

The coupling constant $J_{5,6}$ was consistently about 3 Hz for the *S*-isomers and 5 to 7 Hz for the *R*-isomers. These results are consistent with those reported previously for ampicillin and amoxycillin penicilloates (Bird et al 1983) and provide a useful diagnostic tool for the C-5 configuration of penicilloates. The 3-H and C-2 methyl shifts show no consistent pattern between the 5*R*- and 5*S*-isomers. For 3-H this is contrary to the suggestion of Claes et al (1982) that this shift should be downfield in 5*R*-isomers compared with the 5*S*-isomers. The separation between the shifts of the two C-2 methyls is significantly lower in the 5*R*-isomers than in the 5*S*-isomers for most of the penicilloates but those of methicillin and the side-chain *S* isomers of phenethicillin and propicillin are exceptions.

Optical rotation measurements (see Table 1) showed a decrease with time for all the penicilloates except that from carbenicillin, which showed a small increase with time. This change is consistent with the suggestion of Claes et al (1982) that 5*R*-penicilloates have a more positive rotation than their 5*S*-isomers and the result obtained for carbenicillin penicilloate provides further confirmation that this sample is the 5*S*-isomer. Insufficient sample was available to obtain rotation measurements on the ticarcillin penicilloate sample. However, the very low value of -22.3° given by Munro et al (1978) is consistent with the 5*S* assignment for ticarcillin penicilloate.

We wish to thank Mr S. Woroniecki for supply of the penicilloate samples and Miss M. I. Tingley for help with optical rotation measurements.

References

- Bird, A. E., Steele, B. R., Boles, M. O., Gane, P. A. C. (1982) Nuclear Magnetic Resonance and Circular Dichroism of Penicillins derived from Disubstituted Acetic Acids. *J. Chem. Soc. Perkin I*, 563-569
- Bird, A. E., Cutmore, E. A., Jennings, K. R., Marshall, A. C. (1983) Structure re-assignment of a metabolite of ampicillin and amoxycillin and epimerization of their penicilloic acids. *J. Pharm. Pharmacol.* 35: 138-143
- Branch, S. K., Casy, A. F., Ominde, E. M. A. (1987) Application of ^1H nuclear magnetic resonance spectroscopy to the analysis of β -lactam antibiotics and their common degradation products. *J. Pharm. Biomed. Anal.* 5: 73-103
- Busson, R., Claes, P. J., Vanderhaeghe, H. (1976) Determination of the Configuration of the Four D-Benzylpenicilloates. *J. Org. Chem.* 41: 2556-2561
- Carroll, R. D., Jung, S., Sklavounos, C. G. (1977) Base-Catalyzed Hydrolysis of 6-Aminopenicillanic Acid. The Kinetic and Thermodynamic Products. *J. Heterocyclic Chem.* 14: 503-505
- Claes, P. J., Herdewijn, P., Vanderhaeghe, H. (1982) Penicilloates derived from Penicillanic Acid. *Nouveau Journal de Chimie* 6: 273-275
- Degelaen, J. P., Loukas, S. L., Feeney, J., Roberts, G. C. K., Burgen, A. S. V. (1979) A Nuclear Magnetic Resonance Study of the Degradation of Penicillin G in Acidic Solution. *J. Chem. Soc. Perkin II*, 86-90
- Everett, J. R., Jennings, K. R., Woodnutt, G., Buckingham, M. J. (1984) Spin-echo ^1H NMR Spectroscopy: A new method for studying Penicillin Metabolism. *J. Chem. Soc., Chem. Comm.* 894-895
- Everett, J. R., Jennings, K. R., Woodnutt, G. (1985) ^{19}F NMR spectroscopy study of the metabolites of flucloxacillin in rat urine. *J. Pharm. Pharmacol.* 37: 869-873
- Fong, G. W. K., Johnson, R. N., Kho, B. T. (1983) Study on the rate of epimerization of Amoxycillin β -penicilloic acid to its α -form in aqueous solutions using High Performance Liquid Chromatography. *J. Chromatog.* 255: 199-207
- Ghebre-Sellassie, I., Hem, S. L., Knevel, A. M. (1984) Epimerization of Benzylpenicilloic Acid in Alkaline Media. *J. Pharm. Sci.* 73: 125-128
- Haginaka, J., Wakai, J. (1985) Epimerization of Benzylpenicilloate in Alkaline Aqueous Solutions. *Chem. Pharm. Bull.* 33: 2605-2608
- Haginaka, J., Wakai, J. (1987) Liquid Chromatographic determination of Amoxycillin and its metabolites in human urine by postcolumn degradation with Sodium Hypochlorite. *J. Chromatog.* 413: 219-226
- Munro, A. C., Chainey, M. G., Woroniecki, S. R. (1978) Preparation and Immunological cross-reactions of Penicilloic and Penilloic Acids. *J. Pharm. Sci.* 67: 1197-1204

J. Pharm. Pharmacol. 1989, 41: 483-484
Communicated October 21, 1988

© 1989 J. Pharm. Pharmacol.

Solute adsorption and concentration-dependent permeability in certain polymer films

R. S. OKOR, *Department of Pharmaceutics, University of Benin, Benin City, Nigeria*

Abstract—Certain parameters (solute adsorption, permeability and swellability) of films of a cationic acrylatemethacrylate copolymer have been determined as functions of the solute (sulphacetamide sodium) concentrations. Both permeability coefficients and the free (unadsorbed fraction of solute increased almost proportionately during increase in solute concentration 1-5%, above 5%, further increase in the fraction of free solute was slight, while the permeability coefficients decreased slightly. The solute also reduced film swellability but the observed concentration-dependent permeability related more to the adsorption phenomenon.

Abdel-Aziz et al (1975) and Okor (1982) have indicated the potential of acrylatemethacrylate copolymer films in controlled release applications. Solutes permeate these films by a pore flow mechanism, (Okor & Anderson 1986a). In a preliminary report aimed at developing an ocular delivery system of sulphaceta-

mid sodium, it was shown that the permeability coefficient versus concentration profile of the solute exhibited an initial increase followed by a decrease (Okor & Anderson 1986b). The suggestion was that electrostatic interaction of the ionic solute with cationic groups in the polymer structure caused the initial increase (the phenomenon being significant only at low solute concentrations), while the decrease was associated with the solute potential for reducing the aqueous swellability of the films. In the present report, physical adsorption of the solute by the polymer is presented as evidence for the proposed mechanism of solute-polymer electrostatic interaction.

Materials and method

A hydrophilic, but water insoluble, acrylate methacrylate polymer containing small proportions of cationic (quaternary

ammonium) groups (Eudragit RL 100) was received from RHOM Pharma, Darmstadt. Glycerol triacetate (reagent grade, BDH) was used as plasticizer while sulphacetamide sodium (Analar, BDH) was used as solute.

Films (thickness, $19.8 \pm 0.3 \mu\text{m}$) were prepared by casting on PTFE mold from an acetone solution containing the polymer (2.5% w/w) and the plasticizer (0.5% w/w) using the method of Abdel-Aziz et al (1975).

Solute permeation rate through the films (exposed film area 23 cm^2) was measured using the method of Abdel-Aziz et al (1975). Initially the donor compartment contained 135 mL permeant solution and the acceptor compartment, 135 mL water. The film lower surface (in contact with mold during casting) was upstream and the experiment was conducted at $30 \pm 0.5^\circ\text{C}$, stirring the compartment fluids at 300 rev min^{-1} with magnetic stirrers. The amount (M) of sulphacetamide sodium appearing in time (t) in the acceptor fluid was determined spectrophotometrically (using the Unicam SP800) at λ_{max} 260 nm. Plots of M versus t were constructed and the slopes used to calculate the permeability coefficient (P) based on the steady state equation (Flynn et al 1974):

$$M/t = \frac{P C_0}{L} \quad (1)$$

C_0 is the initial donor fluid concentration and L , the film thickness. The amount of solute transferred to the acceptor compartment was much less than the donor concentration, thus approximating to an acceptor sink situation. The experiment was carried in 5 replicates, individual results were reproducible to $\pm 7.5\%$ of the mean.

The amount of fluid in the wet films (after contact with water or permeant solutions at 30°C for 3 h) was obtained from the difference between its wet weight and the weight after drying at 70°C for 3 days to a constant weight. The volume fraction of fluid V in the wet film was calculated using the formula (Okor & Anderson 1986b):

$$V (\text{index of film swelling}) = \frac{1.0044 (m - md)}{1.0044 (m - md) + 0.8855 md}$$

where m is the wet film weight, and md is the dried film weight. 1.0044 and 0.8855 are the specific volumes $\text{cm}^3 \text{ g}^{-1}$ of water and polymer, respectively, at 30°C determined by fluid displacement method.

Adsorption of solute by the polymer was determined as follows: The polymer (1 g, in fine powder to increase surface area) was placed in a 50 mL conical flask with stopper, and 20 mL permeant solution (previously equilibrated at 30°C) added. The flask was shaken 100 rev min^{-1} in a water bath at 30°C for 10 min (time for maximum adsorption). After 5 min standing, 10 mL supernatant was centrifuged for 2 h and samples of the clear layer removed for analysis to determine the residual (unadsorbed) solute. The fraction adsorbed was calculated as the difference between the initial and final concentration divided by the initial concentration.

Results

Data from the adsorption experiment revealed a decrease in the fraction of the initial concentration of permeant adsorbed as the concentration of the permeant increased from 0.1 to 10% w/v. The unadsorbed fraction (free for permeation) increased consequently (Fig. 1A); this increase was more rapid between 0.1 to 5% w/v permeant and became less prominent above 5% w/v. The pattern of change in permeability coefficients was similar (Fig. 1C) suggesting a correlation between these two (adsorption and permeability) parameters. Film swellability decreased generally with increase in permeant concentration (Fig. 1B).

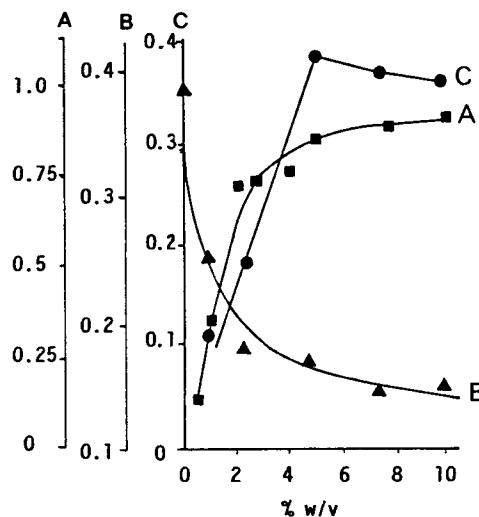


FIG. 1. Changes in the fraction of free (unadsorbed) permeant (ordinate A), swellability of the films (B), and film permeability coefficients, $\text{Cm}^2\text{S}^{-1} \times 10^{-7}$ (C), with increase in permeant concentration (abscissa: % w/v).

Discussion

The observed decrease in film swellability was perhaps a consequence of solute adsorption on the hydrophilic (cationic) sites to impair film hydration. This aspect was expected to lead to a decrease in film permeability generally in the test permeant concentration range 1 to 10%. The initial increase in the apparent permeability coefficients observed in the permeant concentration range, 1 to 5% may be associated with a more dominant factor, the increase in the fraction of permeant available in a unit concentration for permeation (see Fig. 1A). The actual amount of solute adsorbed per gram polymer was maximum at 5% permeant concentration suggesting a saturation of adsorption sites at this point. Consequently the effect of solute adsorption on film permeability did not extend beyond this point. The slight decrease in film permeability in the permeant concentration range, 5 to 10% therefore relates to the corresponding slight decrease in film swellability.

Modification of film plasticization and swellability form a basis for concentration-dependent permeability (Craver 1970; Okor & Anderson 1986b). The present finding suggests that solute adsorption may also contribute to concentration-dependent permeability in polymer films.

The author wishes to thank Professor W. Anderson, formerly of the department of Pharmaceutics, University of Strathclyde, Glasgow, for his advice in this work.

References

- Abdel-Aziz, S. A. M., Anderson W., Armstrong, P. A. M. (1975) Transit in free films. Casting solvent effects. *J. Appl. Polym. Sci.* 19: 1181-1192
- Craver, J. K. (1970) Classification of hydrogen-bonding solvents by sonic velocity methods. *Ibid.* 14: 1755-1762
- Flynn, G. I., Yalkowsky, S. H., Roseman, T. J. (1974) Mass transport phenomena and Models: Theoretical concepts. *J. Pharm. Sci.* 63: 479-510
- Okor, R. S. (1982) Effect of polymer cation content on certain film properties. *J. Pharm. Pharmacol.* 34: 83-86
- Okor, R. S., Anderson, W. (1986a) Variation in polymer film structure and thickness-dependent permeability. *J. Appl. Polym. Sci.* 31: 291-293
- Okor, R. S., Anderson, W. (1986b) Swellability of cast films of an acrylate-methacrylate copolymer in aqueous solutions of certain permeants and concentration-dependent permeability. *J. Macromol. Sci.-Phys.* B25 (4): 505-513