J. Pharm. Pharmacol. 1993, 45: 748–749
Communicated November 24, 1992

The effect of surfactant on drug-plastic sorption phenomenon in solution

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Abstract—The sorption of calcitriol into PVC from an injectable formulation containing Tween 20, a nonionic surfactant, was studied. The amount of drug sorbed by the plastic decreased as the concentration of the surfactant increased. The apparent partition parameter of the drug between PVC strips and the solution was experimentally determined at three different concentrations of the surfactant. A physical model was developed to describe mathematically the partition equilibrium of the drug between the plastic solid phase, the micellar phase of the surfactant, and the aqueous phase of the solution. This model also allowed the calculation of the drug/plastic and drug/micelle partition parameters using the experimentally determined apparent partition parameters.

The loss of drugs from aqueous solutions stored in polyvinyl chloride (PVC) plastic intravenous infusion bags and administration sets has been well documented (Moorhatch & Chiou 1974; Cossum & Roberts 1981; Kowaluk et al 1981; Illum & Bundgaard 1982; Nation et al 1983; Atkinson & Duffull 1991). The uptake of drugs into plastic materials occurs primarily through a diffusion-controlled sorption process (Roberts et al 1991). The sorption of drugs by plastic is considered clinically important because this may result in a reduction in the anticipated amount of drug delivered to the patient.

Calcitriol, the active form of vitamin D_3, is used in the treatment of hypocalcaemia in patients undergoing chronic dialysis. Calcijex, an injectable preparation of calcitriol, is administered as a bolus injection into the bloodline at the end of haemodialysis. Calcitriol in the Calcijex formulation was shown to be physically compatible and chemically stable in 1 mL polypropylene plastic tuberculin syringes for 8 h at ambient temperature (Pecosky et al 1992). A study conducted by Vieth et al (1989) demonstrated that when a dose of Calcijex was added to a 1 L PVC bag of peritoneal dialysis fluid, only 50% of the dose remained 2 h after addition and 26% remained after 20 h of storage at room temperature (21°C). No degradation of calcitriol in the admixture was detected. Vieth et al (1989) concluded that the loss of calcitriol in the admixture was the result of drug sorption into PVC.

Calcitriol is practically insoluble in water. Calcijex is formulated by solubilizing calcitriol in an aqueous solution of Tween 20, a nonionic surfactant. When Calcijex is added to a solution contained in a PVC bag, sorption of calcitriol into the plastic occurs. The extent of calcitriol sorption into the plastic is a function of the partition coefficient of the drug between the PVC and the micelles of the surfactant. The concentration of the surfactant in the system may also play a role in the drug–plastic sorption process. In this study a physical model is developed to describe mathematically the partition equilibrium of calcitriol between the plastic solid phase, the surfactant micellar phase, and the aqueous phase of the system. The effect of dilution of the product on the extent of plastic-drug sorption is also discussed.

Theory. The physical model for the sorption of a drug into a plastic solid phase from a solution containing a surfactant can be derived by treating the micelles of the surfactant as a separate phase. When a partition equilibrium is achieved for the drug between the plastic solid phase, the surfactant micellar phase, and the aqueous phase, and assuming the volume of the surfactant is negligible compared with the aqueous phase, then:

$$K'_p = \frac{(W_{dp}/W_p)}{(W_{dm}+W_{da})/V_{at}} \quad (1)$$

where K'_p is the apparent partition parameter of the drug between the solid plastic and the solution phases; W_{dp}, W_{dm}, and W_{da} are the weight of the drug in the plastic, micellar, and aqueous phases, respectively; W_p is the plastic weight and V_{at} is the solution volume.

Substituting the drug/plastic partition parameter, K_p, and the drug/micelle partition parameter, K_m, in equation 1 gives:

$$K'_p = \frac{K_p W_{da}}{K_m W_m (W_{da}/V_{at}) + W_{da}} \quad (2)$$

Rearranging equation 2 and taking the concentration of the micellar phase as the difference between the surfactant concentration (C_s) and its critical micellular concentration (CMC), then:

$$1/K'_p = (K_m/K_p)(C_s - CMC) + 1/K_p \quad (3)$$

K'_p can be determined experimentally using different concentrations of surfactant in the system; plotting of $1/K'_p$ against $C_s - CMC$ will yield a straight line with the intercept equal to $1/K_p$ and the slope equal to K_m/K_p.

Materials and methods

Materials. Calcijex (2 μg mL^{-1}) and empty PVC containers were obtained from Abbott Laboratories, North Chicago, IL, USA. Tween 20 (Lot 70H0171) was purchased from Sigma Chemical Co., St Louis, MO, USA.

Determination of the CMC of Tween 20 in water. Aqueous solutions of Tween 20 with concentrations of 0·01, 0·02, 0·05, 0·1, 0·2 and 0·5 mg mL^{-1} were prepared using purified water. The surface tension of the above solutions and purified water was determined using the CSC-DuNouy Tensiometer Model 70535 (CSC Scientific Company, Inc., IL). The CMC of Tween 20 was determined from the surface tension vs concentration plot.

Determination of the apparent partition parameter of calcitriol between PVC and the Calcijex formulation. Calcijex (2 μg mL^{-1}) was diluted with a Tween 20 solution to yield a series of 0·5 μg mL^{-1} calcitriol solutions containing 1, 2, 4 mg mL^{-1} of Tween 20. An accurately weighed PVC film strip was added into ampoules containing 3 mL calcitriol solution. Calcitriol solution with no PVC film strip added was used as the control. The ampoules were sealed under nitrogen and subsequently shaken in a mechanical shaker at ambient temperature. The solutions were assayed for calcitriol concentration by HPLC. Equilibrium of the system is achieved when there is no significant difference in calcitriol concentration between two consecutive sampling points.

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Table 1. The effect of surfactant concentration on the amount of drug sorbed into PVC strips.

	Concn of Tween 20 (mg mL^{-1})		
	1·0	2·0	4·0
Drug sorbed by PVC (μg g^{-1})	7·23 (0·06)	6·44 (0·31)	5·38 (0·64)
Drug concn in solution (μg mL^{-1})	0·09 (0·01)	0·13 (0·01)	0·19 (0·02)

Mean (s.d.) for three samples.

HPLC. Separation and quantitation of calcitriol was accomplished using an HPLC system (Shimadzu Scientific Instrument Inc., Columbia, MD) consisting of a single piston pump (Model LC-6A), an auto-injector (Model SIL-9A), a variable wavelength UV detector (Model SPD-6A), and an integrator (Model CR501). The stationary phase was a reverse-phase nonpolar column (Waters, 5 μm spherical C_{18}, 15 cm × 3·9 mm) and the mobile phase was a 69% (v/v) methanol-in-water solution. Mobile phase flow rate was 1·4 mL min^{-1} and the injected sample volume was 150 μL. The wavelength of the detector was set at 264 nm. The retention time for calcitriol was about 20 min. For each of the three concentrations of Tween 20 evaluated in this study, a calibration curve was constructed using a series of standard calcitriol solutions (0·05–0·5 μg mL^{-1}). The concentration of the drug in the sample was determined by comparing the peak area of the drug with the peak area of the external standard on the calibration curve.

Results and discussion

As determined from the Tween 20 concentration and solution surface tension data, the CMC for Tween 20 in water at ambient temperature was found to be approximately 0·02 mg mL^{-1}. Therefore, at a concentration of 1 mg mL^{-1}, the lowest concentration of Tween 20 in the calcitriol solutions evaluated in this study, 98% of the surfactant exists in the micellar form.

The amount of calcitriol lost in the presence of PVC strips at partition equilibrium decreased as the concentration of surfactant in the system increased (Table 1). This phenomenon is attributed to the reduction of the amount of free drug available for plastic sorption because a larger amount of drug is solubilized in the micellar phase at a higher surfactant concentration. The ratio of the concentration of the drug sorbed by the plastic and that remaining in the solution gives the apparent partition parameter at a specific surfactant concentration. When the reciprocal of the mean apparent partition parameters ($1/K_p'$) was plotted against the surfactant micelle concentration ($C_s - CMC$) according to equation 3, the calcitriol/PVC partition parameter (K_p) was calculated to be 200 and the calcitriol micelle partition parameter (K_m) was 1450, i.e. the affinity of calcitriol for the Tween 20 micelles is about 7·5 times that for the PVC.

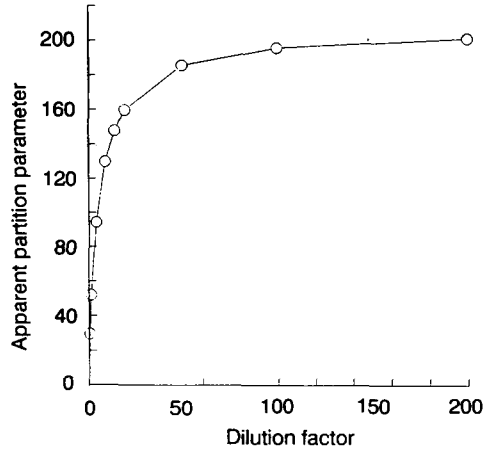

FIG. 1. The predicted effect of dilution on the apparent partition parameter of calcitriol between PVC and the Calcijex formulation.

Fig. 1 depicts the effect of dilution of a Calcijex formulation which contains 4 mg mL^{-1} of Tween 20 on the apparent partition parameter of calcitriol between PVC and the diluted solution. For an undiluted Calcijex formulation, an apparent partition parameter of 29·6 was calculated. When the formulation is diluted, a higher apparent partition parameter is found. As the solution is further diluted to effect a surfactant concentration below its CMC value, the apparent partition parameter approaches the calcitriol/PVC partition parameter.

The physical model and equations developed in this study can be used to determine the drug/plastic and drug/micelle partition parameters using data derived from a single, relatively simple experiment. The results of this study also demonstrate that the extent of sorption of a drug into a plastic material in the presence of a surfactant is dependent on the relative affinity of the drug for the plastic solid phase and the micellar phase of the surfactant. The amount of micellar phase in the system is another determining factor for the amount of drug sorbed into the plastic. Although the apparent partition parameter determined in this study is an equilibrium constant, it represents the driving force for the sorption of the drug into the plastic. Therefore, from a kinetic point of view, a high apparent partition parameter also indicates a faster uptake of the drug into the plastic. Because of the strong affinity of calcitriol for PVC, it is recommended that Calcijex should not be in contact with PVC material. Particularly when it is diluted, transient contact with the plastic material may result in significant loss of the drug.

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