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Characteristics of drug substances in oily solutions. Drug release rate, partitioning and solubility

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Abstract

In vitro rate of drug release from oil solutions was investigated in a rotating dialysis cell. A log linear correlation was established between the rate constant (k_{obs}) for attainment of equilibrium and apparent partition coefficient (P_{app}) between oil vehicle and release media using various weak acids and bases and non-electrolytes. Collander like linear free energy relationships were observed allowing various oil–aqueous buffer partition coefficients to be calculated from known octanol–aqueous buffer partition coefficients. Solubility of the various drug substances in oil vehicles were investigated. A linear correlation was observed between log molar solubility and melting point of the solutes. Release profiles obtained for release of two local anaesthetics dissolved in the same oil vehicle exhibited an unexpected behavior involving an initial delayed release of the most lipophilic local anaesthetic.

Keywords: Parenteral depots; In vitro release; Partition coefficients; Linear free energy relationships; Modified release; Oil solubility

1. Introduction

Modifying in vitro release rate from parenteral oily solutions can be done by changing the composition of oil vehicle e.g. by addition of hydrogen bond donating agents to triglycerides (Fredholt et al., 2000; Larsen et al., 2001a), by making lipophilic prodrug derivatives of active substances (Larsen et al., 2001b) or by a combination of these two approaches. By using a rotating dialysis two phase cell model we have demonstrated a log linear relationship between the in vitro rate constant related to attainment of equilibrium between oily vehicle and aqueous phase (k_{obs}) and the apparent partition coefficient P_{app} between the two phases. Previously investigations have been done for the weak electrolytes naproxen and lidocaine and the non-electrolyte testosterone (Fredholt et al., 2000; Larsen et al., 2000, 2001a). This linear correlation has been established using different oil vehicles and aqueous release media with varying pH values. In addition the release characteristics of a series of nicotinic acid esters (Larsen et al., 2001b) have

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been investigated in this model. The results of the release experiments indicate that the k_{obs} value for a weak electrolyte at a certain value of the pH dependent partition coefficient (P_{app}) equals the k_{obs} value for a non-electrolyte possessing a true partition coefficient P, the magnitude of which is equal to P_{app} (Larsen et al., 2001a). In addition an expression for the release rate constant for transport from oil to aqueous phase k_{ow} has been derived. The latter constant is assumed to constitute the rate limiting step in drug absorption after i.m. injection of oil solutions (Larsen et al., 2000). For $P_{app} \ll 1000$ it has been found that the ratios of k_{ow} values will equal the corresponding k_{obs} ratios (Larsen et al., 2001a).

The primary aim of this study was to extend the relationship obtained between $\log k_{obs}$ and $\log P_{app}$ by examining release rate of a broader spectrum of model compounds including non-electrolytes as well as weak acids and bases using fractionated coconut oil (Viscoleo®) as the chosen oil vehicle.

Leo and Hansch (1971) investigated the Linear Free Energy Relationships (LFER's) between a wide group of partitioning solvent systems based on the work of Collander (Collander, 1950, 1951) who was the first to express relationships of the type: $\log P_2 = a \log P_1 + b$ between partition coefficients in two solvent systems (P_1 and P_2). The majority of published $\log P$ values are obtained from the octanol–water systems. Since the apparent partition coefficient P_{app} between oil vehicle and buffer are linearly related to release rate an establishment of linear free energy relationships between the oil vehicle– and octanol–buffer system would be desirable.

Another parameter of interest is the solubility behaviors of possible drug candidates in the oily vehicle which have been assessed in this study as well.

In addition to providing drug release over an extended period of time parenteral depot formulations should also exhibit a reasonably rapid onset of action. For oil solutions this might be achieved by incorporating two prodrug derivatives differing with respect to lipophilicity or by using two active agents differing in lipophilicity. Thus, a further aim was to study the release characteristics of prilocaine and bupivacaine, exhibiting different P_{app} values from an oil solution containing both local anaesthetics.

2. Materials and methods

2.1. Materials

Fractionated coconut oil (Viscoleo®) was obtained from P. Broeste A/S, Denmark, castor oil was obtained from Sigma chemical Co. and *n*-octanol was obtained from Merck. Zuclopenthixol, 2HCl was a gift from Lundbeck A/S, 5-phenyldiazo-salicylicacid (PDSA) was obtained from Ferring, Copenhagen. Other chemicals, in the highest quality available were obtained from commercial sources (Sigma Chemical Co., Unikem, Fluka Biochemika, Aldrich). Chemicals for preparation of buffers and HPLC mobile phases were of analytical grade. Demineralized water was used throughout. Visking dialysis tubing size 27/32, 21.5 mm with a cut off at 12–14,000 Da was employed for the dialysis cell.

2.2. Preparation of the free baseform of bupivacaine and prilocaine

The free bases of bupivacaine and prilocaine were obtained from the corresponding hydrochlorides. Five grams was dissolved in 300 ml water. The aqueous solution was made alkaline by addition of NaOH. Concerning bupivacaine the precipitate formed was filtered, dried in vacuo and dissolved in dichloromethane. Concerning prilocaine the aqueous phase was extracted with dichloromethane. After washing with water both dichloromethane phases were dried with Na_2SO_4, filtered and evaporated yielding clear oils which crystallized after storage at -18 °C. The free bases were recrystallized from petroleum ether. Melting points were 107–108 °C for bupivacaine (107.5–108 °C, Af Ekenstam et al., 1957) and 37–39 °C for prilocaine (37–38 °C, Löfgren and Tegner, 1960). Purity was examined by HPLC comparing peaks of the chromatograms with those obtained by injection of the respective hydrochlorides.

2.3. Release experiments

Release studies were carried out at 37 ± 0.5 °C using the rotating dialysis cell model previously described (Larsen et al., 2000). Release media consisted of 1000 ml 0.05 M phosphate buffer pH 6.00 or 7.00. The dialysis cell containing 5.00 ml of oil solution of the drug substance (5 mg ml^{-1}) was placed inside the vessel at time zero. The revolution speed of the cell was set at 50 rpm. At appropriate intervals samples were withdrawn from the aqueous phase and analyzed. Sampling was continued until equilibrium between the oil and aqueous phases was established. The amount of drug released (M_t) in percent (corrected for sampling) into the aqueous phase was calculated according to Eq. (1):

$$M_t = \frac{V_s \sum_{n=1}^{n} C_{n-1} + V_m C_n}{M} 100, \quad (1)$$

where V_s and V_m are the volumes of sample and release medium, respectively. C_n is the drug concentration in sample n and M represents the total amount of drug initially applied to the dialysis cell. Release experiments were done in triplicate.

The overall first-order rate constant related to attainment of equilibrium (k_{obs}) is calculated from Eq. (2).

$$\ln(M_e - M_t) = \ln M_e - k_{obs} t \quad (2)$$

where M_e is the total amount released to the aqueous phase at equilibrium.

2.4. Determination of apparent and true partition coefficients

Apparent and true partition coefficients of the drug compounds between Viscoleo, Viscoleo/castor oil 2:1 (v/v) or octanol and 0.05 M phosphate buffer pH 6.00 or 7.00 were determined at 37 ± 0.5 °C. In case of octanol the two phases were mutually saturated before use. After rotating in a water bath for 24 h the phases were allowed to separate at 37 °C. The apparent partition coefficients were calculated according to Eq. (3):

$$P_{app} = \left(\frac{C_i - C_w}{C_w}\right)\left(\frac{V_w}{V_o}\right) \quad (3)$$

where C_i and C_w represent the concentrations in the aqueous phase before and after distribution, respectively. V_w and V_o are the volumes of the aqueous buffer solution and the organic phase, respectively. Each equilibrium constant presented is the mean of three determinations.

2.5. Solubility measurements

To approximately 3 ml of Viscoleo, Viscoleo/castor oil 2:1 (v/v) or castor oil in a screw capped test tube, an amount of model compound was added and the tube was rotated in a thermostate at 37 ± 0.5 °C. Addition of solute was repeated until solid material was remaining after rotating for 24 h. Samples of the supernatant was transferred to three Eppendorf tubes and centrifuged at 37 °C at 15,000 × g for 10 min. A known volume of the supernatant was dissolved in ethanol for UV determination. The reference solution consisted of an identical amount of the pure oil or oil mixture in ethanol.

2.6. Analyses

Samples from solubility studies were measured on a Shimadzu UV-160 spectrophotometer. Samples from release and partitioning experiments were analyzed by an HPLC system consisting of a Merck Hitachi L-6200 pump connected to a Merck Hitachi L-4000 UV detector. A Merck Hitachi L-7200 or 655A-40 autosampler or manual injection was used. The column employed was a reversed phase Inertsil ODS-2 column (250 × 4.6 mm; 5 μm particles), (except for zuclopenthixol, 2HCl where a 125 × 2 mm Inertsil column was used) equipped with an Inertsil ODS-2 pre-column (Chrompack Int., The Netherlands). The mobile phase consisted of 20–70% (v/v) acetonitrile and 0.1% (v/v) phosphoric acid in demineralized water. In particular cases the mobile phase was made 1 mM with respect to triethylamine to prevent tailing. The flow rate was set at 1 ml min^{-1} and the column effluent was measured by UV detection.

3. Results and discussion

3.1. Relationship between P_{app} and in vitro release rate constants

The in vitro release experiments have been carried out using a rotating dialysis cell model previously characterized (Schultz et al., 1997; Larsen et al., 2000).

In the present study we have investigated the correlation between log P_{app} and log k_{obs} for various model compounds: weak acids, weak bases and non-electrolytes (for non-electrolytes the term P_{app} refers to the true partition coefficient P) (Table 1), in Viscoleo–buffer systems. The experimental conditions were kept constant, apart from pH of the phosphate buffer which for each weak electrolyte was chosen so equilibrium was reached within 2 days. Separate studies certified that no degradation of the compounds occurred under the experimental conditions. Experiments were done in triplicate, SD's were below 3% in most cases.

Previously the interfacial transport of naproxen and lidocaine between oily vehicles and aqueous buffer systems was described by reversible first-order kinetics (Larsen et al., 2000).

$$C_{oil} \underset{k_{wo}}{\overset{k_{ow}}{\rightleftarrows}} C_{aq} \quad (4)$$

with C_{oil} and C_{aq} representing the concentration of the non-ionized species of the solute in the oil and aqueous phase, respectively. k_{ow} is the specific rate constant for transfer from the oil phase to the aqueous phase whereas k_{wo} is the rate constant for the opposite transport process. As seen from Table 1 model compounds used in this study consisted of weak electrolytes and two non-electrolytes (testosterone and benzylalcohol). The acid–base equilibrium of the weak electrolytes in the aqueous phase has not been included in Eq. (4) since proton transfer reactions are expected to proceed extremely fast. The rate constant k_{obs} for attainment of equilibrium is given by Eq. (5) (Larsen et al., 2001a).

$$k_{obs} = A\left(\frac{k_{ow}}{V_o} + \frac{k_{wo}}{V_w}\right) \quad (5)$$

where A is the interfacial area between oil and aqueous phase and V_o and V_w represents the volume of oil and aqueous phase, respectively. Although the absolute magnitude of A is unknown the interfacial area is considered to be constant independent of the oil vehicle used due to the construction of the rotating dialysis cell. The magnitude of the obtained k_{obs} values are in the range 0.01–0.7 h^{-1} (Table 2).

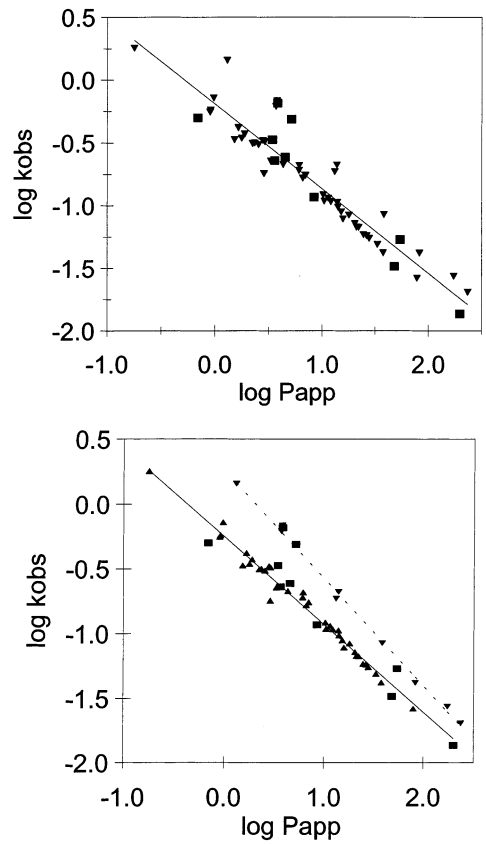


Fig. 1. (a) Linear relationships obtained between log k_{obs} and log P_{app} determined for partitioning of various compounds between different oils–oil mixtures and aqueous buffer solutions with different pH at 37 °C. ▼, data from Larsen et al. (2000, 2001a,b), Fredholt et al. (2000); ■, data from this study. The full line has been drawn according to Eq. (6). (b) Linear relationships obtained between log k_{obs} and log P_{app} determined for partitioning of various compounds between different oils–oil mixtures and aqueous buffer solutions with different pH at 37 °C. ▲, data from Larsen et al. (2000, 2001a), Fredholt et al. (2000); ▼, data from Larsen et al. (2001b); ■, data from this study. The line (—) has been drawn according to Eq. (7); the line (----) has been drawn according to: $\log k_{obs} = -0.83 \log P_{app} + 0.26$ (Larsen et al., 2001b).

The apparent and true partition coefficients of the electrolytes and non-electrolytes, respectively, between Viscoleo and buffer systems determined in triplicate by the shake flask method (SD's below 3% in most cases) are shown in Table 2.

The following relationship between k_{obs} and P_{app} (Eq. (6), Fig. 1a) has been obtained by compilation of the present data with those previously reported (Fredholt et al., 2000; Larsen et al., 2000, 2001a Larsen et al., 2001b)

$$\log k_{obs} = -0.67 \log P_{app} - 0.19$$

$$(n = 57,\ r = 0.942,\ k_{obs} \text{ in } h^{-1}) \quad (6)$$

With this study the linear relationship between $\log k_{obs}$ and $\log P_{app}$ formerly established by changing the aqueous buffer phase and the oil

Table 1
Chemical structures and molecular weights (M_w) for compounds used in release studies.

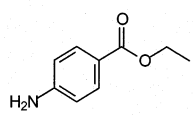
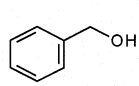
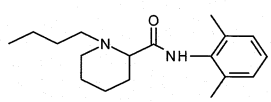
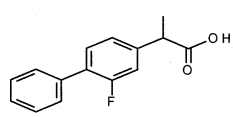
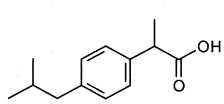
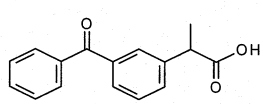
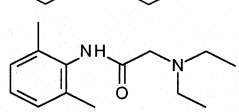
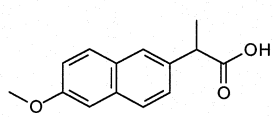
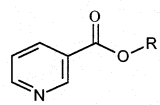
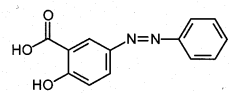
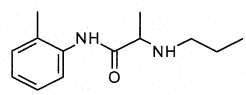
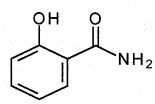
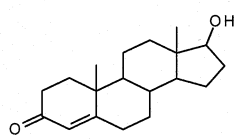
compound	chemical structure	M_w
benzocaine		165
benzylalcohol		106
bupivacaine		288
flurbiprofen		244
ibuprofen		206
ketoprofen		254
lidocaine		234
naproxen		230

Table 1 (*Continued*)

compound	chemical structure	M_w
nicotinic acid esters*		
R = methyl, ethyl, isopropyl, butyl and hexyl chains		137-207
5-phenyldiazo-salicylic acid (PDSA)		224
prilocaine		220
salicylamide		137
testosterone		288

*From Larsen et al. (2001b).

vehicle has now been shown to apply for a larger group of different compounds.

As illustrated in Fig. 1b slightly better correlations appear when separating the compounds into two lines the one containing data from nicotinic acids esters (Larsen et al., 2001b) and salicylamide and benzylalcohol. When excluding the data for the nicotinic acid esters, salicylamide and benzylalcohol from Eq. (6) the following correlation is established:

$$\log k_{obs} = -0.68 \log P_{app} - 0.25$$
$$(n = 46,\ r = 0.988,\ k_{obs} \text{ in } h^{-1}) \quad (7)$$

Fig. 1b shows the line drawn from this correlation together with the correlation established from the nicotinic acid esters (Larsen et al., 2001b).

No obvious explanation was found that the latter linear correlation differs to some extent from that previously established (Larsen et al., 2001b). In the present study a broader group of model compounds have been investigated. The only apparently shared property for salicylamide, benzylalcohol and the nicotinic acid esters is a lower molecular weight and more flexible structure of these compounds compared to those of the other group of compounds (Table 1).

If the molecular weight of the individual compounds are included in the correlation the following relationship is obtained:

$$\log(k_{obs} M_w) = -0.68 \log P_{app} + 2.15$$
$$(n = 57,\ r = 0.979,\ k_{obs} \text{ in } h^{-1}) \quad (8)$$

revealing a slightly better correlation as compared to Eq. (6) indicating that the size of the molecules to a certain extent might influence the release rates.

The specific rate constant related to interfacial transfer from oil to aqueous phase in the two-phase model can be calculated (Larsen et al., 2001a):

$$k_{ow} = \frac{k_{obs}}{A(1/V_o + P_{app}/V_w)} \quad (9)$$

When comparing the in vitro sustained release properties of two compounds or vehicles the k_{ow} ratio can be calculated. In the rotating dialysis cell model $V_w \gg V_o$ and in cases of $P_{app} \ll 1000$ the k_{ow} ratio therefore, almost equals the corresponding k_{obs} ratio. For more lipophilic compounds the ratio must be calculated as described in Larsen et al. (2001a).

Since the two relationships presented in Fig. 1b are nearly parallel, deviations in calculation of k_{obs} ratios from these correlations are considered to be of minor significance. Thus, Eq. (6) is considered to be adequate when the objective is to compare the relative release rates of: (i) compounds differing in lipophilicities; or (ii) a particular drug substance dissolved in oil formulations of different composition.

3.2. Linear free energy relationships

The majority of published log P values are obtained from the octanol–water system (Smith et al., 1975) and such values for a high number of compounds are available from log P databases in literature pioneered by Leo et al. (1971) and more recently established internet databases. Therefore, the possibility of establishing linear free energy relationships between partition coefficients derived from oily vehicles, and octanol, respectively, for various weak acids, bases and non-electrolytes was investigated. The apparent partition coefficients for partitioning of the compounds between Viscoleo, Viscoleo/castor oil 2:1 (v/v) or octanol and phosphate buffer were determined in triplicate by the shake flask method. (SD's below 3% in most cases). The obtained data are presented in Table 2. The 2:1 oil mixture was chosen

Table 2
Apparent overall (k_{obs}, h^{-1}) rate constants for partitioning of various compounds between Viscoleo and buffer and apparent partition coefficients for partitioning between Viscoleo ($P_{app,v}$), Viscoleo/castor oil 2:1 (v/v) ($P_{app,v/c}$) or octanol ($P_{app,o}$) and 0.05 M phosphate buffer

Compound	pH	k_{obs}	$P_{app,v}$	$P_{app,v/c}$	$P_{app,o}$
Benzocaine	7	0.054	54.5	58.6	326
Benzylalcohol	6	0.657	3.84	–	–
Bupivacaine	6	0.117	8.44	11	48.6
Chloramphenicol	6	–	0.774	1.79	14.2
Flurbiprofen	7	0.244	4.53	–	15.8
Flurbiprofen	6	–	46.7	96.1	161
Hydrocortisone	7	–	1.75	4.3	47.4
Ibuprofen	6	0.033	48.1	92.9	399
Ketoprofen	6	0.23	3.63	8.36	18.1
Lidocaine	6	0.419[a]	1.66[a]	2.55[a]	18.7
Metronidazole	6	–	0.113	0.192	0.914
Naproxen	6	0.122[a]	10.3[a]	20.4[a]	27.9
Paracetamol	6	–	0.058	0.177	0.28
PDSA	6	0.336	3.74	7.75	14.7
Prilocaine	6	0.501	0.696	1.22	3.01
Salicylamide	6	0.49	5.18	–	–
Testosterone	7	0.0137[a]	199[a]	347	1800
Zuclopenthixol	6	–	126	–	1270

[a] From previous studies (Fredholt et al., 2000; Larsen et al., 2000, 2001a).

according to results from Larsen et al. (2001a), where P_{app} values obtained from partitioning of lidocaine were increasing by addition of increasing amount of castor oil in the oil vehicle. However, the effect leveled of in the range of 30–40% (v/v) castor oil in the vehicle. Therefore, the castor oil level in the present study was maintained at 33% which also ensures a relatively low viscosity essential for the syringeability of the oil solution. Plots of log P_{app} values for Viscoleo and Viscoleo/castor oil 2:1 (v/v) against log P_{app} for octanol are shown in Fig. 2a and b and the linear correlations can be expressed:

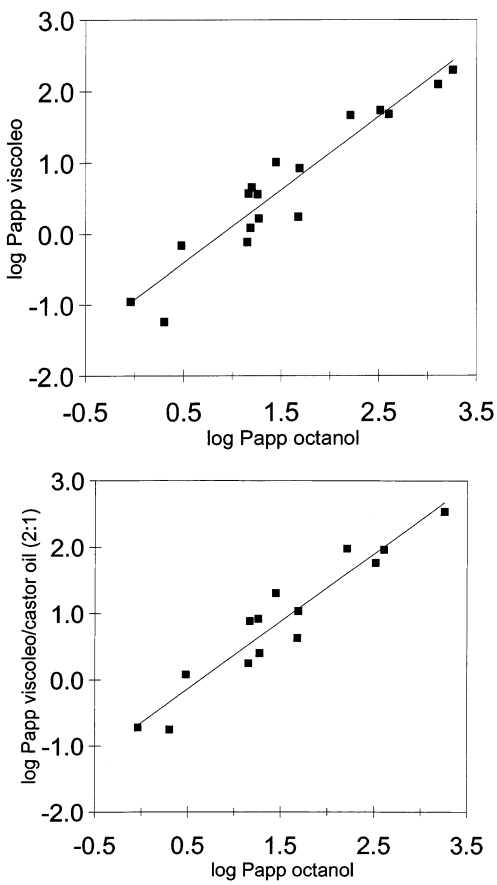


Fig. 2. (a) Linear relationship between P_{app} values determined for various compounds in an octanol– and in a Viscoleo–buffer system. The full line has been drawn according to Eq. (10). (b) Linear relationship between P_{app} values determined for various compounds in an octanol–buffer system and in a Viscoleo/castor oil 2:1 (v/v)–buffer system. The full line has been drawn according to Eq. (11).

$$\log P_{app,v} = 1.03 \log P_{app,oct} - 0.922 \quad (n = 16,\ r = 0.950) \tag{10}$$

$$\log P_{app,v/c} = 1.02 \log P_{app,oct} - 0.646 \quad (n = 14,\ r = 0.953) \tag{11}$$

where $P_{app,oct}$ represents the partition coefficient between octanol and buffer, $P_{app,v}$ represents the partition coefficient between Viscoleo and buffer and $P_{app,v/c}$ the partition coefficient between Viscoleo/castor oil 2:1 (v/v) and buffer. Although the oil vehicles differ significantly from octanol with respect to physicochemical characteristics reasonable linear correlations are established for both systems.

Similar relationships have been obtained in several other solvent systems (Collander, 1950, 1951; Leo and Hansch, 1971). The slopes of Eqs. (10) and (11) are almost identical and close to unity revealing that the sensitivity of the oil vehicles to changes in lipophilicity of solutes resembles that of octanol. The intercepts are different in accordance with that pure Viscoleo exhibits the highest lipophilicity and the Viscoleo/castor oil mixture exhibits a lipophilicity in between that of Viscoleo and octanol. Since castor oil possesses hydroxy groups in the fatty acid chains it has the ability to act as a hydrogen bond donor (Larsen et al., 2001a), suggesting that the solubility properties of the oil mixture are closer to those of octanol than the solubility properties of pure Viscoleo which is reflected in the difference of the intercepts.

A similar equation has been found for 'oils' representing unspecified triglycerides (Leo and Hansch, 1971):

$$\log P_{oils} = 1.10 \log P_{oct} - 1.15 \quad (n = 79,\ r = 0.945) \tag{12}$$

The slope obtained is consistent with those given by Eqs. (10) and (11). The size of the latter intercept indicating that the employed triglycerides are more lipophilic than Viscoleo.

From the above discussion it appears reasonably that Eqs. (10) and (11) can be used for an overall estimation of a P_{app} value for partitioning of a solute between oil vehicle and water by knowledge of $P_{app,oct}$ from one of the well estab-

lished experimental log $P_{app,oct}$ databases, e.g. (http: esc.syrres.com) with both estimated and experimental determined values. Thereby, facilitation of estimating the in vitro rate constant for establishment of equilibrium, k_{obs} from Eq. (6) is achievable.

3.3. Oil solubility

Solubility studies were made in the three oil systems Viscoleo, Viscoleo/castor oil 2:1 (v/v) and castor oil at 37 °C. Studies were done in triplicate (SD's below 10% in most cases), and the results are presented in Table 3. Solubility has been determined for the compounds employed in the release studies except from prilocaine and salicylamide the latter compounds being partly or totally liquid at 37 °C and PDSA which was only available in very small amounts.

According to Yalkowsky et al. (1983) the ideal solubility of organic compounds might, as an approximation, be correlated with their melting point. Although the structurally different compounds examined in the present study were not expected to behave as ideal solutes in triglycerides approximately linear relationships between melting points and log molar solubilities in Viscoleo, Viscoleo/castor oil 2:1 (v/v) and castor oil were observed (Fig. 3).

Similar linear correlations between melting point and log mole fraction solubility (or log molar solubility) have been observed in case of various non- and weak electrolytes in octanol (Yalkowsky et al., 1983), phenytoin prodrugs in ethyl oleate and triglycerides (Yamaoka et al., 1983), and various hydrophobic compounds in trioleylglycerol (Patton et al., 1984). The linear relationships found in the present study are not meant to imply anything else than the solubility of the examined drug compounds in triglycerides varies with melting points reflecting differences in crystal lattice forces. This suggests that solubility of a potential drug-candidate in oily vehicles might be roughly estimated from the melting point of the solute, at least for relatively low melting solutes.

From solubility studies of 10 phenytoin prodrugs in tributyrin, trioctanoin, and triolein it was found that S (tributyrin) > S (trioctanoin) > S (triolein) for each prodrug derivative (Yamaoka et al., 1983). Calculating the molar concentration of the polar triglyceride functionality from solvent density and molecular weights of the three solvents, a linear correlation between the logarithm of solubility of three of the derivatives in the solvents and the molar triglyceride functional group concentration was found. It was suggested that the increased solubility of the prodrugs in going from tributyrin to triolein which vary with respect to chain length and degree of unsaturation

Table 3
Melting points (m.p. °C) and molar solubility of various compounds in Viscoleo (S_v) Viscoleo/castor oil 2:1 (v/v) ($S_{v/c}$) and castor oil (S_c) at 37 °C (solubilities in mmol ml^{-1})

Compound	m.p.[a]	S_v	$S_{v/c}$	S_c
Benzocaine	88–90	0.497	0.474	0.784
Bupivacaine	107–108	0.202	0.294	0.286
Flurbiprofen	110–111	0.266	0.282	0.400
Ibuprofen	75–77	0.732	0.848	0.911
Ketoprofen	94	0.111	0.235	0.377
Lidocaine	68–69	1.05	1.13	1.74
Naproxen	155.3	0.0517	0.0912	0.125
Salicylamide	140	0.115	0.159	0.193
Testosterone	155	0.0385	0.0818	0.0784

[a] Data obtained from The Merck Index (1983).

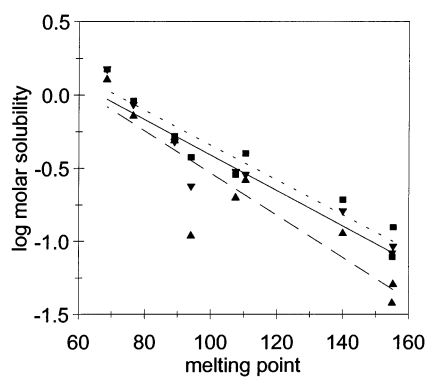


Fig. 3. The effect of melting point (°C) on the molar solubility in Viscoleo, Viscoleo/castor oil 2:1 (v/v) and castor oil of different crystalline compounds at 37 °C. ▲, solubility in Viscoleo; ▼, solubility in Viscoleo/castor oil 2:1 (v/v); ■, solubility in castor oil. The lines represents, the respectively linear correlations.

was largely due to specific interaction between the prodrugs and the triglyceride functional group of the solvents (Yamaoka et al., 1983).

It appears from Table 3 that solubility, S, in the three oil vehicles examined in the present study declines in the order S (castor oil) > S (Viscoleo). This observation is in consistence with the P_{app} values for Viscoleo and Viscoleo/castor oil 2:1 (v/v) listed in Table 2 and P_{app} values obtained in castor oil (Fredholt et al., 2000).

The triglyceride fatty acids in Viscoleo are C_8 and C_{10} acids, whereas the dominant fatty acid component of castor oil is a $C_{18:1}$ acid containing a hydroxy functional group. The densities of the two investigated oils are almost identical (Schultz, 1997) and consequently the Viscoleo triglyceride concentration is considerably higher than that of castor oil. In case the oil solubility of the investigated solutes which all possess both hydrogen donor and acceptor properties, was governed by intermolecular solute–triglyceride ester interactions enhanced solubility in Viscoleo compared to that in castor oil was expected. Therefore, the observed significant solubilizing effect of castor oil suggests that hydroxy groups are more accessible for hydrogen bonding than the triglyceride ester functionalities.

3.4. Release profile for a combined vehicle

Combining a reasonably rapid onset of action with a prolonged drug release has been obtained in vitro with a formulation containing the two local anaesthetics prilocaine and bupivacaine differing with respect to lipophilicity. Fig. 4 shows release profiles obtained from the two drug substances dissolved in Viscoleo. The experiment was run in triplicate and mean values are plotted in the figure. Prilocaine follows the expected release profile characterized by first order kinetics and fitted to the k_{obs} value listed in Table 2. Bupivacaine on the other hand exhibits a more complex release profile, exhibiting a 'pseudo-lag time' of release. Calculation of k_{obs} by using the first six time points results in a value of 0.0523 h^{-1} while calculation based on time points from 4 to 15 h results in a k_{obs} value of 0.113 h^{-1}. The latter is similar to the value presented in Table 2 representing the calculated value from a release study with bupivacaine as the only compound dissolved in the oil vehicle.

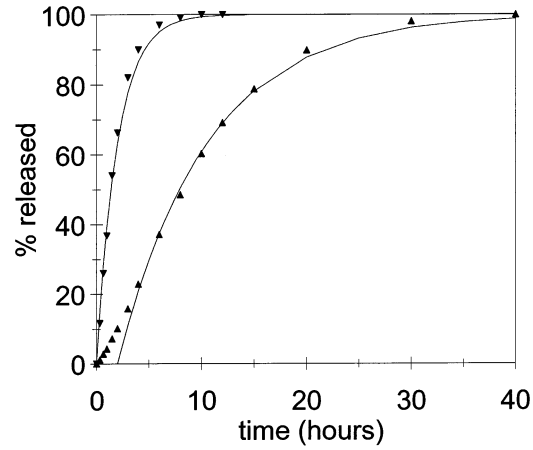


Fig. 4. Percentage prilocaine and bupivacaine released to 0.05 M phosphate buffer pH 6.00 as a function of time when initially disssolved in Viscoleo. ▼, prilocaine; ▲, bupivacaine. Full lines have been derived using Eq. (2) with a 'pseudo-lag time' up to approximately 2 h for bupivacaine.

Similar release characteristics were seen from release of the two compounds from a vehicle consisting of Viscoleo/castor oil 2:1 (v/v) with k_{obs} values in consistence with the P_{app} values presented in Table 2.

A plausible explanation for these profiles might be, that the less lipophilic prilocaine is concentrated near the water–oil interface. The more lipophilic bupivacaine competing with prilocaine therefore, exhibits an initial delayed release. After 2 h when approximately 65% of the prilocaine has left the oil phase the rate of bupivacaine release is increased to the expected level. The full lines in Fig. 4 have been derived using Eq. (2) and the calculated rate constants listed in Table 2. In the line drawn for bupivacaine a 'pseudo-lag time' of 2 h has been incorporated.

The results suggest, that this principle might be exploited in an alternative manner by addition of a more polar non-active compound to the oil vehicle in cases where an initial delayed release of drug is desired.

4. Conclusions

The linear correlation between $\log k_{obs}$ and $\log P_{app}$ has been shown to be valid for a broader

group of compounds within a log P_{app} range of -1 to 2.5. Linear free energy relationships has been established between partitioning systems where the organic phase consists of octanol and oil vehicle, respectively. This enables a screening for potential drug substances with partitioning characteristics suitable for formulation in oily vehicles. Furthermore, the solubility of a potential drug candidate in oily vehicles might be roughly estimated from the melting point, for relatively low melting compounds. When applying more than one drug compound to an oil vehicle deviations from the expected release profile can appear.

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