International Journal of Pharmaceutics, 80 (1992) 277–281

IJP 02692

Wettability study of clofazimine and poly(vinyl methyl ether/maleic anhydride) copolymer coevaporates

T.R. Krishnan, I. Abraham and E.I. Vargha Butler

College of Pharmacy, Dalhousie University, Halifax, Nova Scotia B3H 3J5 (Canada)

(Received 29 April 1991)
(Modified version received 15 October 1991)
(Accepted 25 October 1991)

Key words: Clofazimine; PVM/MA copolymer carrier; Coevaporate; Wettability; Contact angle; Enhanced dissolution

Summary

Solid coevaporates of the antileprotic drug, clofazimine, with a poly(vinyl methyl ether/maleic anhydride) copolymer (PVM/MA, Mol Wt 20000) were prepared by the solvent evaporation method. The drug/polymer carrier weight ratios in the coevaporates examined were 1:5, 1:10 and 1:20. The effect of the hydrophilic PVM/MA copolymer on the surface characteristics of the hydrophobic drug clofazimine was studied by performing contact angle measurements on tablets compressed from powders of both the pure components (drug and carrier) and their coevaporates. Contact angles, θ, of sessile drops of both distilled water and acidic, neutral and alkaline aqueous solutions, previously used as dissolution media for the coevaporates, were determined at 37°C. It was found that θ decreased (i.e. the wettability of the coevaporates increased) with increasing PVM/MA copolymer content. The increasing wettability of the coevaporates is consistent with the results obtained on dissolution for the relevant powder samples.

Clofazimine (CLF [3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-(isopropylimino)-phenazine]) is one of the three principal drugs recommended by the World Health Organization (WHO) in the treatment of leprosy (WHO Program Report, 1989). Currently, the drug is being tested in patients with acquired immune deficiency syndrome (AIDS) complicated by *Mycobacterium avium* infection (Medical Letter, 1987).

Correspondence: E.I. Vargha Butler, College of Pharmacy, Dalhousie University, Halifax, Nova Scotia B3H 3J5, Canada.

Clofazimine is a very hydrophobic drug, and practically insoluble in water. The currently marketed formulation of soft gelatin capsule (Lamprene®, Ciba Geigy), containing micronised clofazimine suspended in an oil-wax base, provides a rather low and erratic drug release rate and the extent of absorption differs from patient to patient (Banerjee et al., 1974; Holdiness, 1989). To improve the degree of aqueous dissolution and to enhance systemic drug availability predictably, Krishnan and Abraham (1991) prepared coevaporates (solid dispersions) of clofazimine using the hydrophilic copolymer PVM/MA as carrier.

In a solid dispersion, each individual microcrystal of the drug is intimately encircled by the hydrophilic 'carrier', which readily dissolves in the aqueous medium, leaving the drug in a finely dispersed state. The crystalline state of the drug may be so altered as to change its solubility and dissolution rate, both in vitro and in vivo, hence improving its biopharmaceutical properties. The influence of the properties of both drug and carrier on the change in solubility and/or dissolution rate has been investigated by several researchers. The effects of particle size, shape, surface area, crystallinity and polymorphism of the drug powders (Hilton and Summers, 1986; Westerberg et al., 1986; Flego et al., 1988; Sjökvist et al., 1988, 1989) have extensively been studied. The chemical structure of the carrier (Westenberg et al., 1986; Jafari et al., 1988) and the drug/carrier ratio (Flego et al., 1988) have also been investigated, to mention only a few examples. As stated by Ford (1986) in his review article, during the past 25 years approx. 120 drugs in over 30 carriers have been investigated. However, relatively few wettability studies have been reported on solid dispersions (Flego et al., 1988; Jafari et al., 1988; Imai et al., 1989; Sjökvist et al., 1989) in spite of the fact that the contact angle determined on the surface of such solid dispersions is a direct macroscopic measure of the hydrophobic or hydrophilic character of the substance.

Dissolution tests (Krishnan and Abraham, 1991) indicated a marked increase in the dissolution of clofazimine from its coevaporates, as compared to the untreated drug or physical admixtures of the components in the same proportions as in the coevaporates. The purpose of this work was to gain insight into the mechanism of enhancement of drug dissolution in the coevaporates. In order to reach this goal, we sought to establish the factors which might affect this process. As a first step, the wettability of the coevaporates was monitored by measuring the contact angle, so as to obtain information on the change in hydrophobicity of the surface.

The copolymer (PVM/MA) was received from GAF Chemical Corp. (NJ., U.S.A.). The drug clofazimine was supplied by Astra-IDL Ltd (Bangalore, India) and was used as received. This product matched the British Pharmacopoeia (1988) specifications with respect to its identification. All other chemicals and reagents were of analytical grade. The various coevaporates containing different weight ratios of drug and copolymer (1:5, 1:10 and 1:20) were prepared by evaporating a mixture of solutions of the two in acetone in a rotary evaporator (Buchi Rotavapor®, Switzerland) under reduced pressure. Details of the preparative procedure and their assay are reported elsewhere (Krishnan and Abraham, 1991). The flaky coevaporates were powdered, dried under vacuum and finally passed through no. 85 mesh sieve ($d < 170$ μm). The physical admixtures of the same composition as the coevaporates were prepared by intimately mixing drug and copolymer, followed by treatment as described above.

A mass of 0.150 g powder was compressed into a tablet by using a laboratory press (Carver Laboratory Press, U.S.A.) with a custom-made, highly polished punch-die set of 11.2 mm diameter. The punches were carefully cleaned, rinsed with distilled water and acetone and dried prior to tablet preparation. A pressure of 5530 kg/cm^2 was applied for 2 min. Thin films of the samples on highly cleaned glass slides were prepared by using the solvent casting method, from 2 mg/ml acetone solutions. The wettability of pure clofazimine and copolymer, as well as that of the coevaporates and selected admixtures, was characterised by measuring the advancing contact angles, θ, of different liquid droplets on the surface of each sample. The contact angles of distilled water (on both films and tablets) and three selected liquids (N/10 HCl, pH 1.2; 0.5 mM monobasic potassium phosphate buffer, pH 7.5; N/1500 NaOH, pH 10.0 [on tablets only]) were determined by means of the sessile drop method (Neumann and Good, 1979), using a Rame-Hart type Contact Angle Goniometer (Model NRL-100; NJ, U.S.A.). Advancing contact angles were measured on freshly prepared tablets immediately (within 30 s) after positioning the liquid drop onto the surface, to minimise errors due to the possible penetration of liquid into the tablet. The size of the liquid drop was chosen as 0.2 ml;

TABLE 1

Contact angles of water and aqueous solutions of different pH measured at 37°C on films and / or tablets of pure clofazimine (CLF), PVM / MA copolymer and the coevaporates

Measuring liquid	Contact angle (θ°) (±95% confidence limits) (Weight ratio of CLF/PVM-MA coevaporates)				
	Pure CLF	1:5	1:10	1:20	Pure PVM/MA
On films					
Water	76.2 ± 1.2	71.0 ± 0.7	68.2 ± 0.9	58.8 ± 1.9	44.9 ± 0.9
On tablets					
Water	74.8 ± 0.8	73.6 ± 1.2	71.0 ± 1.3	60.4 ± 1.6	46.5 ± 1.1
Acidic, pH 1.2	73.1 ± 1.2	73.6 ± 1.2	68.3 ± 2.6	59.1 ± 1.4	42.2 ± 1.1
Neutral, pH 7.5	75.2 ± 1.4	71.3 ± 1.7	69.8 ± 1.6	58.3 ± 1.6	45.0 ± 1.4
Alkaline, pH 10.0	74.1 ± 1.7	67.1 ± 2.0	66.7 ± 1.7	53.0 ± 1.6	42.7 ± 1.5

droplets were placed using a 2.0 ml Gilmont® micrometer syringe. Readings were taken on both sides of the droplets to check drop symmetry. The θ measurements were performed at 37.0 ± 0.5°C and at a constant relative humidity. The arithmetic mean of the contact angles was calculated from the 14–32 readings carried out for a given surface with each liquid.

The contact angle results obtained for the films and tablets are summarised in Table 1. The 95% confidence limits are shown, assuming a 't' distribution. The results obtained for the tablets clearly demonstrate a decreasing trend in contact angles (i.e., an increasing trend in wettability) with increasing concentration of PVM/MA in the coevaporates. However, truly significant ($p < 0.05$) decreases in the θ values were exhibited only for the 1:20 coevaporate (the one with the highest polymer content), with all the liquids used. The above trend was also consistent with the contact angles of water measured on the relevant thin films. The overall wettability results reflect the same trend as that observed for dissolution in a preceding report (Krishnan and Abraham, 1991) and is partially reproduced in Table 2 for comparison. Quantitative investigation and analysis of the correlation between wettability and dissolution are deemed to be beyond the scope of the present communication. However, it is evident that as the hydrophilic copolymer component in the coevaporate increases, both the extent of dissolution and the wettability of the coevaporate samples increase. This observation underlines the fact that the process of wetting a solute surface is a prerequisite for its dissolution. No significant difference ($p > 0.05$) in the θ values was found for the drug and the copolymer among the different liquids, using a two-way ANOVA regression

TABLE 2

Percentage of total clofazimine dissolved from powder coevaporates after 2 h in three dissolution media, using U.S.P. Type II apparatus at 50 rpm and at 37°C

Dissolution media	Percentage of total clofazimine dissolved (Weight ratio of CLF/PVM-MA coevaporates)			
	Pure CLF	1:5	1:10	1:20
Acidic, pH 1.2	ND [a]	84.3	90.8	92.5
Neutral, pH 7.5	ND	83.1	88.4	92.5
Alkaline, pH 10.0	ND	88.4	96.0	96.0

[a] Not detectable.

model. The contact angles determined with alkaline droplets for the three coevaporates, however, were significantly ($p < 0.05$) lower than those for the coevaporates with water, acidic and neutral (buffered) solutions. The reason for the occurrence of this phenomenon is not clear at this time.

Advancing contact angles of water (from the height and length of the drop image) measured on the same copolymer carrier (PVM/MA, Mol. Wt 20000) and its coevaporates with another drug, griseofulvin, were reported by Flego et al. (1988). Their contact angle data for the drug, 1:5, 1:10 coevaporates and for the copolymer were given as 57, 41, 22 and 0°, respectively. Since θ_{water} measured for the drug tablet was much higher for clofazimine (75°), than that for griseofulvin (57°), it is not surprising that larger contact angles were also observed for the clofazimine coevaporates. However, it should be noted, that for the PVM/MA copolymer, Flego and coworkers observed a complete wetting with water ($\theta = 0°$), whereas $\theta_{water} = 46°$ was determined in our laboratory. This very large difference in wettability of the copolymer might be attributed to various factors, such as different particle sizes of the powders used ($d < 250$ μm, no. 60 mesh in Flego's work and $d < 170$ μm, no. 85 mesh in our study), also the possibility of using a different compaction force for tablet preparation, different measuring temperatures and even measuring the contact angles in different ways. These factors might considerably influence the porosity and surface smoothness and hence the contact angle obtained, especially for the highly hydrophilic surface.

Wettability characterization for selected physical admixtures was also attempted, without any reliable results.The scatter of contact angles for admixture tablet surface was so large, that no 'true' mean value could be derived from the data. The surface of these tablets exhibited both chemical and mechanical (e.g., roughness) inhomogeneity. Therefore, the contact angles determined for these surfaces are not presented here.

Summarising the results, it is evident that the hydrophilic copolymer PVM/MA improves the aqueous wettability of the hydrophobic drug clofazimine, and that the wettability increases with increasing copolymer concentration in the coevaporate. This method of determining contact angles of aqueous solutions on compressed tablet surfaces could be a useful tool, not only in estimating tablet wettability, establishing a change in hydrophobicity of the surface but also in indirectly predicting the dissolution pattern of active ingredients incorporated within the tablets.

Acknowledgements

The wettability studies were supported by the Natural Science and Engineering Research Council of Canada, through Grant no. 0GP0037393; the authors express their appreciation for the funding. We would also like to thank GAF Chemical Corp., NJ, U.S.A., and Astra-IDL Ltd, Bangalore, India, for donating the samples of PVM/MA copolymer (Gantrez®) and clofazimine, respectively.

References

Banerjee, D.K., Ellard, G.A., Gammon, P.T. and Waters, M.F.R., Some observations on the pharmacology of clofazimine (B663). *Am. J. Trop. Med. Hyg.*, 23 (1974) 1110–1115.

Flego, C., Lovrecich, M. and Rubessa, F., Dissolution rate of griseofulvin from solid dispersions with poly(vinylmethyl ether/maleic anhydride). *Drug. Dev. Ind. Pharm.*, 14 (1988) 1185–1202.

Ford, J.L., The current status of solid dispersions. *Pharm. Acta Helv.*, 61 (1986) 69–88.

Hilton, J.E. and Summers, M.P., A comparison between the *in vivo* serum levels and *in vitro* dissolution of indomethacin-polymer dispersion systems. *Int. J. Pharm.*, 33 (1986) 219–224.

Holdiness, M.R., Clinical pharmacokinetics of clofazimine. *Clin. Pharmacokinet.*, 16 (1989) 74–85.

Imai, T., Nishiyama, T., Ueno, M. and Otagiry, M., Enhancement of the dissolution rates of poorly water-soluble drugs by water-soluble gelatin. *Chem. Pharm. Bull.*, 37 (1989) 2251–2252.

Jafari, M.R., Danti, A.G. and Ahmed, I., Comparison of polyethylene glycol, polyvinyl pyrrolidone and urea as excipients for solid dispersion systems of miconazole nitrate. *Int. J. Pharm.*, 48 (1988) 207–215.

Krishnan, T.R. and Abraham, T., Improved aqueous dissolution of clofazimine from coevaporates using poly(vinyl

methyl ether/maleic anhydride) copolymer. *Drug. Dev. Ind. Pharm.*, 17 (1991) 1823–1842.

Neumann, A.W. and Good, R.J., Techniques of measuring contact angles. In Good, R.J. and Stromberg, R.R. (Eds), *Surface and Colloid Science*, Vol. 11, Plenum, New York, 1979, pp. 31–91.

Sjökvist, E. and Nyström, C., Physicochemical aspects of drug release. VI. Drug dissolution rate from solid particulate dispersion and the importance of carrier and drug particle properties. *Int. J. Pharm.*, 47 (1988) 51–66.

Sjökvist, E., Nyström, C. and Alden, M., Physicochemical aspects of drug release. IX. Investigation of some factors that impair dissolution of drugs from solid particulate dispersion systems. *Int. J. Pharm.*, 54 (1989) 161–170.

The medical letter on drugs and therapeutics, Clofazimine for leprosy and *Mycobacterium avium complex* infections. The Medical Letter Inc., New Rochelle, NY, 29 (1987) 77–78.

Tropical diseases. In Progress in International Research, 1987–1988, 9th Program report, WHO, Geneva, 1989, pp. 93–100.

Westerberg, M., Jonsson, B. and Nyström, C., Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from powdered mixtures. *Int. J. Pharm.*, 28 (1986) 23–31.