ELSEVIER

International Journal of Pharmaceutics 200 (2000) 217–222

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Relationship between Polysorbate 80 solubilization descriptors and octanol–water partition coefficients of drugs

F.A. Alvarez-Núñez [a,*], S.H. Yalkowsky [b]

[a] *Formulation R & D, Pharmaceutical Delivery Systems, Parke-Davis R&D, Morris Plains, NJ 07950, USA*
[b] *College of Pharmacy, The University of Arizona, Tucson, AZ 85721, USA*

Received 30 August 1999; received in revised form 12 January 2000; accepted 21 February 2000

Abstract

The molar solubilization capacities (κ) and the molar micelle–water partition coefficients (K_M^N) in Polysorbate 80 of several drugs (including barbiturates, steroids, and benzoic acid derivatives) are related to their log octanol–water partition coefficients (log P). Both κ and K_M^N values were calculated from solubility versus Polysorbate 80 concentration profiles, which were either experimentally determined or obtained from the literature. There is a linear relationship between log P of the tested compounds and the logarithm of the molar micelle–water partition coefficient (log K_M^N). On the other hand molar solubilization capacities are nearly independent of log P. It is shown that the ability of Polysorbate 80 to solubilize a drug can be predicted from its log P value.

Keywords: Polysorbate 80; Octanol–water; Solubilization descriptors; Partition coefficients

1. Introduction

Although there are many types of surfactants, only a few have precedence for use in parenteral products. By far the most popular surfactant used in FDA-approved parenteral products is Polysorbate 80. Recent reviews show that Polysorbate 80 is added into about 60% of all injectable formulations that contain solubilizing, suspending, or emulsifying agents (Nema et al., 1997) and it is present in about 40 parenteral formulations (Powell et al., 1998).

The most common descriptors of surfactant solubilization are the molar solubilization capacity, κ, and the micelle–water partition coefficient, K_M. (Atwood and Florence, 1983 and Yalkowsky, 1999). The κ value is defined as the number of moles of the solute that can be solubilized by 1 mol of micellar surfactant. It characterizes the ability of the surfactant to solubilize the solute. Its value is equal to the slope of the line, S_{tot} versus C_{surf}. The general equation for micellar solubilization is:

$$S_{tot} = S_w + \kappa(C_{surf} - CMC)$$

$$= S_w + \kappa C_{mic} \quad (1)$$

* Corresponding author.

0378-5173/00/$ - see front matter
PII: S0378-5173(00)00386-0

where S_{tot} is the total solute solubility, S_w is the water solubility, C_{surf} is the number of moles of surfactant in solution, CMC is the critical micellar concentration, and C_{mic} is the molar concentration of the micellar surfactant. If the surfactant concentration is much greater than the CMC, C_{surf} approximates the term C_{mic} in the above equation and

$$S_{tot} \approx S_w + \kappa C_{surf} \quad (2)$$

The micelle–water partition coefficient, K_M, is defined as the ratio of solute concentration in the micelle to the solute concentration in water for a particular concentration of surfactant. K_M is related to the solubilization capacity by means of

$$K_M \approx \frac{\kappa C_{surf}}{S_w} \quad (3)$$

Note that, both κ and K_M describe the ability of a surfactant to solubilize a particular drug, but in different ways. The value of K_M is related to the water solubility of the compound, whereas the κ value is not.

Since K_M is restricted by the surfactant concentration, it will be convenient to define a molar micelle–water partition coefficient K_M^N as the micelle–water partition coefficient in a one molar surfactant solution, i.e.

$$K_M^N = K_M^{C_{surf}=1\,M} = \frac{\kappa}{S_w} \quad (4)$$

The above normalized molar micelle–water partition coefficient is also equal to the solubilization capacity normalized by the intrinsic solubility of the solute.

Since the driving forces for the partitioning of a compound into a micelle and into octanol are similar, Collete and Koo (1975) and Tomida et al. (1978) correlate them for some benzoic acid derivatives in Polysorbate 20 and Polyoxyethylene-23 lauryl ether solutions, respectively. Thus, K_M^N and log P can be expected to be correlated by:

$$\log K_M^N = a + b \log P \quad (5)$$

where a and b are constants which are dependent upon the surfactant. Combining the above equations gives:

$$S_{tot} = S_w(1 + C_{surf} \times 10^{(a + b \log P)}) \quad (6)$$

which relates the total solubility of any solute to its water solubility, its octanol–water partition coefficient, the surfactant concentration, and the surfactant specific constants a and b.

The objective of this investigation is to evaluate the constants of Eq. (5) so that Polysorbate 80 solubilization can be estimated from octanol–water partition coefficient via Eq. (6).

2. Experimental section

2.1. Solubility determination

The solubilities of testosterone and its propionate and enanthate derivatives were determined in Polysorbate 80–water mixtures at concentrations between 0 and 0.23 M (0–20%). Excess drug was added directly into the surfactant–water mixture. Equilibrium was reached by gentle agitation over 2 days at room temperature (24 ± 2°C). After equilibration, the solutions were centrifuged, filtrated through 0.22 μm Durapore PVDF/PVC Millipore membranes, and analyzed by HPLC. The solubility versus Polysorbate 80 concentration profiles for other compounds were obtained from literature data.

2.2. Calculation of κ, K_M^N, and log P values

κ and K_M^N values were calculated from the drug S_{tot} versus Polysorbate 80 concentration profiles and Eqs. (2) and (4). The ClogP® software, which estimates the log P value of a molecule from the sum of its component molecular fragment values and some of the interactions among these fragments, was used to obtain log P values (Leo and Hansch, 1986). Besides calculated values, ClogP® includes experimental values of thousands of compounds. When ClogP® reported both experimental and calculated values the former was preferred.

3. Results and discussion

Fig. 1 shows the S_{tot} versus Polysorbate 80 concentration profiles for testosterone and its propionate and enanthate derivatives. Although Fig. 1 suggests that the solubilization capacity (κ), appears to be correlated to the $\log P$ of testosterone and its derivatives, Table 1 indicates that such relationship is not observed for most compounds considered in this study.

Table 1 lists the compounds considered in this study along with the logarithms of their octanol–water partition coefficients ($\log P$), their solubilization capacities ($\log \kappa$), and their molar micelle–water partition coefficients ($\log K_M^N$). The values of octanol–water partition coefficients (P) and molar micelle–water partition coefficients (K_M^N) in Table 1, each range over more than ten orders of magnitude. This table shows that the logarithms of these values are highly correlated with each other. On the other hand this table shows that the molar solubilization capacity, κ, range with a few exceptions over only two orders of magnitude and in most cases its logarithm is not correlated with the logarithm octanol–water partition coefficient. This suggests that molar solubilization capacity can not be used to compare the ability of Polysorbate 80 to solubilize most drugs with different hydrophobicities.

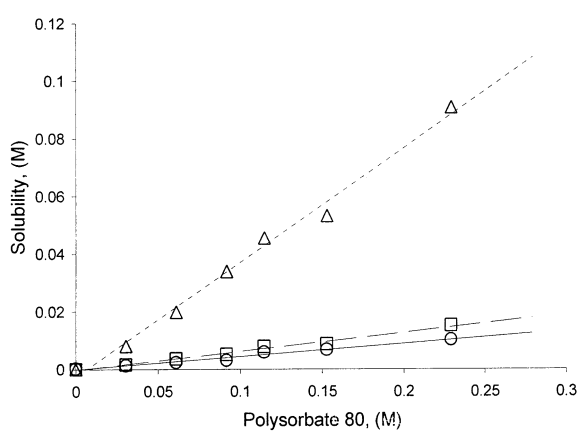

Fig. 1. S_{tot} versus Polysorbate 80 concentration profiles for testosterone (○) and its propionate (□) and enanthate (△) derivatives, $\log P$ values of 3.32, 4.69, and 6.81, respectively.

Fig. 2 shows a strong correlation between logarithm of the octanol–water partition coefficient and the logarithm of the molar micelle-water partition coefficient for the tested compounds ($r^2 = 0.94$). Since the driving force for micelle solubilization increases as the hydrophobicity of the solute increases, the relationship between the solute $\log P$ and the Polysorbate 80–water partition coefficient to solubilize it is expected.

This relationship is described by:

$$\log K_M^N = 0.9201 \times \log P + 0.0690 (r^2 = 0.94) \quad (7)$$

If K_M^N units, M^{-1}, are converted into, (g Polysorbate 80/l of solution)$^{-1}$, then Eq. (6) becomes:

$$\log K_M^N = 0.9201 \times \log P + 3.1856 \quad (8)$$

Inserting Eq. (7) into Eq. (6) gives:

$$S_{tot} = S_w(1 + C_{Polysorbate\ 80} \times 10^{(0.92 \times \log P - 0.07)}) \quad (9)$$

According to the Student's t-test the coefficients a and b of the Eq. (9) are not statistically different from 0.0 and 1.0, respectively. Therefore, Eq. (9) can be approximated by:

$$S_{tot} = S_w(1 + P \times C_{Polysorbate\ 80}) \quad (10)$$

which relates the total solubility of a drug to its partition coefficient and the Polysorbate 80 concentration. The above equations assume a linear relationship between S_{tot} and $C_{Polysorbate\ 80}$. This assumption is reasonable for concentrations of Polysorbate 80 used in pharmaceutical field. Note that Eq. (9) is capable of predicting the S_{tot} versus Polysorbate 80 concentration profile of any drug from its octanol–water partition coefficient.

4. Conclusions

A linear relationship between logarithm of octanol–water partition coefficient ($\log P$) and logarithm of normalized micelle–water partition

Table 1
Log P values, logarithm of solubilization capacity values, log κ logarithm of normalized micellar partition coefficient, log K_M^N, in Polysorbate 80 for the tested compounds

Drug	log P	log κ	log K_M^N	Reference
Barbital	0.65	−0.60	0.76	Ismail et al. (1970)
Codeine	1.14	−0.14	1.41	Kuttel (1968)
Allobarbital	1.15	−0.77	1.28	Ismail et al. (1970)
Acetanilide	1.16	−0.10	1.33	Kuttel (1964)
Aspirin	1.19	−0.07	1.45	Ahsan and Blaug (1960)
Phenobarbital[a]	1.47	−0.41	1.83	Ismail et al. (1970)
Phenobarbital[a]	1.47	−0.39	1.90	Ahsan and Blaug (1960)
p-hydroxybenzoic acid	1.58	−0.13	1.14	Ahsan and Blaug (1960)
Butethal[a]	1.73	−0.12	1.87	Kuttel (1964)
Butethal[a]	1.73	−0.13	1.57	Ismail et al. (1970)
Cyclobarbital	1.77	−0.48	1.62	Ismail et al. (1970)
Atropine	1.83	−0.36	1.76	Kuttel (1968)
Benzocaine	1.86	−0.15	1.95	Hamid and Parrot (1971)
Benzoic acid	1.87	0.07	1.63	Gerakis et al. (1993)
Methyl paraben	1.96	0.11	1.92	Patel and Kostenbauder (1958)
Secobarbital	1.97	−0.09	2.12	Ismail et al. (1970)
Furosemide	2.03	−1.74	2.49	Shihab et al. (1979)
Amobarbital	2.07	−0.65	1.89	Ismail et al. (1970)
Camphor	2.18	−0.83	1.86	Kuttel (1964)
Griseofulvin	2.18	−1.82	2.77	Sjokvist et al. (1992)
Carbamazepine	2.19	−0.60	2.17	Samaha and Cadalla (1987)
Menadione	2.19	−0.51	2.19	El-Khawas and Daabis (1969)
o-Hydroxybenzoic acid	2.26	0.03	1.92	Ahsan and Blaug (1960)
Quinine	2.64	−0.58	2.15	Kuttel (1968)
Papaverine	2.95	0.74	2.95	Kuttel (1968)
17-Hydroxy-progesterone	3.17	−2.12	2.58	Lundberg (1980)
Ethisterone	3.30	−3.02	2.64	Lundberg (1980)
Testosterone	3.32	−1.46	2.63	This paper
p-Dichlorobenzene	3.44	−0.06	2.08	Kuttel (1964)
Ibuprofen	3.50	0.07	3.50	Devi and Rao (1995)
Timobesone acetate	3.50	−2.29	3.93	Ong and Manoukian (1988)
Ethynylestradiol	3.67	−0.68	3.76	Lundberg (1980)
Progesterone	3.87	−1.33	3.22	Lundberg (1980)
Estradiol	4.01	−1.85	4.37	Lundberg (1980)
Indomethacin	4.27	−1.08	3.47	Krasowska (1976)
Testosterone propionate	4.69*	−1.19	4.62	This paper
Felodipine	4.80	−1.36	5.05	Anderberg et al. (1988)
DMP 323[b]	4.86*	−0.84	3.91	Maurin et al. (1996)
Cinmethacin	4.97	−1.76	3.78	Krasowska (1976)
Tolfenamic acid	5.17	−1.31	3.75	Raunio and Turakka (1982)
Testosterone enanthate	6.81*	−0.40	5.66	This paper
Calciferol	9.39*	−0.63	9.60	Chung-Ti et al. (1984)
α-Tocopherol	11.20*	0.51	11.00	Imai et al. (1983)

[a] Data from two sources.
[b] 4*R*-(4α, 5α, 6β, 7β)-hexahydro-5,6-bis (hydroxy)-1,3-bis (4-hydroxymethyl)phenyl-methyl-4,7-bis (phenylmethyl)-2H-1,3-diazepin-2-one.
* Calculated log P values.

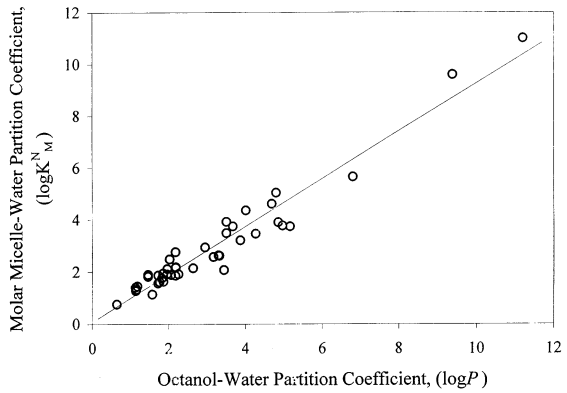

Fig. 2. Logarithm of the Polysorbate 80 molar micelle–water partition coefficient, log K_M^N versus log P profile of the tested drugs.

coefficient is observed (log K_M^N). This relationship uses the log P of the drug in order to estimate the ability of Polysorbate 80 to solubilize it. No correlation between log P and logarithm of molar solubilization capacity was found.

Acknowledgements

The work of Mi Jin Kim and Kia Sepasi is appreciated.

References

Ahsan, S.S., Blaug, S.M., 1960. Interactions of Tweens with some pharmaceuticals. Drug Stand. 28, 95–100.

Anderberg, E.K., Bisrat, M., Nyström, C., 1988. Physicochemical aspects of drug release, VII: the effect of surfactant concentration and drug particle size on solubility and dissolution rate of felodipine, a sparingly soluble drug. Int. J. Pharm. Sci. 47, 67–77.

Atwood, D., Florence, A.T., 1983. Surfactant Systems. Chapman and Hall, New York.

Chung-Ti, L., Da-Wei, Q., Ga-Lin, Z., 1984. Studies on the efficiencies of polyoxyethylene castor oil C-125 and Polysorbate 80 in the solubilization of calciferol and stability of solubilized calciferol. Acta Pharm. Sinica 19, 524–527.

Collete, J.H., Koo, L., 1975. Interaction of substituted benzoic acid derivatives with polysorbate 20 micelles. J. Pharm. Sci. 64, 1253–1255.

Devi, P.N., Rao, Y.M., 1995. Solubilization of ibuprofen by using cosolvents, surfactants, and formulation of an elixir and injectable preparation. East. Pharm. 38, 137–140.

El-Khawas, E., Daabis, N., 1969. The solubility of menadione (vitamin K3) in systems containing non-ionic surface-active agents. Pharmazie 24, 684–686.

Gerakis, A.M., Koupparis, M.A., Efstathiou, C.E., 1993. Micellar acid–base potentiometric titrations of weak acidic and/or isoluble drugs. J. Pharm. Biomed. Anal. 11, 33–41.

Hamid, I.A., Parrot, E.L., 1971. Effect of temperature on solubilization and hydrolytic degradation of solubilized benzocaine and homatropine. J. Pharm. Sci. 60, 901–906.

Imai, J., Hayashi, M., Awazu, S., Hanano, M., 1983. Solubilization of DL-α-tocopherol by bile salts, Polysorbate 80, and egg lecithin. Chem. Pharm. Bull. 31, 4077–4082.

Ismail, A.A., Gouda, M.W., Motawi, M.M., 1970. Micellar solubilization of barbiturates I: solubilities of certain barbiturates in polysorbates of varying hydrophobic chain length. J. Pharm. Sci. 59, 220–223.

Krasowska, H., 1976. Solubilization of indomethacin and cinmethacin by non-ionic surfactants of polyoxyethylene type. Il Farmaco 31, 462–472.

Kuttel, V.D., 1964. Die Solubilisationsfahigkeit des Tween 20, 40, 80 bei einigen in wasser schlecht loslichen medikamenten. Pharmazeutishche Zentralhalle 103, 10–16.

Kuttel, V.D., 1968. Die Solubiliierungsmoglichkeit einger alkalodbasen mit Polysorbate 80. Pharmazeutishche Zentralhalle 107, 593–600.

Leo, A. and Hansch, C., 1986. CLOGP3 Users Guide, MedChem Software Release 3.32. Pomona College, Pomona, CA.

Lundberg, B., 1980. Simultaneous solubilization of steroid hormones III: thermodynamic evaluation. J. Pharm. Sci. 69, 20–24.

Maurin, M.M., Vickery, R.D., Carney, R.F., Hussain, M.A., 1996. Physicochemical properties of nonpeptide cyclic urea HIV protease inhibitor DMP 323. Int. J. Pharm. Sci. 144, 99–106.

Nema, S., Washkuhn, R.J., Brendel, R.J., 1997. Excipients and their use in injectable products. PDA J. Pharm. Sci. Tech. 51, 166–171.

Ong, J.T.H., Manoukian, E., 1988. Micellar solubilization of timobesone acetate in aqueous and aqueous propylene glycol solutions of nonionic surfactants. Pharm. Res. 5, 704–708.

Powell, M.F., Nguyen, T., Baloian, L., 1998. Compendium of excipients for parenteral formulations. PDA J. Pharm. Sci. Tech. 52, 238–311.

Patel, N.K., Kostenbauder, H.B., 1958. Interaction of preservatives with macromolecules I: binding of parahydroxybenzoic acid esters by polyoxyethylene 20 sorbitan monooleate (Polysorbate 80). J. Pharm. Sci. 59, 289–293.

Raunio, O., Turakka, L., 1982. The solubility of tolfenamic acid in surfactant solutions. Pharm. Ind. 44, 750–752.

Samaha, M.W., Cadalla, M.A.F., 1987. Solubilization of carbamazepine by different classes of nonionic surfactants and bile salts. Drug. Dev. Ind. Pharm. 13, 93–112.

Shihab, F.A., Ebian, A.R., Mustafa, R.M., 1979. Effect of polyethylene glycol, sodium lauryl sulfate and Polysorbate 80 on the solubility of furosemide. Int. J. Pharm. Sci. 4, 13–20.

Sjokvist, E., Nysrom, C., Alden, M., Caram-Lelham, N., 1992. Physicochemical aspects of drug release. XIV: the effects of some ionic and non-ionic surfactants on properties of sparingly soluble drug in solid dispersions. Int. J. Pharm. Sci. 79, 123–133.

Tomida, H., Yotsuyanagi, T., Ikeda, K., 1978. Solubilization of benzoic acid derivatives by polyoxyethylene lauryl ether. Chem. Pharm. Bull. 26, 2821–2831.

Yalkowsky, S., 1999. Solubility and Solubilization in Aqueous Media. ACS, NY.