurately determined.

Comparison of the small size with large size preparations: In small size preparations, where the effect of the variation in the site of the crude drug, where the components are found, on the transfer ratio is smaller, the transfer ratios of the hydrophobic components were clearly reduced in both single and mixed-drug decoctions. In large size preparations, on the other hand, the unevenness in the distribution of the components was clear. Components **15** and **28** of Shisandrae Fructus were hardly transferred unless the seeds were broken into small fragments.[8] However, the transfer ratio generally tended to decrease as the hydrophobicity of the component increased and this was true for large as well as small size preparations.

Comparison of single-drug decoctions with mixed-drug decoctions: The transfer ratios of weakly hydrophobic glycosides such as **3** were similar in all decoctions. Moderately hydrophobic components such as **25**, **26** and **27**, whose transfer ratios into single-drug decoctions were about 50%, showed remarkable decreases in the transfer ratio in mixed-drug decoctions prepared using 9 times the amount of crude drugs. Interestingly, the transfer ratio of oily fat **29**, the extremely hydrophobic component of Trichosanthis Semen, was higher in the mixed-drug decoction than in the single-drug decoction and higher than that of **28**, which is more hydrophilic than **29**. A similar phenomenon was observed also in large size preparations, suggesting that the proportion of the components transferred without dissolution increases even in such weak decoctions of mixtures of more than two kinds of crude drugs.

Correlation between the Transfer Ratio and Extrapolated log k' The correlation between the transfer ratios of the components into model decoctions and the extrapolated log k' was estimated from Eq. 8. High correlations were observed between the transfer ratio and the extrapolated log k' for all model decoctions (Figs. 2—5). Especially in the small size preparations, very high correlations were also observed for both the glycosides and non-glycosides of single-drug decoctions, even those which were independently decocted (Fig. 3). In particular, very high correlations were observed for non-glycosides of the mixed-drug decoctions prepared using small size preparations (Fig. 5). Since the correlation could be evaluated accurately by mincing crude drugs into a small particles of uniform size and decocting them by the same procedure, the validity of the theoretical inference leading to Eq. 8 could be confirmed. This suggests that Eq. 8 or 9 can be used as the basic equation for estimating the transfer ratio of crude drug components.

When the relationship between the transfer ratios of the crude drug components and the extrapolated log k' was applied to Eq. 8, high correlations for non-glycosides were observed in spite of considerable differences in the ratio of the crude drug to the extractant and the decoction system used for various prescriptions[1] (Fig. 6). These findings suggest that the transfer ratio remains within a narrow range even when many crude drugs are compounded as large fragments; in such cases a partition equilibrium is difficult to achieve. The correlation coefficient between the transfer ratio and the extrapolated log k' was lower in the case of glycosides than non-glycosides because the glycosides used in this study had a similar hydrophobicity. The standard deviation of the transfer ratios for both glycosides and non-glycosides was 7.8%, with no large differences among the components. These findings suggest that the theory of a trans-

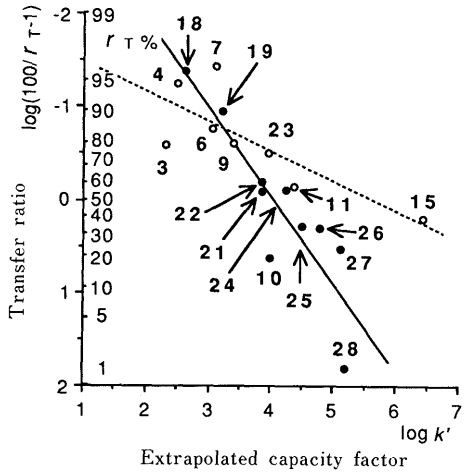


Fig. 2. Relationships between Extrapolated Capacity Factors of Crude Drug Components and Their Transfer Ratios into Single-Drug Decoctions Using Large Size Preparation

Component: ○, glycoside; ●, non-glycoside. Regression equation: glycoside, $y=0.3182x-1.7963$ ($r=0.789$, $n=8$); non-glycoside, $y=0.9540x-3.8689$ ($r=0.884$, $n=10$).

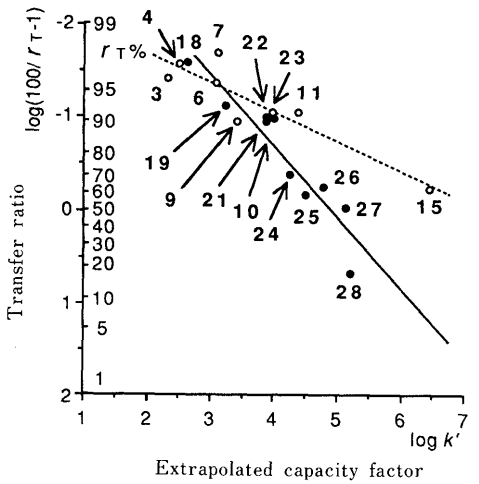


Fig. 3. Relationships between Extrapolated Capacity Factors of Crude Drug Components and Their Transfer Ratios into Single-Drug Decoctions Using Small Size Preparation

Symbols are the same as in Fig. 2. Regression equation: glycoside, $y=0.3164x-2.3220$ ($r=0.909$, $n=8$); non-glycoside, $y=0.7673x-3.7551$ ($r=0.938$, $n=10$).

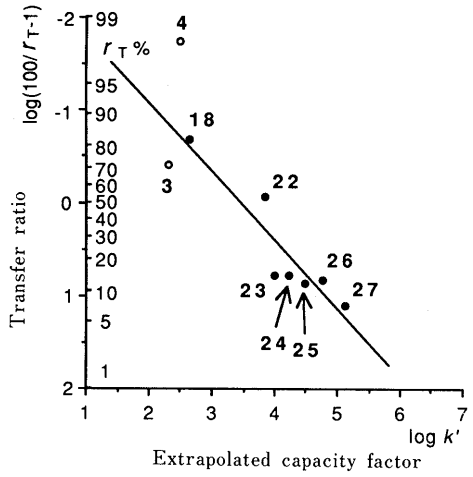


Fig. 4. Relationship between Extrapolated Capacity Factors of Crude Drug Components and Their Transfer Ratios into Mixed-Drug Decoctions Using Large Size Preparations

Symbols are the same as in Fig. 2. Regression equation: non-glycoside, $y=0.7367x-2.5465$ ($r=0.922$, $n=7$).

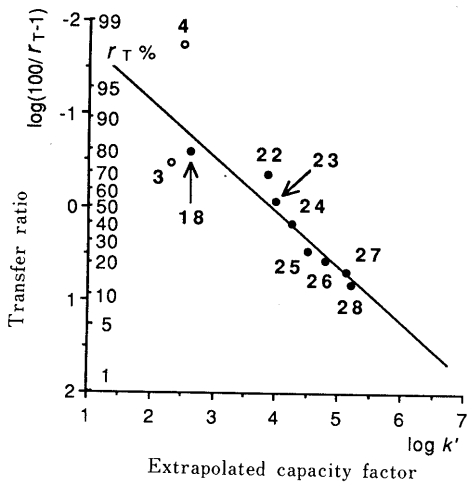


Fig. 5. Relationship between Extrapolated Capacity Factors of Crude Drug Components and Their Transfer Ratios into Mixed-Drug Decoctions Using Small Size Preparations

Symbols are the same as in Fig. 2. Regression equation: non-glycoside, $y=0.5908x-2.3167$ ($r=0.955$, $n=8$).

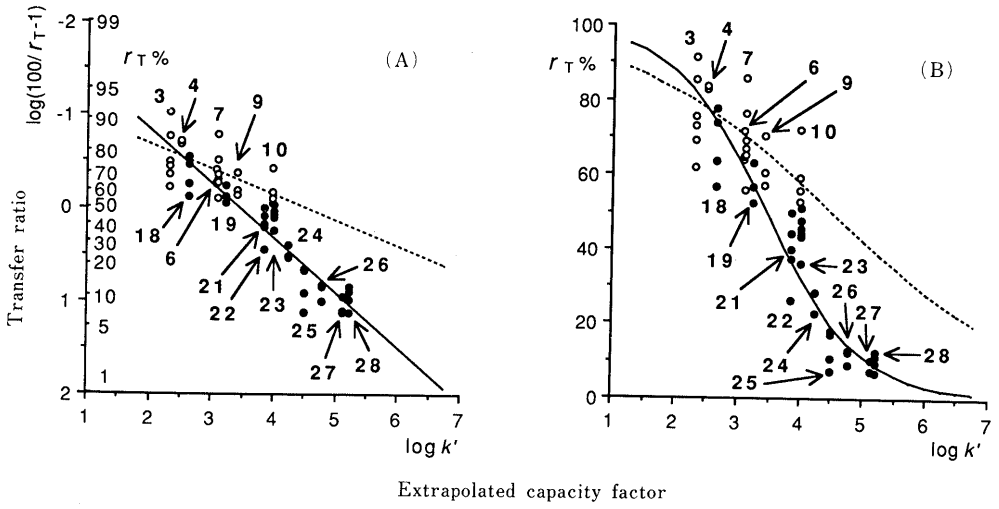


Fig. 6. Relationships between Extrapolated Capacity Factors of Crude Drug Components and Their Transfer Ratios into Kampo Decoctions

Symbols are the same as in Fig. 2. (A), log $(100/r_T-1)$ *vs.* extrapolated log k'. Regression equation: glycoside, $y=0.2706x-1.2154$ ($r=0.608$, $n=24$); non-glycoside, $y=0.5817x-1.9981$ ($r=0.928$, $n=37$). (B), r_T *vs.* extrapolated log k'.

fer ratio based on the partition equilibrium can be applied to kampo decoctions within the activity range of the crude drug components (solutes). This theory does not hold when the solubility of the components (solutes) is extremely high or when the ratio of the crude drug to the extractant is very large.

Transfer without Dissolution in Water The slope of the correlation equation between the transfer ratio and the extrapolated log k' of glycosides in various decoctions decreased in the order of single-drug decoction with large size preparations, that with small size preparations, and kampo decoctions in the previous study.[1] As for as non-glycosides were concerned, the slope decreased in the order of single-drug decoctions with large size preparations, single-drug with small size preparations, mixed-drug decoction with large size preparations, mixed-drug with small size preparations and kampo decoctions (Figs. 2—6). Changes in "*a*" in Eq. 8 indicate qualitative changes and suggest that the proportion of hydrophobic components becomes greater in more complex decoctions. As stated above, the transfer ratio without dissolution could not be determined accurately because of technical difficulties; however, the transfer without dissolution accounted for a large proportion of the total transfer ratio of highly hydrophobic components in the mixed-drug decoctions (Fig. 1). This is probably because part of the crude drug components is transferred into decoctions by adsorption and/or partition to materials called "dregs." This transfer occurs without dissolution, and/or by dispersion involving suspension and/or emulsification of the components themselves. Moreover, a high correlation in Eq. 8 was observed for the model involving weak decoctions, but the transfer ratio of the extremely hydrophobic **29**, deviated considerably from the equation. Therefore, further investigation on the transfer of crude drug components without dissolution is required.

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