

# Effect of polymer cation content on certain film properties

R. S. OKOR

*Department of Pharmaceutics, University of Benin, Benin City, Nigeria*

Mixing of two acrylate-methacrylate copolymers designated A and B and differing only in cation (quaternary ammonium) content in the ratio 2:1 (A:B) provided a means of varying polymer cation content in resulting films. Film permeability to the permeant urea, increased with increase in cation content; a two phase change characterized by a slow increase at a low cation content level followed by about 13 times more rapid increase at a high cation content level. The point of transition from the slow to the rapid phase was 53 moles cation per mole polymer chain. On average a 2 fold increase in cation content resulted in a 500 fold increase in permeation rate. Increases in film swelling and pore size also accompanied the increase in cation content, but the change in permeability was more positively correlated with the corresponding change in film pore size. Mutual repulsion by charged groups during film formation is suggested as a factor promoting the formation of large pores in the film at high cation content.

The phenomena of drug transit through polymer films have been frequently exploited in the design of controlled release devices. Under given conditions the rate of molecular transport through such films may be affected by changes in film (single or layered) structure (Okor & Anderson 1978), casting solvent type (Abdel-Aziz & Anderson 1974), inclusion of additives (plasticizers) in film composition (Donbrow & Friedman 1975), film thickness, and polymer chemical structure, e.g. presence of functional groups. Earlier studies (Lehmann 1968; Okor & Anderson 1979) have shown that a small addition of an acrylate-methacrylate copolymer, containing a small proportion of quaternary ammonium (cationic) groups, to a similar polymer but having a higher cation content, caused a drastic fall in the permeabilities of resulting films. Changes in hydrophilic (swelling) properties and film pore structure were adduced by the previous workers to account for the observed changes in film permeability as polymer cation content varied; however no evidences for these effects of cationic groups have been reported. A study of the effect of polymer cation content on film swelling and pore structure has therefore been undertaken with a view to establishing correlations which may exist between these properties (swellings and/or pore structure) and permeability.

## MATERIALS AND METHODS

Two acrylate-methacrylate copolymers containing small proportions of cationic (quaternary ammonium) groups and designated here as A and B were

received (Rhom Pharma Darmstadt) under the trade names Eudragit RL 100 and RS 100, respectively. A and B differ only in cation content in the ratio 2:1 (A:B) and have an average molecular weight of 150 000. Glycerol triacetate (reagent grade) and acetone (analar) were used as plasticizer and casting solvent, respectively. Urea (analar grade) was selected as test permeant because of its ease of analysis and its high permeability generally in the polymer films studied.

## *Determination of polymer cation (quaternary ammonium) content*

Total nitrogen in the polymer was determined using the micro-Kjeldahl method (Steyermark 1961). 1 mol of cationic group contains 1 mol of nitrogen; on this basis the formula for calculation of cation content (mol cation mol<sup>-1</sup> polymer chain) was derived (Okor 1980) thus, cation content

$$= \frac{1500}{14} X$$

where X is the % w/w nitrogen in the polymer A or B. The average cation content in a mixed polymer (containing A and B) was calculated from the proportions of A and B in the mixed polymer.

## *Film preparation and evaluation*

Single films of polymers A and B,  $19.8 \pm 0.3$  and  $39.4 \pm 0.7$   $\mu\text{m}$  thick, were cast on PTFE moulds from acetone solution containing 2.5% w/w of polymer and 0.5% w/w of glycerol triacetate as

plasticizer, using the casting technique of Abdel-Aziz et al (1975). From the two polymers A and B containing cationic groups, 66 and 33 mol mol<sup>-1</sup> polymer chain, respectively, films of intermediate cation contents were prepared by mixing appropriate quantities of A and B in the casting solution (see Table 1). Resulting films were placed in a desiccator (charged with dried silica gel) 24 h before their evaluation.

Table 1. Cation content of polymers obtained by mixing polymers A and B.

Polymer I	Polymer A	Composition % B	Polymer cation content; mol mol <sup>-1</sup> polymer chain
A	100	0	66
A1.8	80	20	59
A1.6	60	40	53
A1.4	40	60	46
A1.2	20	80	40
B	0	100	33

Urea permeation rate through the film was determined according to Abdel-Aziz et al (1975) in a double compartment (donor and acceptor) permeation cell. The experiment was conducted at 30 ± 0.05 °C with stirring of compartment fluids, 300 rev min<sup>-1</sup> with magnetic stirrers. At zero time the donor compartment contained urea 10% w/v solution in water, whilst the acceptor contained water, each 135 cm<sup>3</sup>. The exposed film area was 23 cm<sup>2</sup> and the amount of urea appearing in the acceptor fluid was determined spectrophotometrically (Watt & Chrisp 1954) at 1 hourly intervals for 5 h. Film lower surface (in contact with substrate during film formation) was upstream in all permeation experiments and each determination was carried out in four replicates. The results were used to calculate the mean permeation rate.

Film strips (length 4.6 cm, width 1.3 cm, and thickness 39.4 × 10<sup>-4</sup> cm) were equilibrated in water, 30 °C for 3 h (time for maximal swelling) to determine increases in film dimensions which were used to calculate the % increase in film volume (index of film swelling).

Surface and cross section of film specimens were coated with carbon and gold and examined electronmicroscopically (Phillips SEM 500) to determine film pore structure (size and number). Coating and electronmicroscopic technique were described by Okor (1980). Films were stored in a desiccator containing dried silica gel (not more than 7 days) after casting. Specimen of the dry films (1 cm

diameter) were mounted on aluminium stubs of diameter, 1 cm, using a double sided pressure sensitive adhesive tape. The specimens were vacuum coated, first with carbon in a coating machine (Balzer evaporator, BA 3) for a sufficient time to produce a change in colour of the specimen from colourless to blue, indicating that a carbon coat of thickness 0.024 µm has been deposited on the film surface. A very thin gold coat (gold shadow) was then applied on the carbon coat by evaporating gold particles in vacuo from a piece of gold wire using the Nanotech (mini 250) vacuum coating machine. Cross sections of the films were made using a sharp scapel blade and were similarly coated with carbon followed by gold shadowing. Coated film specimens were examined using a scanning electron microscope at several magnifications up to a maximum of 10 000 which was the limit for clear resolution films, previously wetted (to simulate the conditions of permeation experiment) became brittle rapidly after blotting out surface water, hence this pretreatment of the films was avoided. As a result of the hydrophilic character of the polymers the films may swell to various degrees in an aqueous medium (see Fig. 1).

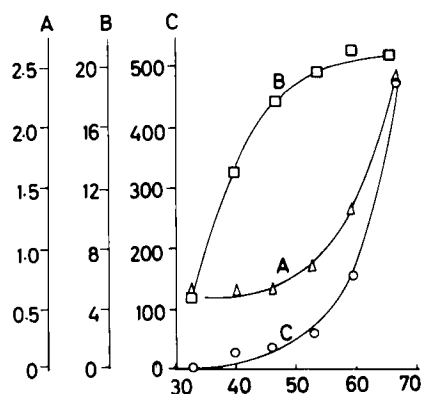


Fig. 1. Changes in film properties at 30 °C with variations in polymer cation content (abscissa: mol cation mol<sup>-1</sup> polymer chain). Ordinate: A = film internal pore size µm B = film swelling %; C = permeation rate, mg h<sup>-1</sup>.

Film specimens were examined at several magnifications up to a maximum of 10 000 which was the limit for clear resolution. Mean pore size  $\bar{X}_p$  was calculated using the formula:

$$\bar{X}_p = \frac{\sum F X_p}{\sum F}$$

where F is the frequency of each size  $X_p$ . For each film three representative micrographs were used for pore size determination.

The volume fraction of water in the films after contact with water 30 °C, 3 h (time for maximal water uptake) was calculated and used as the index of film porosity.

#### RESULTS AND DISCUSSION

The mass of urea, mg, permeating through the film from donor to acceptor compartment was plotted against time h. Permeation rates, mg h<sup>-1</sup> were calculated from slopes of the linear portions of such plots. A two fold increase in cation content, from 33 to 66 mol mol<sup>-1</sup> polymer chain resulted in about 500 fold increase in urea permeation rate (Fig. 1). However, this change in permeability was complex characterized by a slow increase at the low cation content level (33 to 53 mol mol<sup>-1</sup> polymer chain) followed by a more rapid increase at the higher cation content level (see Fig. 1); for example the slow and rapid increase in urea permeation rate as cation content varied (Fig. 1) were on average 2.6 and 33 mg h<sup>-1</sup> respectively for each 1 mol increase in cation content. 53 mol cation mol<sup>-1</sup> polymer chain thus represents the critical cation content for the transition from the slow to the rapid increase phase.

These findings may be associated with—(a) the potential of the cationic group for promoting water uptake by the polymer and hence film swelling during aqueous permeation experiments and/or (b) the mutual repulsion of cationic groups during film formation which may promote the formation of large size pores in resulting films.

##### (a) Film swelling and permeability

Water has a potential for plasticizing the polymer chains and the resultant increase in film flexibility in turn facilitates water swelling of the films. This relation between film flexibility and swelling is supported by the well known effects of cross linking in minimizing film flexibility and decreasing film swelling (Ratner & Miller 1972; Yasuda & Lamaze 1971). In the present study an increase in cation content was accompanied by an increase in film swelling (index of film flexibility), the extent of which is shown in Fig. 1. Swelling may be expected to increase porous permeation by increasing the pore diameters; solute permeation through the polymer films studied has been shown to occur mainly by a sieve (pore flow) mechanism (Abdel-Aziz et al 1975).

It can be seen (Fig. 1) that the increase in film swelling was accompanied by an increase in urea permeation rate. However absence of parallelism in these two changes suggests that the increase in film

permeability did not depend on film swelling only but may depend more significantly on other factors such as the changes in film pore structure.

##### (b) Film pore structure and permeability

Sizeable pores could not be demonstrated electronmicroscopically on film surfaces; perhaps the surface pores were smaller than the limit of resolution of the microscope which was 0.03 μm calculated on the basis that the maximum magnification for clear resolution was 10 000.

An alternative method for pore size determination, e.g. gas (nitrogen) adsorption technique was not readily amenable to this work as preliminary sample treatment would cause film swelling and alter pore size and shape. Film internal pores, however, were readily demonstrated electronmicroscopically using cross sections of film specimens. Electronmicrographs of internal pores of films of polymers B, A1.8 and A reveal that a four fold increase in pore size resulted when polymer cation content was raised from 33 to 66 mol cation mol<sup>-1</sup> polymer chain. Pore size distribution (cumulative % over size versus pore diameter) curves for the three films of polymers B, A1.8 and A (Fig. 2) clearly reveal a four fold increase in median pore diameter (i.e. pore diameter corresponding to 50% over size) as polymer cation content was doubled. Unlike the change in film swelling the increase in the film internal pore size can be positively correlated with the increase in the film permeability (see Fig. 1); thus during a change in cation content from 33 to 53 mol mol<sup>-1</sup> polymer chain, both pore size and urea permeation rate increased slowly, about 0.01 μm and 2.6 mg h<sup>-1</sup> respectively, for each 1 mol increase in cation content; Above 53 mol cation mol<sup>-1</sup> polymer chain both film internal pore size and urea permeation rate

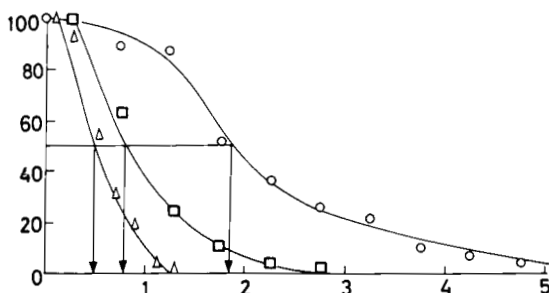


Fig. 2. Pore size distribution in the internal structure of films differing in cation content: (mol cation mol<sup>-1</sup> polymer chain) ○ 66; □ 53; △ 33. Ordinates: Cumulative % oversize, abscissa: pore diameter, μm.

now increased rapidly by about 0.13  $\mu\text{m}$  and 33  $\text{mg h}^{-1}$  respectively for each 1 mol increase in cation content. Porosities of film of polymers A and B were virtually equal, 0.387 and 0.329 respectively; films of polymer A which has the larger pore size had the fewer pores compared with films of polymer B.

The 500 fold difference in the permeabilities of the two types of films might therefore be more significantly associated with the four fold difference in mean pore size, rather than pore number. The greater difference in film permeabilities compared with the difference in the mean pore size could be explained by assuming firstly that the change in surface pore size with polymer cation content would almost parallel the observed changes in the film internal pore size (see Fig. 1), and secondly that surface pores in films containing fewer cationic groups (less than 53 mol cation  $\text{mol}^{-1}$  polymer chain) could be critically small (of sizes comparable to permeant molecular size) resulting in restricted permeation.

The formation of large pores when polymers of high cation content are used in film casting may relate to the mutual repulsion of the cationic groups during film formation. Pore formation theory (Koenhen et al 1977) suggests that the gelation of the cast polymer solution into a film commences by the separation of polymer solid in the form of solid droplets from a supersaturated solution; the droplets enclose an internal fluid solvent phase and they will eventually contact each other to form an interconnected porous structure, with the polymer as continuous phase and solvent the disperse or pore phase. Eventual pore size in such a system will be governed by the balance between the intermolecular attractive and repulsive forces. The lesser repulsive forces with decrease in cation content will result in the operation of greater cohesive forces during film formation culminating in smaller but more numerous pores. High cation content (as in films of polymer A) should

by mutual repulsion of cationic groups surrounding the internal solvent (disperse) phase lead to the formation of large pores.

Thus the introduction of charged functional groups (with mutual repulsion) in polymer structure provides a means of increasing pore size, swelling, and hence permeability of resulting films, however no simple relationships between cation content and these properties emerged. The basis of the cation effects suggest that similar changes in film properties should be obtained whether or not the content of charged groups in the polymer had been varied by using mixed polymers (as in this work) or pure polymers. These findings may be exploited in the optimization of drug delivery through polymer films.

#### Acknowledgement

The author wishes to thank Professor W. Anderson of the Department of Pharmaceutics, University of Strathclyde, Glasgow, U.K. for his valuable advice in this work.

#### REFERENCES

- Abdel-Aziz, S. A. M., Armstrong, P. A. M., Anderson, W. (1974) *J. Pharm. Pharmacol.* 26: Suppl. 131P-132P
- Abdel-Aziz, S. A. M., Anderson, W., Armstrong, P. (1975) *J. Appl. Polym. Sci.* 19: 1181-1192
- Donbrow, M., Friedman, M. (1975) *J. Pharm. Pharmacol.* 27: 633-646
- Koenhen, D. M., Mulder, M. H. V., Smolders, C. A. (1977) *J. Appl. Polym. Sci.* 21: 199-205
- Lehmann, K. (1968) *Drugs made in Germany* 11: 34-36
- Okor, R. S., Anderson, W. (1979) *J. Pharm. Pharmacol.* 31: 78p
- Okor, R. S. (1980) 'A study of certain factors which influence solute permeability of polymer films? Ph.D. Thesis, University of Strathclyde, Glasgow, U.K.
- Ratner, B. D., Miller, I. F. (1972) *J. Polym. Sci. A1*. 10: 2425-2429
- Steyermark, A. L. (1961) 'Quantitative organic micro-analysis', Academic Press, New York
- Watt, G. W., Chrisp, J. D. (1954) *Anal. Chem.* 26: 452-454
- Yasuda, H., Lamaze, C. E. (1971) *J. Macromol. Sci. Phys.* B5 (1): 111-114