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Assessment of Drug Release from Oil Depot Formulations Using an In Vitro Model—Potential Applicability in Accelerated Release Testing

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In vitro drug release and transport rates from oil depot formulations under nonsink conditions have been investigated in the rotating dialysis cell model. Eight model drug compounds and eight oil vehicle compositions were used for the release-experiments. The experimentally obtained apparent first-order rate constants related to the drug appearance in the acceptor phase after initial instillation of a drug-containing oil solution were found to be in excellent agreement with the rate constants obtained from a theoretically derived expression. It was observed that the drug oil-water distribution coefficient was the key parameter influencing the release characteristics. As compared with ketoprofen, flurbiprofen exhibited a higher affinity for the oil, resulting in a significantly lower and more slowly decreasing drug concentrations in the aqueous donor compartment. Release profiles for prilocaine and the more lipophilic agent bupivacaine after incorporation of both drugs in fractionated coconut oil were characterized by a fast release of prilocaine, whereas bupivacaine was liberated much slower to the acceptor phase. The high oil-buffer interfacial area generated in vitro by rotation of the donor cell tends to overestimate release rates in comparison to those expected in vivo, for example, after intra-articular administration of oil solutions. The present in vitro method may constitute a valuable tool in accelerated in vitro release testing of parenteral oil depot formulations in areas comprising formulation design and product quality control.

Keywords oil solution; depot formulation; intra-articular drug delivery; rotating dialysis cell; in vitro release testing

INTRODUCTION

In contrast to oral depot formulations, no regulatory standards for in vitro release testing of controlled-release parenteral products exist. However, science-based guidance is strongly needed in the latter area. A further challenge arises from the fact that investigations of parenteral depot formulations with duration of action of weeks or months may advocate the use of accelerated in vitro release methods (Burgess, Hussain, Ingallinera, & Chen, 2002; Burgess, Crommelin, Hussain, & Chen, 2004a, 2004b). United States Pharmacopeia (USP) Apparatus 3 (reciprocating cylinder) and 4 (flow-through cell) may be of interest for in vitro testing of controlled-release parenterals (Burgess et al., 2002; Burgess et al., 2004a, 2004b; Iyer, Barr, & Karnes, 2006). Likewise, dialysis membrane–based models may be feasible in vitro techniques for investigations of drug release from injectable polymeric particulate systems (D'Souza & DeLuca, 2006). The utility of dialysis membrane methods is, however, confined to depot formulations intended for administration sites where drug release proceeds under nonsink conditions (Washington, 1989, 1990), as is the case after intra-articular injection. After administration of a depot formulation into the joint cavity, the duration of local drug action is governed by the interplay between the rate of drug release from the immobile depot into the synovial fluid and the rate of drug transport out of the synovial space into the blood (Simkin, Wu, & Foster, 1993; Pedersen, Østergaard, Larsen, & Larsen, 2005). The transfer of small molecules across the non-continuous synovial cell lining into the systemic circulation results mainly from passive diffusion (Simkin et al., 1993). Thus, a rotating dialysis cell model may be useful for simulation of events influencing drug residence time in the joint cavity after intra-articular injection (Pedersen et al., 2005). Previously, this dialysis cell model has been used to investigate drug release characteristics from aqueous drug solutions (Pedersen et al., 2005) and drug salt suspensions (Østergaard, Larsen, Parshad, & Larsen, 2005). Oil depots for intramuscular injection containing lipophilic prodrugs of steroids and antipsychotics have been used in the marketplace for decades (Chien, 1981; Zuidema, Kadir, Titulaer, & Oussoren, 1994; Benson & Prankerd, 1998). Preliminary in vitro data have indicated that oil drug solutions injected into the joint cavity are potentially capable of providing sustained drug release profiles (Larsen, Østergaard, Friberg-Johansen, Jessen, & Larsen, 2006). Based on experiments employing sesame oil solutions of lidocaine and naproxen, a mathematical expression for drug appearance in the acceptor phase was derived (Larsen

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et al., 2006). The aim of the present study was to investigate the general applicability of this expression for the overall first-order rate constant related to the release and transport processes in the three-compartment system by determination of drug release characteristics from oil solutions using several model drug compounds and oil vehicles of different compositions.

MATERIALS AND METHODS

Materials

Castor oil, flurbiprofen, ketoprofen, naproxen, prilocaine, and sesame oil were obtained from Sigma-Aldrich (Steinheim, Germany). Bupivacaine and lidocaine were purchased from Unikem (Copenhagen, Denmark), and isopropyl myristate (IPM) and salicylamide were obtained from Fluka Chemie GmbH (Buchs, Switzerland). Medium-chain partial glycerides (Imwitor® 742) and partial glycerides of ricinoleic acid (Softigen® 701) were kindly donated from Sasol Germany GmbH (Witten, Germany). Fractionated coconut oil (Myritol 318 PH) was supplied by Broste A/S (Lyngby, Denmark). Naropin® 10 mg/ml from AstraZeneca was obtained from Nomeco (Copenhagen, Denmark). Other reagents, buffer substances, and solvents were of analytical or reagent grade. For the distribution and release experiments a 0.067 M phosphate buffer pH 7.4 or a 0.14 M phosphate buffer pH 6.0 (both having an ionic strength of 0.18) were used. Deionized water was used throughout the study. Visking dialysis tubing size 27″ to 32″, 21.5 mm, MW cut-off 12 kDa to 14 kDa (VWR International, West Chester, Pennsylvania) was employed for the dialysis cell.

Preparation of the Free Base Form of Bupivacaine, Prilocaine, and Ropivacaine

The free bases of bupivacaine and prilocaine were obtained from the corresponding hydrochlorides as previously described (Larsen, Parshad, Fredholt, & Larsen, 2002). The free base of ropivacaine was extracted from Naropin® 10 mg/ml containing ropivacaine hydrochloride. The injection solution was made alkaline by addition of NaOH and the precipitate was filtered, washed with water, and dried in vacuo. The melting point was determined from hot stage microscopy to 146° to 147°C (144°C–146°C (Merck index)). Elemental analyses confirmed that the isolated precipitate was ropivacaine base: Anal ($C_{17}H_{26}N_2O$); calc: C 74.41, H 9.55, N 10.21; found: C 74.12, H 9.49, N 10.28.

Determination of Solubility and Distribution Coefficient

The solubility of naproxen in different oil vehicles at 37°C was determined as previously described (Larsen et al., 2006) and the saturated oil phase was analyzed after dilution with 2-propanol by ultraviolet (UV) spectrophotometry. The distribution of model drug compounds between the different oil vehicles and buffer solutions was determined at 37°C using the shake-flask method. The pH-dependent distribution coefficients (D) were obtained from high-performance liquid chromatography (HPLC) measurements of the concentration of test compounds in the aqueous phase, initially and after attainment of equilibrium. All sample preparations were carried out in the incubator hood and the equipment used was preheated to the temperature of the study. Solubility and distribution experiments were conducted in triplicate.

In Vitro Release Experiments

The release experiments were carried out at 37°C using the rotating dialysis cell model as previously described (Pedersen et al., 2005; Larsen et al., 2006). At time zero, the dialysis cell containing (a) 5.0 ml aqueous buffer solution of the drug compound or (b) 0.5 or 1.0 ml oil drug solution added to 5.0 ml buffer solution was placed inside a round-bottomed vessel containing 1000 ml preheated release medium. The revolution speed of the dialysis cell was set to 50 rpm. At appropriate time intervals, samples were withdrawn from the acceptor phase and analyzed by HPLC. All release experiments (in triplicate) were followed until equilibrium was attained in the system. The cumulated amount of drug compound released in percent (corrected for sampling) was calculated according to:

$$\%\ released = \frac{V_S \sum_{n=1}^{n} C_{n-1} + V_A C_n}{M_T} \times 100 \quad (1)$$

where V_A and V_S are the volumes of acceptor phase and samples withdrawn from the acceptor phase, respectively. C_n is the drug concentration in sample n. M_T represents the total amount of drug in the system derived from the cumulated amount of drug in the acceptor phase at equilibrium ($M_{A,\infty}$) according to (Larsen et al., 2006):

$$M_T = M_{A,\infty}\left(1 + \frac{V_{Dw} + V_o D}{V_A}\right) \quad (2)$$

where V_{Dw} and V_o are the volumes of the aqueous and oil donor phase, respectively.

Analysis

Samples from the release and distribution experiments were analysed by an HPLC system consisting of a Merck-Hitachi L-7100 pump connected to a Merck-Hitachi L-4400 UV detector and a Merck-Hitachi L-7200 autosampler (VWR International, Tokyo, Japan). Reversed phase chromatography was performed using an RP-18 SymmetrySchield™ column (150 mm × 4.6 mm, 5 µm particles; Waters Corporation, Milford, MA) equipped with a Varian precolumn filter and the flow rate was set at 1 ml min^{-1}. The column effluent was monitored at 215, 247, 260, 220, 230, 205, 215, and 235 nm for bupivacaine, flurbiprofen,

ketoprofen, lidocaine, naproxen, prilocaine, ropivacaine, and salicylamide, respectively. The mobile phases consisted of 10% to 55% (v/v) acetonitrile and 0.1% phosphoric acid, which were made 1 mM with respect to triethylamine. Quantitation of the compounds was done from peak area measurements in relation to those of standards chromatographed under the same conditions. The quantification limits were approximately $2\times10^{-7} - 8\times10^{-7}$ M for bupivacaine, flurbiprofen, ketoprofen, lidocaine, prilocaine, and ropivacaine, 2×10^{-8} M for naproxen, and 2×10^{-6} M for salicylamide.

The amount of naproxen in the oil solutions was quantified by UV absorbance measurements at 230 nm in relation to those of standards analyzed under the same conditions. The reference consisted of a solution of oil in 2-propanol with a concentration of the oil vehicle similar to that of the diluted samples. An Aquarius CE7200 UV spectrophotometer (Cecil Instruments, Cambridge, England) was used for the measurements.

RESULTS AND DISCUSSION

Determination of Drug Transfer Rate Constants

The rotating dialysis cell model consists of a small donor compartment and a large acceptor compartment separated by a dialysis membrane (Dibbern & Wirbitzki, 1983; Larsen, Fredholt, & Larsen, 2000). After instillation of small volumes of oil drug solutions (V_o) into the aqueous donor phase (V_{Dw}), the consecutive transport processes leading to drug appearance in the aqueous acceptor phase (V_A) comprise (a) drug transfer from oil vehicle into the aqueous donor phase and (b) diffusion of drug across the membrane from the aqueous donor phase into the acceptor phase (Figure 1). In a preliminary study it was observed that rates of drug appearance in the acceptor phase applied to first-order kinetics (Larsen et al., 2006). The apparent first-order rate constants, k_{app}, were calculated from Equation 3.

$$\ln(M_{A,\infty} - M_{A,t}) = -k_{app}t + \ln(M_{A,\infty}) \quad (3)$$

where $M_{A,\infty}$ and $M_{A,t}$ refer to the amount of drug in the acceptor phase at equilibrium and time t, respectively.

The rotation of the dialysis cell creates a large oil-water interface. Thus, under the assumption that drug distribution equilibrium in the donor cell is established instantaneously between the oil and aqueous phase, an expression of k_{app} can be derived:

$$k_{app} = PA\left(\frac{1}{V_{Dw} + V_o D} + \frac{1}{V_A}\right) \quad (4)$$

where P and D represent the drug permeability coefficient and the pH-dependent oil-buffer distribution coefficient, respectively. A is the effective membrane area for diffusion (in this model, set to 22 cm^2). For model drug delivery systems consisting of sesame oil solutions of naproxen and lidocaine, a linear correlation was found between the calculated and experimentally determined rate constants (Larsen et al., 2006).

To investigate the general applicability of Equation 4, a series of in vitro release kinetic studies were performed employing different oil vehicles and drug compounds (Table 1). In addition, oil-buffer distribution coefficients, determined at the pH values used for the release studies, are presented in Table 1 together with the drug membrane permeability coefficients and the first-order rate constants related to drug appearance in the acceptor phase (obtained from Equation 3). The P value for each compound was determined from release studies initially applying an aqueous buffer solution (pH 6.0 or 7.4) of the drug into the donor cell using Equation 4 (inserting $V_o = 0$ as previously described; Pedersen et al., 2005). The permeation abilities of various solutes across the applied dialysis membrane have been shown to be independent of pH in the range 6.2 to 8.2 and ionic strength (0.2–0.5 M) of the buffer media employed as well as the revolution speed (40–200 rpm) of the dialysis cell (Pedersen et al., 2005). Two different batches of dialysis membranes with slightly different permeation properties were used. The measured permeability coefficients differed by 10%, and consequently, to facilitate comparison, the reported k_{app} values have been corrected for this variation (Table 1).

In addition to the experimentally determined first-order release rate constants, the apparent rate constants (k_{calc}) were calculated according to Equation 4, employing the experimentally obtained P and D values (Table 1). A good correlation between the k_{calc} values and the experimentally determined first-order release rate constants (k_{app}) was observed (Figure 2; n = 29, r = 0.993, slope = 0.978), demonstrating the adequacy

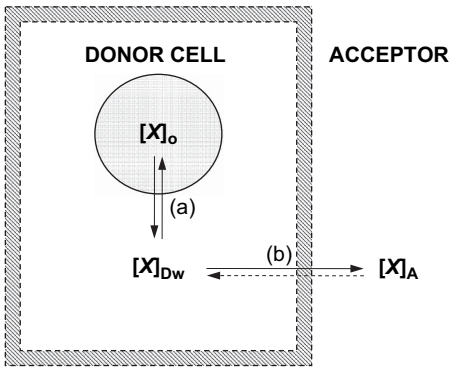

FIGURE 1. Schematic presentation of the transport processes in the three compartment model obtained after instillation of an oil drug solution into an aqueous donor compartment separated from a large aqueous acceptor compartment by a dialysis membrane. The transport processes include (a) drug release from the oil vehicle ($[X]_o$) into the aqueous donor phase ($[X]_{Dw}$), governed by the partitioning process between the two immiscible phases, and (b) diffusion of drug out of the donor cell into the acceptor phase ($[X]_A$).

TABLE 1
Release Data for Model Drug Compounds Obtained in the Rotating Dialysis Cell Model at 37°C

Drug Compound	$P \times 10^3$ (cm min^{-1})	Oil Vehicle	pH	D[a]	V_o (cm^3)	$k_{app} \times 10^3$ (min^{-1})
Bupivacaine	3.3 ± 0.1	Myritol 318 PH	6.0	8.44[b]	1.0	5.6 ± 0.1
		Sesame oil	7.4	114	0.5	1.2 ± 0.05
Flurbiprofen	5.0 ± 0.1	Myritol 318 PH	6.0	46.7[b]	1.0	2.53 ± 0.1
Ketoprofen	4.6 ± 0.3	Myritol 318 PH	6.0	3.63[b]	1.0	10.2[c]
Lidocaine	4.1 ± 0.2	Myritol 318 PH	6.0	1.66[d]	1.0	13.5[c]
Naproxen	5.2 ± 0.3	IPM[e]	6.0	5.32	1.0	11.5 ± 0.4
		Myritol 318 PH	6.0	10.3[d]	1.0	7.7 ± 0.4[f]
		Castor oil	6.0	33.4[d]	1.0	3.4 ± 0.1[f]
		Softigen® 701	6.0	33.7	1.0	3.0[f]
		50% (v/v) Softigen® 701 in IPM	6.0	26.5	1.0	3.9 ± 0.1
		50% (v/v) Imwitor® 742 in IPM	6.0	23.6	1.0	4.3 ± 0.04
Prilocaine	4.4 ± 0.2	Myritol 318 PH	6.0	1.13	1.0	16.7 ± 0.5
Ropivacaine	3.4 ± 0.1	Myritol 318 PH	6.0	2.98	1.0	9.5 ± 0.5
		Sesame oil	7.4	38.3	0.5	3.2 ± 0.2
Salicylamide	11.4 ± 0.7	Myritol 318 PH	6.0	5.49	1.0	22.4 ± 0.2

The drug membrane permeability coefficients ($P \pm SD$ [standard deviation]; $n = 3$), the experimentally determined apparent first-order release rate constants ($k_{app} \pm SD$; $n = 3$) after initial instillation of a volume of oil solution (V_o) into 5.0 ml aqueous buffer phase in the donor cell and the corresponding oil-buffer distribution coefficient (D; $n = 3$).

[a]Relative $SD < 10\%$.

[b]Larsen et al., 2000.

[c]$n = 2$.

[d]Fredholt et al., 2000.

[e]Isopropyl myristate (IPM).

[f]The k_{app} value was corrected due to employment of another batch of dialysis membrane.

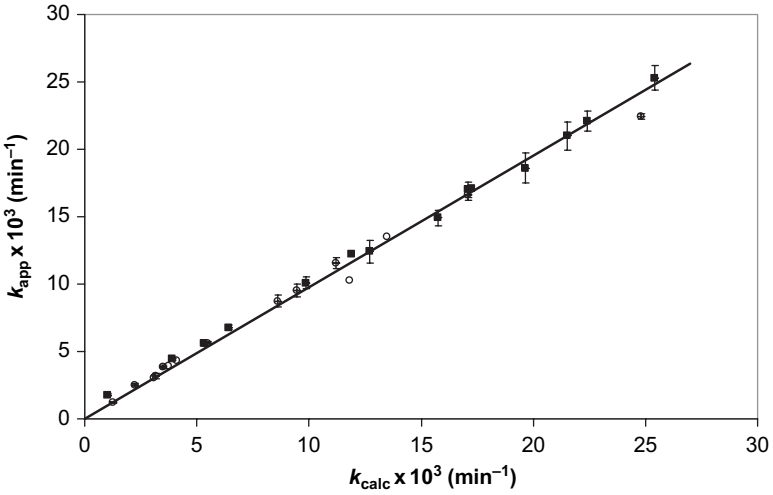

FIGURE 2. Correlation between the calculated (k_{calc}) and the experimentally determined (k_{app}) apparent first-order release constants at 37°C obtained in the rotating dialysis cell model after applying oil solutions of the model drug compounds to the donor cell containing aqueous buffer solution. ■: data from Larsen et al., 2006; ○: data from the present study.

of Equation 4 to describe the rates of mass transfer under the experimental conditions. In the release experiments involving eight model drugs, the following parameters varied: (a) volume of oil (V_o: 0.25–1.0 ml), (b) volume of aqueous donor phase (V_{Dw}: 5.0–7.0 ml), and (c) drug permeability coefficient (P: 5.2×10^{-3}–1.2×10^{-2} cm min^{-1}). The pH-dependent oil-buffer drug distribution coefficients used were varied covering a D range from 0.13 to 139 by applying oil vehicles of different compositions, altering the pH of the aqueous buffer phase in addition to the employment of compounds exhibiting different lipophilicities (Table 1). Furthermore, the oil vehicles investigated varied with respect to viscosity ranging from 5 to 7 mPa s for isopropyl myristate (IPM; at 25°C; Wade & Weller, 1994) to 681 mPa s for castor oil (at 25°C; Larsen, Fredholt, & Larsen, 2001). The observed 1:1 correlation between k_{app} and k_{calc} values strongly indicates that the viscosity had no effect on the release kinetics. The generated release data suggest that in the development phase, the relative influence of the employment of various excipients on drug release profiles from oil solutions might be estimated by Equation 4 with knowledge of the drug distribution coefficient between the respective oil composition and aqueous buffer.

Effect of Oil Composition on In Vitro Release Rates

Besides the study of pure vegetable or synthetic oils, drug release characteristics from mixed oil vehicles containing Softigen® 701 and Imwitor® 742 were investigated. The latter investigations were undertaken based on previous observations that drug release rates from castor oil were slower than from other vegetable oils, most likely reflecting the hydrogen bond donating capability of the ricinoleic acid hydroxy group (Fredholt, Larsen, & Larsen, 2000; Larsen, Fredholt, et al., 2001; Larsen et al., 2006). Softigen® 701 and Imwitor® 742 are commercially available partial glycerides containing ricinoleic acid and caprylic/capric acids, respectively. According to the manufacturer (Sasol Germany GmbH), the content of monoglycerides in these two pharmaceutical excipients exceeds 50%. Thus, the "molarity" of hydroxy groups in the two products should be comparable to or larger than that of castor oil. Addition of the two excipients to IPM resulted in a 2- to 3-fold reduction of the apparent rate constant as compared with that obtained from the release of naproxen from a pure IPM solution (Table 1 and Figure 3). As apparent from Table 1, highly comparable naproxen D values were determined for oil-buffer partitioning systems comprising castor oil, Softigen® 701 and Imwitor® 742 (D = 45.4 at pH 6.0). According to Equation 4 it is therefore to be expected that the three lipids will prolong drug release in mixed oil vehicles to quite the same extent. Thus, castor oil is considered the preferred excipient to modify drug release from oil solutions based on its history of parenteral administration (Akers, 2002; Strickley, 2004) and due to the fact that some oil mixtures containing Softigen® 701 and Imwitor® 742 were found to undergo phase separation on prolonged storage at room temperature.

Release Profiles for Coadministered Drugs

Effective postoperative pain control after, for example, arthroscopic knee surgery relies on fast onset of drug action as well as sufficiently long duration of action (Møiniche., Mikkelsen, Wetterslev, & Dahl, 1999). Such attributable therapeutic properties might be achieved from intra-articular injection of oil solutions comprising two analgesic agents differing with respect to lipophilicity. Thus, to test this possibility, in vitro release studies were performed using fractionated coconut oil solutions of prilocaine and the more lipophilic agent bupivacaine, as well as an oil solution containing both local anesthetics. The constructed release profiles are shown in Figure 4, revealing a significantly slower rate of appearance of bupivacaine in the acceptor phase compared with that of prilocaine. Identical apparent rate constants were found for bupivacaine ($k_{app} = 5.5\times10^{-3}$ min^{-1}) and prilocaine ($k_{app} = 1.8\times10^{-2}$ min^{-1}), respectively, independent of whether oil solutions of the individual drugs or a combination of the two analgesic compounds were initially applied to the aqueous donor compartment. The identical oil-buffer partitioning behavior of each drug alone or in the presence of the other drug compound is in keeping with the above release characteristics. The release profiles for bupivacaine and prilocaine (full lines in Figure 4) derived using the experimental D and P values in Equation 4 are in excellent agreement with the experimentally determined release data. Thus, in this model, simultaneous drug release may be predicted from knowledge of the oil buffer distribution coefficient of the active agents to be incorporated in a given oil vehicle.

Estimation of Drug Concentrations in the Donor Compartment

In the in vitro release experiments using the rotating dialysis cell model, drug appearance in the acceptor phase is monitored as a function of time. In relation to simulation of the activity of the drug in the joint cavity after intra-articular administration of oil drug solutions, the key parameter of interest is, however, estimation of the time dependence of the drug concentration in the aqueous donor compartment. Thus, the measured $M_{A,t}$ values can be converted into the amount of drug dissolved in the aqueous donor phase ($M_{Dw,t}$) at time t according to Equation 5 (Larsen et al., 2006).

$$M_{Dw,t} = 1 + \frac{V_{Dw}}{V_{Dw} + V_o D}(M_T - M_{A,t}) \qquad (5)$$

where M_T is the total amount of drug in the system. From the obtained release profiles of flurbiprofen and ketoprofen in

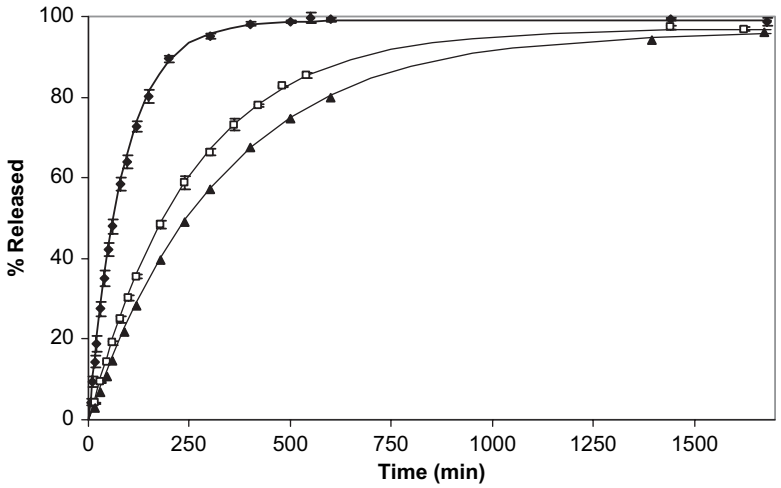

FIGURE 3. Release profiles of naproxen at 37°C obtained after applying 1.0 ml oil solution of naproxen to the donor cell containing 5.0 ml 0.14 M phosphate buffer pH 6.0. ♦: IPM (n = 3); □: 50 % (v/v) Softigen® 701 in IPM (n = 3); ▲: Softigen® 701 (n = 2). The full lines have been drawn according to the experimentally obtained apparent first-order rate constants.

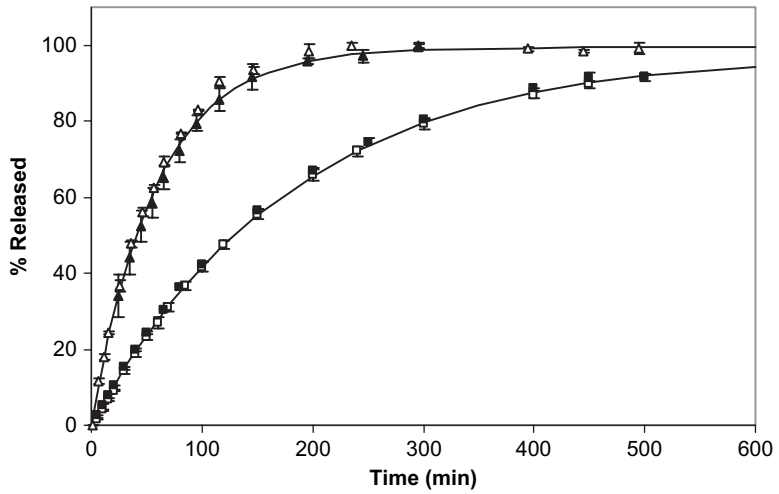

FIGURE 4. Release profiles of prilocaine and bupivacaine at 37°C in 0.14 M phosphate buffer pH 6.0 employing 1.0 ml fractionated coconut oil containing 18 µmol bupivacaine (■), 1.5 µmol prilocaine (▲), or 6.2 µmol bupivacaine (□), and 1.3 µmol prilocaine (△), respectively (n = 3). The full lines have been drawn according to the calculated apparent first-order rate constants (Equation 4).

fractionated coconut oil solutions (Figure 5A), the time dependent drug concentrations in the aqueous donor compartment (5.0 ml phosphate buffer pH 6.0) were obtained from the calculated $M_{Dw,t}$ values (Figure 5B). For each drug the actual drug concentration in the aqueous donor phase is a function of the D value, the volumes of the oil (V_o), and aqueous donor phase (V_{Dw}), as well as the initial drug concentration in the oil phase (C_o). In the performed release experiments, the ratio C_o(ketoprofen)/C_o(flurbiprofen) amounted to a factor of 2. Thus, in order to directly compare the drug concentration versus time profiles for the two drugs, a theoretically obtained curve has been incorporated in Figure 5 representing the flurbiprofen profile after applying an oil solution of this drug in a molar concentration identical to that of ketoprofen. An initially larger drug concentration of 5.8-fold of ketoprofen in the aqueous donor phase compared with that of flurbiprofen was estimated as a result of the significantly smaller oil-buffer distribution coefficient of ketoprofen in relation to that of flurbiprofen (Table 1). Interestingly, the relatively high D value of flurbiprofen gives rise to an only slightly decreasing drug concentration in the aqueous donor compartment. The data suggest, at least for low protein bound drugs, that achievement of therapeutic drug concentration in the synovial fluid over extended periods of time after intra-articular injection of drug substances in the form of oil solutions is only possible for drugs (or prodrug derivatives) endowed

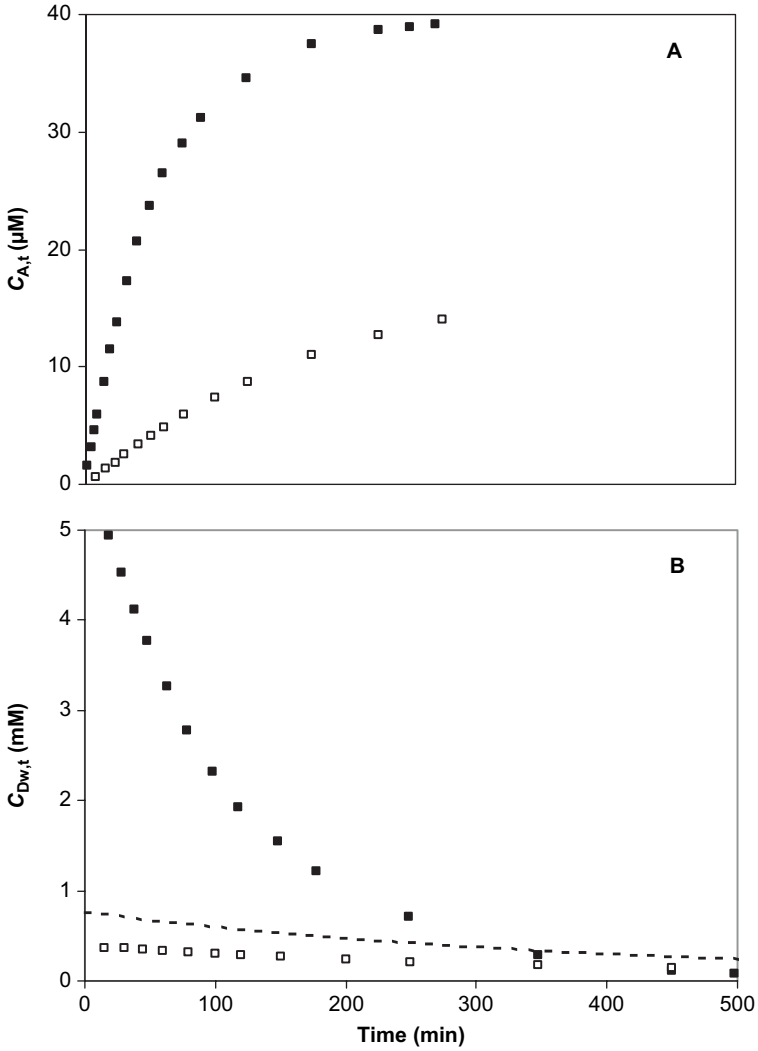

FIGURE 5. Release data obtained at 37°C after applying 1.0 ml fractionated coconut oil solution of 0.02 M flurbiprofen (□; n = 3) and 0.04 M ketoprofen (■; n=2) to the donor cell containing 5.0 ml 0.14 M phosphate buffer pH 6.0, respectively. **(A)** Time dependence of the drug concentration in the acceptor phase ($C_{A,t}$). **(B)** Time dependence of the drug concentration in the aqueous donor phase ($C_{Dw,t}$) calculated from Equation 5. A theoretical curve (dotted line) corresponding to the addition of 0.04 M flurbiprofen in 1.0 ml fractionated coconut oil was drawn according to Equation 5.

with a suitable high oil solubility and a sufficiently high oil-water drug distribution coefficient. As to the intra-articular fate of very lipophilic compounds, clearance of oil vehicles from the joint cavity via the lymphatics also has to be considered (Wallis, Simkin, & Nelp, 1987).

CONCLUSION

In vitro drug release and transport rates from oil drug solutions initially instilled into the donor cell of the rotating dialysis cell model have been determined under nonsink conditions employing several model drug compounds, oil vehicles of different compositions (vegetable oils, mixed oils, synthetic oils, and partial glycerides), and an oil drug solution containing two drug substances. The excellent correlation found between the experimentally determined first-order rate constants and the k_{app} values calculated from a theoretically derived expression was general, that is, independent of the investigated drug structures and the oil vehicle compositions, and indicates that for a specific drug substance, the in vitro drug release rate from oil solutions can be predicted from the oil-buffer distribution coefficient. Administration of drugs exhibiting a high affinity for the oil solution as compared with compounds with lower affinities results in more slowly decreasing drug concentrations in the aqueous donor compartment, that is, increased drug residence times in the donor compartment (joint cavity). Furthermore, to this end, the results indicate that alteration of the oil vehicle composition may be a means for controlling the drug concentration and prolonging the duration of action in the intra-articular cavity.

The drug residence time in the aqueous donor compartment is of particular interest in relation to the in vivo situation after intra-articular administration of oil drug solutions. However, the high oil-water interfacial area generated in vitro by stirring of the donor compartment is less likely to be formed after intra-articular injection of an oil solution into the synovial fluid. Different release kinetics might therefore be operating in vivo and significantly slower drug release rates from the oil depot formulations are to be expected in comparison to those predicted from Equation 4. Despite the inability of the present in vitro model to fully simulate the in vivo situation, it provides reproducible results and may constitute a valuable tool in accelerated release testing of parenteral oil depot formulations (with duration of actions in the order of weeks or months). Due to the large oil-water interface established in the donor cell the drug transfer from the oil phase into the aqueous phase proceeds much faster compared with the relatively slow release rates previously obtained using a two-phase in vitro dialysis model (Larsen et al., 2000; Fredholt et al., 2000; Larsen, Fredholt, et al., 2001; Larsen, Thomsen, Rinvar, Friis, & Larsen, 2001; Larsen et al., 2002). The need of accelerated in vitro release methods in the area of product quality control has recently been emphasized (Burgess et al., 2002; Burgess et al., 2004a, 2004b). Regarding parenteral oil depots, the in vitro dialysis model presented in this study may also be applied in formulation design development and to evaluate the impact of manufacturing process changes on product performance. Modified in vitro release models are presently under development in our laboratory aiming at the study of the influence of the size of the oil-water interface and protein binding on drug release kinetics.

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