International Journal of Pharmaceutics 409 (2011) 206–208

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Note

The effect of polymeric additives on the solubilisation of a poorly-soluble drug in micellar solutions of Pluronic F127

Cristiane P. Oliveira[a], Luiz C.G. Vasconcellos[a], Maria Elenir N.P. Ribeiro[a], Nágila M.P.S. Ricardo[a,*], Ticiane V. de P. Souza[a], Flávia de M.L.L. Costa[a], Chiraphon Chaibundit[b], Stephen G. Yeates[c], David Attwood[d]

[a] Department of Organic and Inorganic Chemistry, Polymer Laboratory, Federal University of Ceará, CX 6.021, CEP 60455-760, Fortaleza, Ceará, Brazil
[b] Department of Materials Science and Technology, Faculty of Science, Prince of Songkla University, Had Yai, Songkhla 90112, Thailand
[c] School of Chemistry, University of Manchester, Manchester M13 9PL, UK
[d] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PL, UK

ARTICLE INFO

Article history:
Received 2 December 2010
Received in revised form 10 February 2011
Accepted 12 February 2011
Available online 25 February 2011

Keywords:
Solubilisation
Micelles
Pluronic F127
PEG
PVP

ABSTRACT

The solubilisation of griseofulvin in 1 wt% aqueous micellar solutions of Pluronic F127 at 37 °C has been modified by adding polyethylene glycol PEG 35000 or poly(vinylpyrrolidone) PVP K30. The solubilisation capacity expressed in terms of unit weight of F127 is increased by the addition of 0.5 wt% PEG 35000 to a value approaching double that of a 2.5 wt% solution of F127 alone, but there is no advantage in adding 0.5 wt% PVP K30.

1. Introduction

Pluronic copolymers of ethylene oxide and propylene oxide, type $E_mP_nE_m$ are available commercially over a wide range of compositions and block lengths. We use the notation $E = OCH_2CH_2$, $P = OCH_2CH(CH_3)$, and subscripts m and n to indicate number-average block lengths in repeat units. As noted in recent reviews (Attwood et al., 2007; Attwood and Booth, 2007), the solubilisation of hydrophobic drugs in dilute micellar solutions of these copolymers is lower than that in solutions of copolymers with more hydrophobic core-forming blocks. Compare, for example, the solubility of the aromatic drug griseofulvin in aqueous solutions of Pluronic copolymer F127 ($E_{98}P_{67}E_{98}$, 30 wt% P) and a copolymer of ethylene oxide and styrene oxide, $E_{66}S_{13}E_{66}$ (23 wt% S, $S = OCH_2CH(C_6H_5)$. The solubilisation capacity of the copolymers, i.e. the solubility of the drug in excess of that in water expressed as mg per gram of copolymer, in 1 wt% solutions at 37 °C is 2.5 mg g^{-1} for F127 (present work) and 4.3 mg g^{-1} for $E_{66}S_{13}E_{66}$ (Crothers et al., 2005). Allowing for the weight fraction of the S hydrophobe in the copolymer, the solubilisation per gram of hydrophobe is in the ratio S/P ≈ 2.2, a considerable advantage for the more hydrophobic S block.

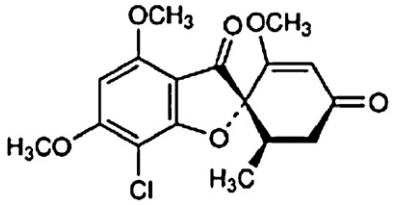
In this note we report an investigation of the possibility of improving the solubilisation capacity of solutions of F127 by adding comparable concentrations of water soluble polymers of moderate molar mass, either polyethylene glycol PEG 35000 or poly(vinylpyrrolidone) PVP K30. We focus on the solubilisation of the hydrophobic drug griseofulvin (see Scheme 1), which has poor water solubility, ca. 12 mg dm^{-3} (Yalkowsky and He, 2003) at 37 °C, and has long been used (e.g. Elworthy and Patel, 1982; Rekatas et al., 2001) as a standard for testing micellar hosts.

2. Experimental

Copolymer F127 was a product of BASF Corp. purchased from Sigma and used as received. A value of the number-average molar mass, M_n = 12,500 g mol^{-1}, was supplied. The value of the ratio of weight-average to number-average molar mass, M_w/M_n = 1.20, was determined by gel permeation chromatography (GPC) using *N*,*N*-dimethylacetamide at 70 °C as solvent as described previously (Chaibundit et al., 2000). PEG 35000 was supplied by Sigma-Aldrich, and values of $M_n \approx 35{,}000$ g mol^{-1}, $M_w/M_n \approx 1.20$ were checked by GPC. PVP K30 was supplied by Fluka: the technical literature and publications (e.g. Segre et al., 1998) vary for this polymer, and

* Corresponding author. Tel.: +55 85 33669367; fax: +55 85 33669978.
E-mail address: naricard@ufc.br (N.M.P.S. Ricardo).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.02.025



Scheme 1. Griseofulvin.

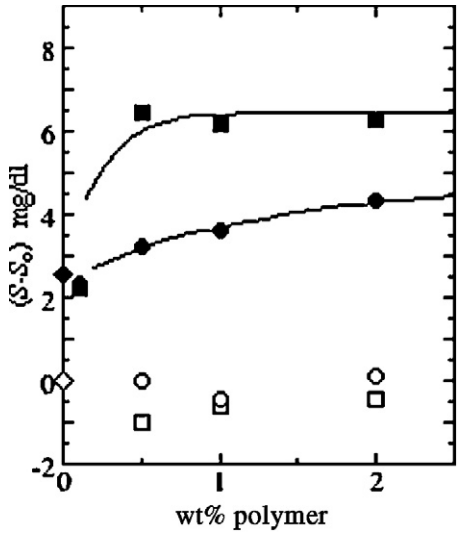


Fig. 1. The effect of addition of (□,■) PEG 35000 and (○,●) PVP K30 on the solubilisation of griseofulvin in excess of that in water alone ($S - S_o$, mg/dl): unfilled symbols, polymers only; filled symbols, polymers with 1 wt% F127. Symbols (◊,♦) indicate values of ($S - S_o$) for water alone and for 1 wt% F127 in water. $T = 37\,^{\circ}C$.

in round figures we assume $M_w \approx 40{,}000\,g\,mol^{-1}$ and $M_w/M_n \approx 3$, making $M_n \approx 13{,}000\,g\,mol^{-1}$. Griseofulvin (Sigma-Aldrich, Poole, Dorset, UK) was passed through a 1 mm^2 mesh sieve before use. Differential scanning calorimetry indicated only one crystalline form of griseofulvin with a melting point of 220.4 °C and a ΔH_f of $115.6\,J\,g^{-1}$; there was no observable transition associated with the presence of an amorphous form of the drug.

A stock solution of 1 wt% F127 in water was used to prepare further stock solutions containing either PEG 35000 or PVP K30 in the range 0.1–2 wt%. Finely powdered griseofulvin (10 mg) was mixed with stock solution (10 ml), and the mixture was stirred at constant temperature (37 °C) for 48 h before being filtered (0.45 μm Millipore filters) to remove unsolubilised drug. The procedure is equivalent to the standard Shake-Flask method. The extent of solubilisation at 37 °C was determined by UV spectroscopy as described by Crothers et al. (2005). The drug-loaded solutions were diluted quantitatively with sufficient methanol to enable determination of the absorbance at optimum wavelength (griseofulvin 292 nm), and this absorbance was compared with a Beer's Law plot for griseofulvin in methanol. The water content after dilution was low enough to allow the calibration with methanol solutions to be used without correction. Blank experiments (no copolymer) gave the solubility of the drug in water. All measurements were carried out in triplicate and the results were averaged.

3. Results

As indicated in Fig. 1 for solutions at 37 °C, dilute solutions of the polymers alone had little effect on the solubility of griseofulvin within the limits of error of our measurements ($\pm 1.5\,mg\,g^{-1}$): at most a slight reduction in solubility over that in water. The solubility of griseofulvin in 1 wt% F127 solutions over that in water, $S - S_o$, was 2.5 mg/dl but this was increased to $S - S_o \approx 6.5$ mg/dl by the addition of 0.5–2 wt% PEG 35000 and to 3–4 mg/dl for PVP K30. The increase in solubility in the F127/PEG solutions, by a factor of ca. 2.5, is comparable with that noted in Section 1 when poly(propylene oxide) is replaced by poly(styrene oxide) as the core forming block.

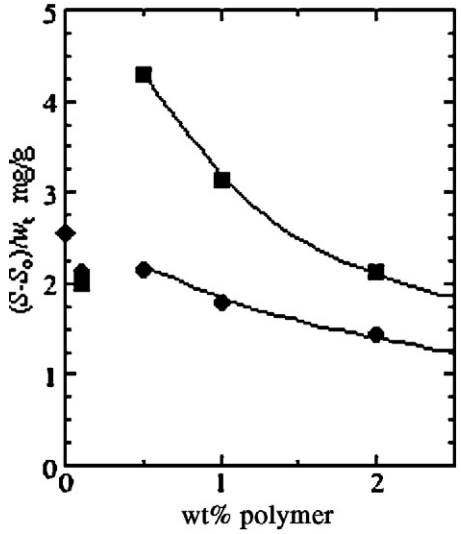


Fig. 2. The effect of addition of (■) PEG 35000 and (●) PVP K30 to 1 wt% solutions of F127 on the solubilisation of griseofulvin in excess of that in water ($S - S_o$, mg/dl) relative to the total concentration (w_t, g/dl) of F127 (1 g/dl) plus that of polymer in solution. Symbol (♦) indicates values of $(S - S_o)/w_t$ for 1 wt% F127 in water alone. $T = 37\,^{\circ}C$.

The results presented in Fig. 2 show the effect of adding polymer on the solubility of griseofulvin per gram of solubiliser in solution, i.e. as $(S - S_o)/w_t$, where w_t is the total concentration of F127 (1 wt%) plus polymer (up to 2 wt%). Considered in this way it is clear that there is no advantage in adding PVP 30K, whereas addition of 0.5 wt% PEG 35000 increases the solubilisation capacity $(S - S_o)/w_t$ to a value approaching double that of 1 wt% F127 alone.

4. Discussion

The increased solubilisation of griseofulvin in the presence of poly(ethylene oxide) is most probably a consequence of the ability of the poly(ethylene oxide) to associate with the micelle corona resulting in an expansion of the micelle and a consequent increase in the amount of this drug that may be solubilised in this region of the micelle; in contrast, PVP is incompatible with the E-blocks of the micelle corona and the effect on solubilisation is expected to be much smaller, as shown by our results.

The solubility of hydrophobic drugs in micellar solutions generally increases with increase in surfactant concentration as a consequence of the increased number of micelles available for solubilisation. Such an increase is seen with solutions of Pluronic F127 alone in water where our measurements, in work associated with this study and yet to be published, indicate a solubilisation capacity for griseofulvin of $S - S_o = 5.6$ mg/dl for 2.5 wt% F127 in water at 37 °C, compared with 2.5 mg/dl for 1 wt% F127. The solubilisation capacity, i.e. the corresponding amount solubilised by a 2.5 wt% F127 solution expressed in terms of unit weight of F127, is 2.24 mg/g. Fig. 2, however, shows that a solubilisation capacity of approximately double this value, $(S - S_o)/w_t \approx 4.5$ mg/g, may be achieved by the addition of a small quantity (0.5 wt%) of PEG 35000 to a 1 wt% F127. This study, therefore, suggests a simple alternative approach to increasing the solubilisation capacity of micellar solu-

tions, avoiding the use of large quantities of surfactant which can be both costly and pharmaceutically undesirable.

Acknowledgements

We thank Dr. Colin Booth for his constant help and advice. This work was supported by the Brazilian Research Council CNPq (N.M.P.S.R.), the PSU Research Fund, Thailand (C.C.) and FUNCAP (C.P.O.), and the Organic Materials Innovation Centre, University of Manchester.

References

Attwood, D., Zhou, Z., Booth, C., 2007. Poly(ethylene oxide) based copolymers: solubilisation capacity and gelation. Expert Opin. Drug Deliv. 4, 533–546.

Attwood, D., Booth, C., 2007. Solubilisation of a poorly aromatic drug by micellar solutions of amphiphilic block copoly(oxyalkylene)s. In: Tadros, Th.F. (Ed.), Colloid Stability and Application in Pharmacy, Colloid and Interface Science Series, vol. 3, pp. 61–68.

Chaibundit, C., Mai, S.-M., Heatley, F., Booth, C., 2000. Association properties of triblock copolymers in aqueous solution: copolymers of ethylene oxide and 1,2-butylene oxide with long E-blocks. Langmuir 16, 9645–9652.

Crothers, M., Zhou, Z., Ricardo, N.M.P.S., Yang, Z., Taboada, P., Chaibundit, C., Attwood, D., Booth, C., 2005. Solubilisation in aqueous micellar solutions of block copoly(oxyalkylene)s. Int. J. Pharm. 293, 91–100.

Elworthy, P.H., Patel, M.S., 1982. Demonstration of maximum solubilization in a polyoxyethylene alkyl ether series of non-ionic surfactants. J. Pharm. Pharmacol. 34, 543–546.

Rekatas, C.J., Mai, S.-M., Crothers, M., Quinn, M., Collett, J.H., Attwood, D., Heatley, F., Martini, L., Booth, C., 2001. The effect of hydrophobe chemical structure and chain length on the solubilisation of griseofulvin in aqueous micellar solutions of copoly(oxyalkylene)s. Phys. Chem. Chem. Phys. 3, 4769–4773.

Segre, A.L., Proietti, N., Sesta, B., D'Aprano, A., Amato, M.E., 1998. Supramolecular structure of the LiPFN-PVP system: ^{19}F NMR studies. J. Phys. Chem. B 102, 10248–10254.

Yalkowsky, S.H., He, Y., 2003. Handbook of Aqueous Solubilities. CRC Press, Boca Raton.