# Thermodynamics of Distribution of Salicylates in Semi-Solid Ointment Bases

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**Abstract:** The distribution behavior of salicylic acid and its various esters (methyl, ethyl, phenyl, and glycol) between different semisolid vehicles (PEG, Carbopol 940, Plastibase) and non-miscible second phases has been examined over a range of temperature. The derived thermodynamics data can be used to discuss drug-vehicle interactions and changes in the thermodynamic activity of the solute. Salicylic acid interacts little, if at all, with inert materials such as Plastibase (mineral oil thickened with polyethylene) but together with its esters shows strong interaction with PEG. An increased interaction with increase in molecular weight (ethylene oxide content) of PEG is demonstrated. The salicylate esters have a lower affinity for Carbopol gels than for PEG because of entropy effects. Glycol salicylate in Carbopol gels demonstrates anomalous behavior. The relevance of the data to studies on drug release, and in particular the evaluation of rheological factors, is discussed.

The percutaneous absorption of a drug from semisolid vehicles can be influenced by a number of physicochemical factors that can be related to the properties of the drug, the base or both. Many workers have attempted to show some correlation between the distribution (partition) coefficient of a compound and its ability to penetrate the skin (1–5).

Since the distribution coefficient between the vehicle and the stratum corneum cannot be easily determined by direct experiment, some other arbitrarily two phase system is selected. One of the phases is usually water while the oil phase selected by different investigators to represent the skin barrier has included benzene, octanol, chloroform, ether, vegetable oil, and other organic solvents immiscible with water. For example, Treherne (4) related the permeability coefficient of a series of compounds to their ether-water distribution coefficients and suggested that a distribution coefficient of unity obtained with this system might indicate favorable skin penetration. Marzulli et al. (3) studied the penetration of various phosphates and phosphoric acid into the human stratum corneum *in vitro*. According to their data, compounds that were easily soluble in both benzene and water gave larger steady state penetration rates, whereas substances with either high benzene or high water solubilities showed lower penetration rates. Similarly, Stoughton et al. (6) have shown that the water-ether distribution coefficient could be related to the percutaneous absorption of nicotinic acid and its derivatives and that the substance with a so-called 'balanced partition characteristic' gave better absorption. Clendenning and Stoughton (2) later reported that the distribution coefficient (water/benzene) played an important role in percutaneous absorption of various boronic acid derivatives.

Other workers have preferred to consider solubility as the relevant physicochemical quantity. For example, Wurster and Kramer (7), using three salicylate esters (ethyl, methyl and glycol salicylate) found that under normal hydration conditions of the stratum corneum, the *in vivo* absorption rate for methyl salicylate was about twice that for ethyl and glycol salicylate. They stated that this was because methyl salicylate had a greater solubility in the lipid phase than the other two compounds. Hadgraft and Somers (8) have stated that percutaneous absorption occurs optimally 'when the medicament combines lipid solubility with moderate solubility in water', and Katz and Shaikh (1) have found that the efficiency of percutaneous absorption is well correlated by an empirical equation containing the product of the distribution coefficient and the square root of the aqueous solubility. While such attempts to relate percutaneous absorption to physicochemical data have been useful, Poulsen (9) has cautioned that conclusions based on optimal partitioning properties are not strictly correct and the general acceptance of the notion has led to erroneous assumptions regarding the importance and significance of the distribution coefficient. Realistically, the only distribution coefficient measurement for a penetrant that can be exactly related to its rate of diffusion through the skin is the value determined for the equilibrium distribution of the penetrant between the vehicle and the stratum corneum (9). Such measurements have been made by Scheuplein (10) and are of great practical value in relating the physical and chemical properties of a compound to its penetration rate. Poulsen (9) has explained why oil/water distribution coefficients often are an unreliable indicator of the relative permeabilities of a series of compounds. By plotting the permeability coefficients of a number of primary alcohols against the olive oil/water and stratum corneum/water distribution coefficient, a reasonably linear correlation between permeability and stratum corneum/water distribution coefficients was obtained for all of the alcohols tested ($C_4$ to $C_8$). However, the olive oil/water distribution coefficients were not nearly so well related to permeability.

Even experimental distribution coefficients determined between stratum corneum and water must be viewed with some caution (9). There are several points to consider: – since distribution coefficients are equilibrium values, a long period of time may be needed in order to obtain the distribution coefficient of the drug between the vehicle and the stratum corneum; if the vehicle is water, the stratum corneum may gain an abnormally high state of hydration, while if the vehicle has hygroscopic properties, such as a glycol, the stratum corneum can be dehydrated to some degree. Scheuplein (10) has observed that changes in the structure and permeability of the stratum corneum do occur after extended immersion in water, but that these changes appeared to be relatively small. Strong reagents that destroy the membrane, and solvents that dissolve

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major constituents cannot be used to represent the donor phase in the experimental measurement of distribution coefficients. Thus it is important to recognize that even the distribution coefficient for stratum corneum/solvent may not accurately represent the situation attained under *in vivo* conditions (9).

The distribution coefficient obtained for a drug, between a semisolid vehicle and a suitable non-miscible solvent can also be used to provide important information about the interaction of the drug with constituents in the vehicle and the resultant escaping tendency or thermodynamic activity of the compound. For example, the effect of thermodynamic activity on the percutaneous absorption of methyl nicotinate from water-glycerol mixtures has been investigated by Hadgraft et al. (11, 12). Vehicle systems of equal thermodynamic activity were prepared from a knowledge of the distribution coefficient of methyl nicotinate between water/glycerol solutions and isopropyl myristate. In a similar manner, Davis and Khanderia (13, 14) and Al-Khamis et al. (15) have discussed the importance of changes in thermodynamic activity when examining vehicle effects on the bioavailability of drugs from semisolid vehicles. Changes that may be made to the vehicle to alter a physical property, for example the viscosity, may well lead to changes in the thermodynamic activity of the drug contained therein. As a consequence many of the literature reports on the effect of rheological properties on drug release can be better explained by changes in the ability of the drug to escape from the vehicle (16). Thus, if possible, experiments designed to study the physicochemical properties of vehicles on drug release should be conducted at constant thermodynamic activity, or the derived values corrected for differences in activity (15).

Previously we have described how the head space analysis technique in gas-liquid chromatography can be used to determine differences in the thermodynamic activity of volatile compounds contained in glycol systems (15). The present work describes an alternative method based on a two phase distribution with three different types of vehicle, inert gels of liquid paraffin thickened with polyethylene (Plastibase), polyethylene glycols and Carbopol gels (neutralized cross-linked acrylic acid polymer containing 56–68 % carboxylic acid groups). The derived data have been used to follow changes in thermodynamic activity with changes in vehicle composition, as well as the nature of vehicle-drug interactions.

## Materials and Methods

### *Materials*

Salicylic acid, methyl salicylate, ethyl salicylate, phenyl salicylate, and light liquid paraffin were all of analytical grade supplied by British Drug Houses, Poole, UK, while glycol salicylate was obtained as a gift from the Boots Company, Nottingham, UK.

Plastibase 5W, 10W, 20W, 30W, and 50W (mineral oil thickened with polyethylene from 0.5 to 5 % w/w) were supplied as gifts from E. R. Squibb Limited, Wirral, UK. Silicone fluid 12 500 CS was supplied by Dow Corning Corporation, Michigan, USA. Carbapol 940 was supplied as a gift by B. F. Goodrich. Polyethylene glycol 200, 600 and 1000 were supplied by British Drug Houses, and polyethylene glycol 1500 and 2000 were supplied by Hoechst. PEG 850 was obtained by mixing 20 % PEG 200 with 80 % PEG 1000.

### Methods

Distribution coefficients ($K_D$) were measured using the following technique. 10 ml of an isotonic solution of sodium chloride or light liquid paraffin, containing known concentrations of the drug, were added to equivalent volumes of the ointment bases (10 ml) in glass stoppered conical flasks. The mixtures were stirred with a teflon coated magnetic stirrer bar, using a synchronous motor (speed 60 rpm), and placed in a thermostatically controlled water bath. In the case of Plastibase 50W and polyethylene glycol vehicles the flasks were placed in a thermostatically controlled water bath at 60 °C for 24 hours and at the end of this period, the temperature of the water bath was reduced to the required temperature of the experiment.

The absorbance of a sample from the aqueous or liquid paraffin layer was measured after 72 hours and then daily until equilibrium has been established. The absorbances were then converted to concentrations by using the previously determined calibration curves. The distribution coefficient was then calculated as the ratio of the concentration of drug in the aqueous phase to that in the immiscible oil phase.

Light liquid paraffin was chosen as a representative immiscible oil layer for distributioning with Carbopol gels or polyethylene glycol systems, while sodium chloride was employed with the Plastibases and the silicone oil.

## Results

The distribution coefficients for salicylic acid between different types of vehicle and isotonic solutions of sodium chloride at different temperatures are presented in Table I. The distribution coefficients of salicylic acid and its derivatives between different types of polyethylene glycol vehicles and different concentrations of Carbopol gel and light liquid paraffin at different temperatures for selected systems are presented in Tables II and III respectively.

The distribution values obtained using salicylic acid and the different mineral oil bases were little affected by the nature of the ointment base or the temperature. The distribution values for the salicylate derivatives in the PEG-liquid paraffin systems were dependent on the nature of the solute and the molecular weight of the glycol. Similarly with the Carbopol 940 systems, the chemical nature of the salicylate derivative is important while the concentration of Carbopol had little influence.

**Table I.** Distribution coefficients for salicylic acid distributed between different types of ointment vehicles and isotonic solution of sodium chloride at different temperatures ($K_D$; water/oil).

| Ointment Vehicle | Temperature °C | Distribution Coefficient ($K_2$) |
|---|---|---|
| Silicone fluid 12 550 cS | 20.0 | 46.8 |
| Silicone fluid 12 500 cS | 40.0 | 51.5 |
| Liquid paraffin | 37.0 | 44.8 |
| Plastibase 5W | 37.0 | 46.7 |
| Plastibase 10W | 37.0 | 47.1 |
| Plastibase 20W | 37.0 | 47.9 |
| Plastibase 30W | 37.0 | 48.1 |
| Plastibase 50W | 20.0 | 46.6 |
| Plastibase 50W | 37.0 | 49.3 |
| Plastibase 50W | 40.0 | 50.1 |

**Table II.** Distribution coefficients for salicylic acid and its derivatives distributed between polyethylene glycol vehicles and light liquid paraffin ($K_D$; PEG/liquid paraffin).

| PEG | Temp °C | Methyl Salicylate (MS) | Ethyl Salicylate (ES) | Phenyl Salicylate (PS) | Glycol Salicylate (GS) | Salicylic Acid (SA) |
|---|---|---|---|---|---|---|
| 600 | 30.0 | 4.3 | 5.4 | 8.4 | 59.4 | 185. |
| 850 | 25.0 | 5.7 | 6.2 | 10.9 | 78.4 | 254.8 |
| 850 | 30.0 | 5.2 | 5.8 | 9.4 | 67.0 | 205.4 |
| 850 | 35.0 | 4.5 | 5.4 | 8.1 | 58.0 | 185.9 |
| 850 | 40.0 | 4.0 | 4.8 | 7.0 | 51.1 | 161.0 |
| 850 | 45.0 | 3.5 | 4.3 | 6.4 | 46.5 | 127.0 |
| 1500 | 30.0 | 7.1 | 7.5 | 12.7 | 89.3 | 233.1 |
| 2000 | 30.0 | 7.8 | 8.7 | 14.4 | 103.8 | 257.8 |

**Table III.** Distribution coefficients for salicylates distributed between different concentrations of Carbopol 940 gel and light liquid paraffin ($K_D$; gel/liquid paraffin).

| % w/w conc. of the gel | Temp °C | Methyl Salicylate | Ethyl Salicylate | Phenyl Salicylate | Glycol Salicylate |
|---|---|---|---|---|---|
| 0.5 | 30.0 | – | – | 0.12 | 5.8 |
| 1.0 | 25.0 | 0.18 | 0.15 | 0.11 | 4.2 |
|  | 30.0 | 0.16 | 0.13 | 0.10 | 5.3 |
|  | 35.0 | 0.14 | 0.11 | 0.08 | 6.3 |
|  | 40.0 | 0.12 | 0.09 | 0.07 | 7.7 |
|  | 45.0 | 0.10 | 0.08 | 0.06 | 9.1 |
| 2.0 | 30.0 | – | – | 0.10 | 5.2 |

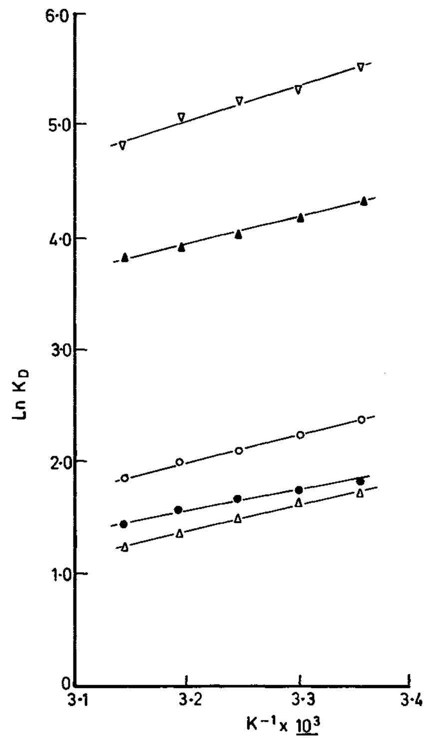


**Fig. 1** Relation between distribution coefficient and temperature (van't Hoff plot) for salicylic acid and its derivatives distributed between PEG 850 and light liquid paraffin.
▿ Salicylic acid
▲ Glycol salicylate
△ Methyl salicylate
● Ethyl salicylate
○ Phenyl salicylate

The effect of temperature on the distribution coefficient can be used to calculate the thermodynamic parameters for the distributioning process (17, 18). A linear (van't Hoff isochore method) plot of ln $K_D$ versus l/T will give a slope of

$$\frac{-\Delta H^\circ_{trs}}{R}$$

where $\Delta H^\circ_{trs}$ is the standard enthalpy of transfer and R the gas constant (Figures 1 and 2). The standard entropy of transfer ($\Delta S^\circ_{trs}$) can be obtained from the relation

$$-RT \ln K_D = \Delta G^\circ_{trs} = \Delta H^\circ_{trs} - T\Delta S^\circ_{trs}$$

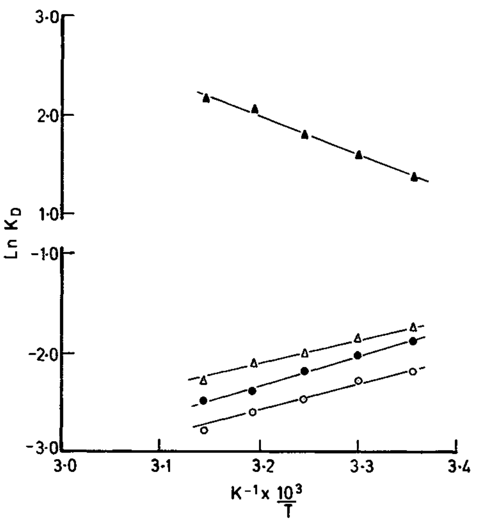


**Fig. 2** Relation between distribution coefficient and temperature (van't Hoff plot) for salicylic acid derivatives distributed between 1 % w/w Carbopol 940 gel and light liquid paraffin.
▲ Glycol salicylate
△ Methyl salicylate
● Ethyl salicylate
○ Phenyl salicylate

Values for the thermodynamic quantities for the transfer of salicylic acid and its derivatives from ointment bases to a second immiscible phase are given in Table IV. For the silicone fluid 12500 CS and Plastibase 50W systems the transfer of salicylic acid from the ointment vehicle to aqueous environment will be energetically favorable ($\Delta G^\circ_{trs} = -9$ kJ $mol^{-1}$). This will be the result of a positive change in entropy (+ 42 J $mol^{-1}$ $deg^{-1}$) which more than compensates an unfavorable enthalpy of transfer (+3 kJ $mol^{-1}$).

**Table IV.** Thermodynamic parameters for the transfer of salicylic acid and its derivatives from various ointment bases to a second immiscible phase at 25 °C.

| Partition System | Compound | $\Delta G^\circ$ ($kJmol^{-1}$) | $\Delta H^\circ$ ($kJmol^{-1}$) | $\Delta S^\circ$ ($Jmol^{-1}$ $deg^{-1}$) |
|---|---|---|---|---|
| Silicone fluid to aqueous NaCl | Salicylic acid | − 9.38 | + 3.1 | + 43 |
| Plastibase 50W to aqueous NaCl | Salicylic acid | − 9.40 | + 2.9 | + 42 |
| PEG 850 to light liquid paraffin | Salicylic acid | +13.7 | +25.9 | + 41 |
| | Methyl salicylate | + 4.3 | +19.2 | + 50 |
| | Ethyl salicylate | + 4.5 | +14.5 | + 33 |
| | Phenyl salicylate | + 5.9 | +21.1 | + 51 |
| | Glycol Salicylate | +10.8 | +20.8 | + 34 |
| Carbopol 940 1 % to light liquid paraffin | Methyl Salicylate | − 4.3 | +20.6 | + 83 |
| | Ethyl Salicylate | − 4.6 | +25.3 | +101 |
| | Phenyl Salicylate | − 5.4 | +24.5 | +100 |
| | Glycol Salicylate | + 3.5 | −30.6 | −115 |

The transfer of salicylic acid and its derivative from PEG 850 to light liquid paraffin will be energetically unfavorable and is due to an unfavorable positive enthalpy that more than compensates a favorable change in entropy. In contrast the transfer of all the salicylates except glycol salicylate from a 1 % Carbopol 940 gel to light liquid paraffin will be energetically favorable, even though the enthalpy of transfer is unfavorable (20 to 25 kJ $mol^{-1}$). The large positive change in entropy more than compensates the enthalpy term leading to a negative value for $\Delta G^\circ_{trs}$. Glycol salicylate is different in that the free energy of transfer will be unfavorable; the enthalpy of transfer is very favorable (−30 kJ $mol^{-1}$) but is compensated by a large unfavorable change in the entropy of transfer (115 J $mol^{-1}$ $deg^{-1}$).

## Discussion

The results for the distribution of salicylic acid between simple inert oily vehicles and aqueous chloride show that the vehicle has little or no effect on the process. The distribution coefficient values are little altered by the chemical nature of the oil (silicone fluid or liquid paraffin), temperature or by the presence of dispersed Polyethylene (0.5 to 5 %) within the Plastibase systems. Thus the dissolved solute interacts little with the vehicle and as a result the thermodynamic activity is almost constant over a range of conditions. In particular it is possible to vary the rheological properties of the vehicle from those of a simple Newtonian fluid (liquid paraffin) to a thick viscoelastic gel (Plastibase 50W) without altering the interactions between dissolved solute and vehicle. Consequently the Plastibase series is an excellent model to explore rheological factors and their effect on drug release and bioavailability (13).

The thermodynamics of transfer show that the process of transfer from the vehicles to an aqueous phase is favorable and entropy controlled. The positive values for $\Delta S^\circ_{trs}$ and $\Delta H^\circ_{trs}$ can be ascribed to the disruption of water structure by the distributing salicylic acid.

The distribution of the salicylates from PEG vehicles to light liquid paraffin is in the order

SA < GS < PS < ES < MS

which reflects the known interaction of salicylates with glycol bases and to a much lesser extent differences in the lipophilicities of the different salicylates (19). The ethylene oxide linkages are the main participants in the interaction with contributions from the hydroxyl groups. Salicylic acid and glycol salicylate show the highest affinity for the glycols because they contain two hydroxyl groups that can interact with polyethylene glycol. The various other esters have a weaker interaction. These effects are also demonstrated in the thermodynamic parameters for transfer. The $\Delta H^\circ_{trs}$ value for SA is higher than for the other salicylates. The transfer of salicylate *from* the PEG bases to light liquid paraffin will be unfavorable because of the positive $\Delta H^\circ_{trs}$ that results from the strong interaction between the solutes and the base. The entropy of transfer will be favorable and reflects the breakup of the salicylate-PEG complex and the transfer of the solute into a less ordered inert liquid environment. The experimental distribution coefficients do not follow the additive-constitutive rules described by Hansch and Leo (20) for the much simpler water-octanol system.

GS < SA < MS < ES < PS

The predicted values are shown in Table V together with their rank order agreement with experimentally determined values for distribution coefficients ($K_D$; oil/water) and aqueous solubility.

The expected effect of an increased lipophilicity on distribution and solubility values is well demonstrated. However, when dealing with a complex phase such as the polyethylene glycol predictions based upon simpler distribution systems or water solubilities are no longer valid. The lower than expected distribution coefficient for phenyl salicylate is noteworthy and indicates a specific interaction process with the vehicle.

The higher the molecular weight of the PEG the higher the distribution coefficient, that is the greater the attraction between solute and vehicle. This affinity can be expressed as a linear relationship (Figure 3). Higuchi and Lach (19) have reported that higher molecular weight PEG exhibits a greater interaction tendency with phenolic compounds than PEG of lower molecular weight. The relative proportions of ethylene oxide and hydroxyl groups change with increase in molecular weight (Figure 3), and the results confirm the dominant role of the ethylene oxide linkages in the interaction process.

In a previous report (15) we described the use of gas chromatographic head space analysis as a means of determining the relative thermodynamic activity of methyl salicylate in PEG ointment bases. The higher the molecular weight of the PEG the lower the escaping tendency of the salicylate. The distribution data in the present work can be expressed in a similar way in terms of the tendency of methyl salicylate to escape from PEG to light liquid paraffin ($1/K_D$). A plot of $1/K_D$ versus head space concentration is linear and as expected passes through the origin (Figure 4). The change of interaction between drug and vehicle with PEG molecular weight means that a constant concentration of salicylate will demonstrate

**Table V.** Distribution coefficient and solubility data for salicylates.

| Compound | Distribution Coefficients$^a$ Experimental$^b$ olive oil/water | Predicted $^c$ octanol/water | LLP/PEG 850 (25°C)$^f$ | LLP/1 % Carbopol (25°C)$^f$ | Water$^e$ | Solubility (mg/ml) Aqueous Sodium chloride (35°C)$^g$ |
|---|---|---|---|---|---|---|
| Salicylic acid | 10$^d$ | 182 | $3.9 \times 10^{-3}$ | – | – | – |
| Glycol salicylate | 7.7$^e$ | 96 | $1.3 \times 10^{-2}$ | 0.23 | 12.7 | 12.0 |
| Methyl salicylate | 343$^e$ | 338 | 0.23 | 5.6 | 0.8 | 1.23 |
| Ethyl salicylate | 1170$^e$ | 1071 | 0.16 | 6.7 | 0.3 | 0.89 |
| Phenyl salicylate | – | $1.2 \times 10^4$ | $9.2 \times 10^{-2}$ | 8.7 | – | 0.20 |

a Data expressed as ratio of oil phase to aqueous phase
b Values for the olive oil-water system
c values for octanol-water system using group contributions (20)
d From Macy (24)
e From Wurster and Kramer (7). No temperature value given.
f Data from Tables 2 and 3 expressed as ratio of oil phase to aqueous phase
g From Al-Khamis (25).

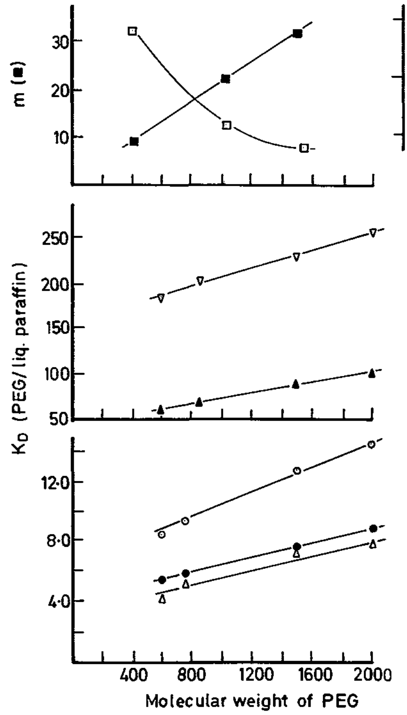


**Fig. 3** Relation between distribution coefficient of salicylates and molecular weight of PEG and ethylene oxide/hydroxy content.
▿ Salicylic acid
▲ Glycol salicylate
△ Methyl salicylate
● Ethyl salicylate
○ Phenyl salicylate
Data on ethylene oxide content (m) [$CH_2(OH)(CH_2\text{-}O\text{-}CH_2)_mCH_2OH$] and hydroxyl number (OH) taken from Higuchi and Lach (19) and Hoechst Polyethylenes, Properties and Application of Polyethylene Glycol.

different release characteristics simply on the grounds of a change in thermodynamic activity. Systems of equal thermodynamic activity can be prepared from a knowledge of the way the distribution coefficients of the solute change with molecular weight of the PEG. Alternatively derived diffusion coefficient data can be corrected for changes in thermodynamic activity with one of the PEG systems as an arbitrary standard state (15).

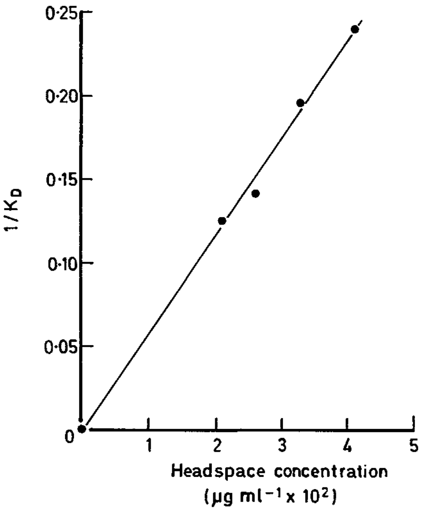


**Fig. 4** Relation between distribution coefficient (PEG/LLP) and head space concentration data for methyl salicylate (15).

The Carbopol gel system shows that the distribution coefficient is little affected by the concentration of the gelling material over the concentration range 0.5 to 2.0 % w/w for phenyl salicylate and glycol salicylate, indicating that systems with different rheological properties can be prepared (21) which will have little influence on the thermodynamic activity of the dissolved solute, thereby allowing the effect of rheological factors of drug release from semisolid gels to be examined without major complicating effects due to changes in drug vehicle interactions.

The distribution of the salicylate *from* the gels into light liquid paraffin is closer to the expected order on the basis of relative lipophilicity

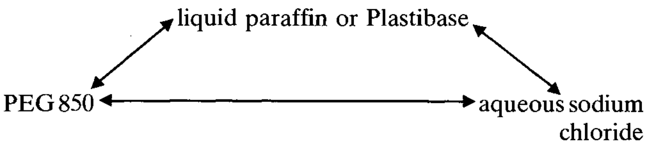
GS << ES = MS < PS.

However, there is not a greater difference between data for methyl, ethyl and phenyl salicylate, and at higher temperatures the order for methyl and ethyl salicylate is reversed. Once again predictions based on simple distribution systems and relative water solubilities can be misleading.

All salicylates studied, except for glycol salicylate, have a higher affinity for the liquid paraffin phase than for the Carbopol gel. The thermodynamics of transfer of these salicylates from gel to oil phase will be favorable as a result of the large gain in entropy that occurs in going from structured aqueous environment to non-structured inert liquid. It is noted that the enthalpy of transfer values are of a similar magnitude to those obtained for the same esters (except for glycol salicylate) with PEG 850. This indicates that significant vehicle-solute interactions are opposed by large unfavorable changes in the entropy of the system. In contrast, glycol salicylate demonstrates an interesting and opposite picture. The transfer from gel to oil phase will be unfavorable because of the high negative value for $\Delta S^\circ_{trs}$, even though $\Delta H^\circ_{trs}$ is favorable. The signs of $\Delta H^\circ_{trs}$ and $\Delta S^\circ_{trs}$ indicate that glycol salicylate causes a disturbance to the gel structure of the Carbopol gel, probably by interaction of the solute with bound water molecules in the gel and possibly with the polymer itself, since incompatibilities with phenolic compounds but not with salicylic acid itself, have been reported in a qualitative study by Carver et al. (22). The transfer of the solute to the second phase allows water-water and gel-water gel-gel interactions to lead to a negative $\Delta H^\circ_{trs}$. However, this restructuring also leads to a loss in entropy reflected in a negative $\Delta S^\circ_{trs}$.

In general terms the derivation of distribution data over a range of temperature and the associated thermodynamic analysis is a useful means of studying drug-vehicle interactions. The derivation of distribution coefficient data at just one temperature indicates a difference only in the magnitude of the free energy term but not the underlying mechanisms (23). For example we can compare the transfer of glycol salicylate from Carbopol gel to light liquid paraffin and the transfer of methyl salicylate from PEG 850 to the same oil phase. The free energies of transfer (distribution coefficients) are similar, being +3.5 and +4.3 kJmol$^{-1}$ respectively. However, the enthalpy and entropy contributions are very different, namely $\Delta H^\circ_{trs} = -30.6$ kJmol$^{-1}$ and $\Delta S^\circ_{trs} = -115$ Jmol$^{-1}$ deg$^{-1}$ for glycol salicylate in Carbopol and $\Delta H^\circ_{trs} = +19.2$ kJmol$^{-1}$ and $\Delta S^\circ_{trs} = +50$ Jmol$^{-1}$ deg$^{-1}$ for methyl salicylate and PEG 850, respectively.

The thermodynamic analysis also allows the calculation of values for the energetics of transfer that are not directly attainable experimentally because of miscibility problems. For example, it is possible to calculate the values for the thermodynamics of transfer of salicylic acid from PEG 850 to aqueous sodium chloride by using the derived data for the liquid paraffin and Plastibase systems.



This gives
$\Delta G^\circ_{trs} = +4.3$ kJmol$^{-1}$
$\Delta H^\circ_{trs} = +30$ kJmol$^{-1}$
$\Delta S^\circ_{trs} = +82$ Jmol$^{-1}$deg$^{-1}$

Therefore the transfer of salicylic acid from PEG 850 to aqueous sodium chloride is unfavorable because of the positive value for $\Delta H^\circ_{trs}$ that arises from interactions between the solute and the vehicle. The entropy term $\Delta S^\circ_{trs}$ is favourable but is more than compensated by the $\Delta H^\circ_{trs}$ term.

The derived information on the thermodynamic activity of the various solutes in the various ointment vehicles and the existence of drug-vehicle interactions will be of value in interpreting data from *in vitro* and *in vivo* studies on drug release from ointment bases as will be described in future publications in this series.

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