

Surface Differences and Solute Permeability in Films of Certain Acrylic-Methacrylic Ester Polymers

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Synopsis

The influence of certain aspects of film surface on the diffusion of urea in aqueous solutions through films cast from two acrylic-methacrylic ester polymers has been investigated. Greater rate of permeation by urea occurred in films of both polymers when the lower surface (that in contact with the substrate during casting) was the entry surface for urea than when the upper surface (that in contact with the atmosphere during casting) was the entry surface. Furthermore, this difference between the upper and lower surfaces was more marked in film cast from one of the polymers; and scanning electron micrographs of films of the two polymers revealed differences in gross surface structure. Changes occurred in both upper and lower film surfaces during exposure to urea solution, the lower surface developing larger pores on exposure while smaller pores were observed on the upper side after exposure. The upper-lower surface differences occurred in films of both polymers. The less hydrophilic film (Eudragit RS100) was associated with lower overall permeation rate for urea and smaller postpermeation mean pore size on both upper and lower surfaces than the more hydrophilic film (Eudragit RL100). The relationship between permeability and changing microscopic appearance of the surfaces is discussed and pictorial evidence of porous structure presented.

INTRODUCTION

Polymeric films permit the transport of liquids, gases, and vapors, a property termed permeation. This property may determine the potential or actual usefulness of the polymer in applications related to the study and use of drugs. Thus, drug particles and medicinal tablets are frequently coated with films; medicines containing drugs for external application can take the form of films; biologic investigation of drug absorption frequently calls for films as model absorbing membranes; replacement artificial kidneys in hemodialysis are essentially films; films are used in packaging medicines and other substances. In every instance, passage of substances through the film in one or both directions bears directly on its effective integrity and usefulness. Polymeric materials, for example, ethylcellulose and acrylates, which are generally insoluble in the pH range of gastrointestinal content, are frequently used to coat tablets and drug particles, the active ingredient being released from such dosage forms by permeation through the polymer film.

While the water vapor permeability of free polymer film has been frequently measured^{1,2} with the purpose of indicating general film permeability, few studies

appear to have been published on the drug permeation characteristics of films cast specifically for this purpose, reliance usually being placed on commercially available films for which bilateral homogeneity is tacitly assumed. At best, correspondence between results from model film systems and performance of the film in practice must be tenuous or imagined, and much more requires to be done to characterize in realistic manner the films used in model systems.

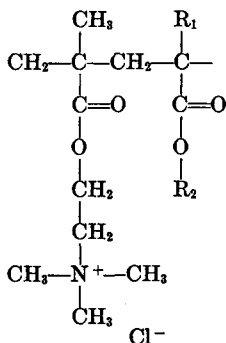
One area of current interest where the characteristics of drug passage through a film are important is that of release of drugs from film-coated tablets, and this investigation originated during work in that area. It appears that hitherto the techniques used in testing permeability properties of polymeric films generally have not called for definition of film surface relative to any effect it may have on drug transit properties.^{3,4} Our preliminary investigations have shown that this can be important,⁵ and we now consider the effect of film surface on solute passage in greater detail.

EXPERIMENTAL

Materials

Eudragit RL100 and RS100 were obtained from Rohm and Haas G.m.b.H., Darmstadt, Germany. Eudragit polymers are formed by polymerization of acrylic and methacrylic esters; they contain a small proportion of quaternary ammonium groups which confer hydrophilic properties on the film.

Units of Eudragit RL and RS are as follows:



where $R_1 = \text{H}$ or CH_3 , and $R_2 = \text{CH}_3$ or C_2H_5 . The molar ratios of quaternary ammonium groups to polymer chain are 1:20 and 1:40 for Eudragit RL100 and RS100, respectively; and this is stated by the manufacturers to be the sole difference between the two polymers. The solubility of these polymers is unaffected by pH,⁶ although swelling occurs in aqueous media. Swelling characteristics, determined after the method of Ratner⁷ but using an oven temperature of 70° gave 24-hr swelling at 37°C of 9.3% and 58.7% for Eudragit RS100 and RL100, respectively, in urea (10% w/v) solution and 6.7% and 62.0% for Eudragit RS100 and RL100, respectively, in water.

Casting Technique

A solution containing 2.5% w/w polymer and 0.5% w/w glycerol triacetate was prepared in acetone using overnight stirring in a flask sealed to prevent evaporation. The solution was filtered through sintered glass (porosity 3), and 5

cm³ of the clear filtrate was poured into circular PTFE molds (diameter, 7.30 cm; depth, 1.0 mm), which had been machined on a lathe from 1/4-in. PTFE sheet with a round-nosed facing tool with fine cross feed giving best possible finish but leaving a spiral core of maximum depth 1 μm and maximum width 25 μm .

The mold was covered with an inverted funnel (stem orifice diameter 0.565 cm) to control solvent evaporation⁸ and placed on a leveled surface in a laminar flow hood (Microflow laminar airflow station), airflow 0.5 msec⁻¹, and relative humidity approx. 50%. Solvent was permitted to evaporate for 24 hr at ambient temperature before transference of the formed film to a desiccator containing silica gel, where it was stored for a further 24 hr before use. No residual acetone could be detected using gas-liquid chromatography or a gas cell in conjunction with infrared spectroscopy. Film thickness (digital Mutatoyo micrometer reading to 1 μm) averaged 21.0 μm with a coefficient of variation of 5.7%.

The film surface exposed to the atmosphere during casting is designated *upper surface*; the surface in contact with the mold, *lower surface*.

Film Evaluation

Permeability. A permeability cell (Fig. 1) was constructed in perspex after Gonzales et al.⁹ It consists of two chambers separated by the film under investigation. The assembled cell was ascertained leak proof,⁵ and the experiment was conducted in a thermostatically controlled waterbath at 36.98° (standard deviation, 0.005°).

Aqueous urea solution, 137 cm³ of 10% w/v, and distilled water, or solvent heated to bath temperature, were simultaneously introduced into the donor and acceptor compartments, respectively, at the commencement of the experiment. Mixing in both compartments was by magnetic stirring at 300 rpm calibrated stroboscopically. Samples of 2 cm³ were removed from the acceptor compartment at time intervals and the urea concentration determined spectrophotometrically.¹⁰ Corresponding volumes were removed from the donor compartment to maintain hydrostatic balance, this, however, having the disadvantage of limiting the number of samples which could be withdrawn.

Upper and lower film surfaces were exposed to the donor compartment using a fresh film for each exposure, and results from at least four film samples were used in each experiment.

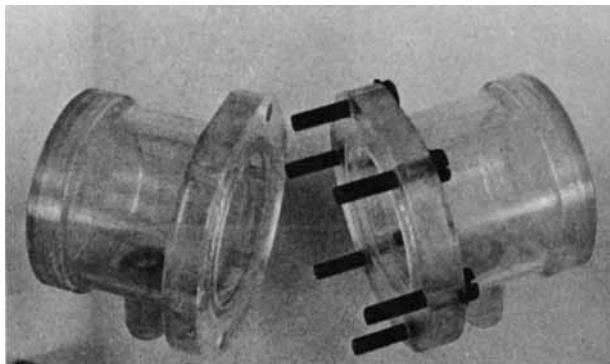


Fig. 1. Dismantled dialysis cell.

Scanning Electron Microscopy. Films were stored seven days in a desiccator containing silica gel after use in permeability studies before processing for electron micrographs, and specimens of the films were examined both before and after permeability studies using a Cambridge scanning electron microscope. Photographs were taken of both upper and lower surface of each film which had been exposed to urea.

Films were mounted using double-sided pressure-sensitive adhesive tape and were vacuum coated with a gold/palladium mixture. Magnifications best suited to revealing the surface structure were selected.

Pore Size Determination. Each photomicrograph was further enlarged so that final magnifications were as follows: 11,200 and 11,400 for lower and upper surface, respectively, of Eudragit RS100; 1,380 and 1,279 for upper and lower surface, respectively, of Eudragit RL100. The pore size distribution was determined by measuring the diameters of all pores appearing in the field.

RESULTS

Figure 2 shows the difference in urea content of the two compartments with time using film of Eudragit RL100. It can be seen that exposure of the upper surface to the donor urea-containing compartment is associated with a small rate of transfer of the solute to the acceptor compartment, while when the lower surface of the film is exposed to urea a greater rate of transfer to the acceptor compartment occurs. Figure 3 shows the results of the same experiment using Eudragit RS100, the lower side of the film again exhibiting greater permeability to urea. Comparison of Figures 2 and 3, however, shows that the less hydro-

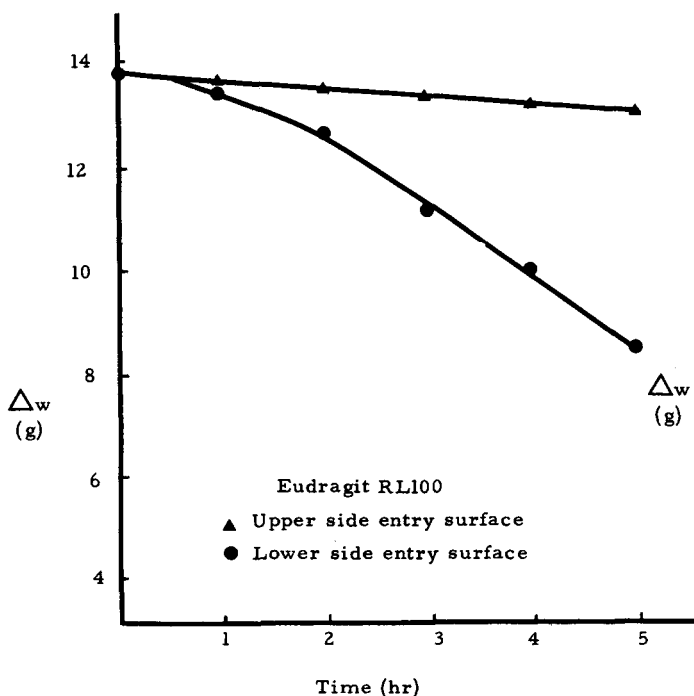


Fig. 2. Rate of passage of urea: RL100.

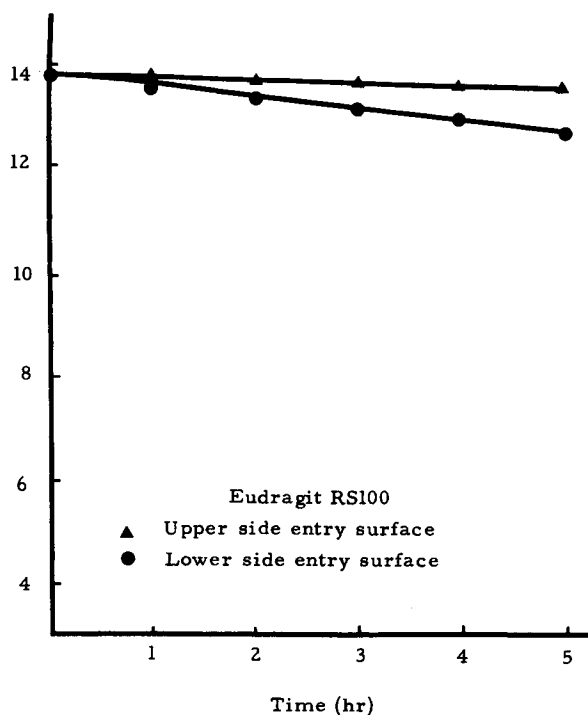


Fig. 3. Rate of passage of urea: RS100. Δw , Difference in weights (g) of urea between donor and acceptor compartments.

philic film Eudragit RS100 also exhibits lower permeability to urea than the more hydrophilic Eudragit RL100. The rate of transfer is such that after 2 hr of permeation, 26.2 mg/cm² more urea has passed through the lower than the upper surface with RL100, and 13.1 mg/cm² more urea has passed through the lower than the upper surface with RS100.

Figure 4 shows scanning electron photomicrographs of the upper and lower surfaces of the two types of film freshly cast; 4a and 4c are upper surfaces, 4b and 4d, lower surfaces of Eudragit RL100 and RS100, respectively. The striations in the lower surfaces are moldings of the machined surfaces of the PTFE casting molds.

Figures 5a and 5b show the upper and lower surface of Eudragit RL100, respectively, after the lower surface had been exposed to urea permeation for a period of 5 hr. Figures 5c and 5d show the same type of film when the upper surface has been exposed to urea. Considering Figure 5 as a whole, it appears that when the lower side of the film has been exposed to urea, larger and more numerous pores develop. These pores appear as craters in 5a and 5b whereas, in 5c and 5d, a blister-like appearance is observed. What the relationship is between these two forms has yet to be elucidated.

For comparison, Figures 6a and 6b show the appearance of the less hydrophilic Eudragit RS100, greater magnification being required for definition of the surface. The pores are much smaller in RS100, and this is in accord with the results of the permeability studies (Fig. 3), smaller pore size seemingly being associated with lower rate of urea transfer.

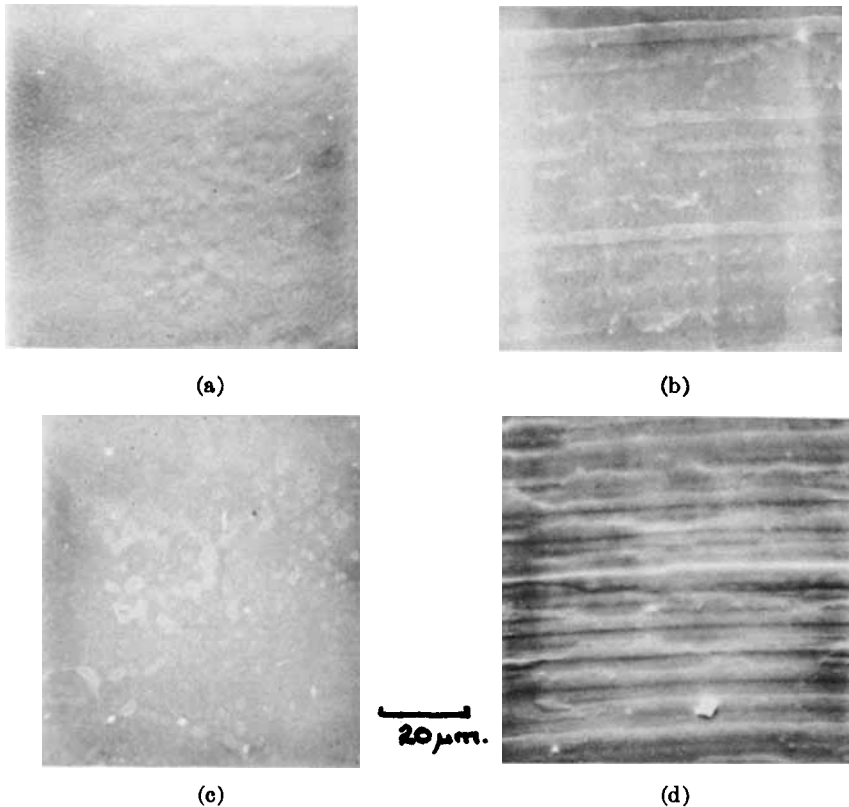


Fig. 4. Cast films of Eudragit polymer on Teflon: (a) upper surface RL100; (b) lower surface RL100; (c) upper surface RS100; (d) lower surface RL100.

Pore size distribution of the film (Fig. 7) reveals a striking difference by one order of magnitude in the size of pore appearing in the two films after urea permeation. Furthermore, there is a difference in mean pore size where upper rather than lower surface has been exposed to urea, the lower side giving rise to larger pores in films of both polymers. Following exposure of upper and lower surfaces to urea, Eudragit RL100 displays a normal pore size distribution (Fig. 8); so also does Eudragit RS100 when the lower side is exposed, but results for pore size when the upper side of film of this polymer is exposed appear not to be normally distributed due to the preponderance of small pores. Mean pore sizes for lower surface after lower surface exposure to urea were 3.6 and 0.45 μm (RL100 and RS100, respectively), while after upper surface exposure had taken place they were 2.42 and 0.075 μm , respectively.

DISCUSSION

The various inhomogeneities which became more pronounced and more readily observable after polymer films had been used in permeability testing have been termed "pores." While inhomogeneities have doubtless been observed and called pores by other authors, it has not yet been proved that they are in fact surface openings of channels which are continuous between the upper and lower surfaces, but at present it is surmised that they represent at least possible areas of dis-

continuity in the film and, as such, resemble pores. Similar structures have been interpreted¹¹ as pores without comment.

Scanning electron micrographs of cross sections, particularly those taken at a very small angle to the vertical plane so as to include a perspective view of part of

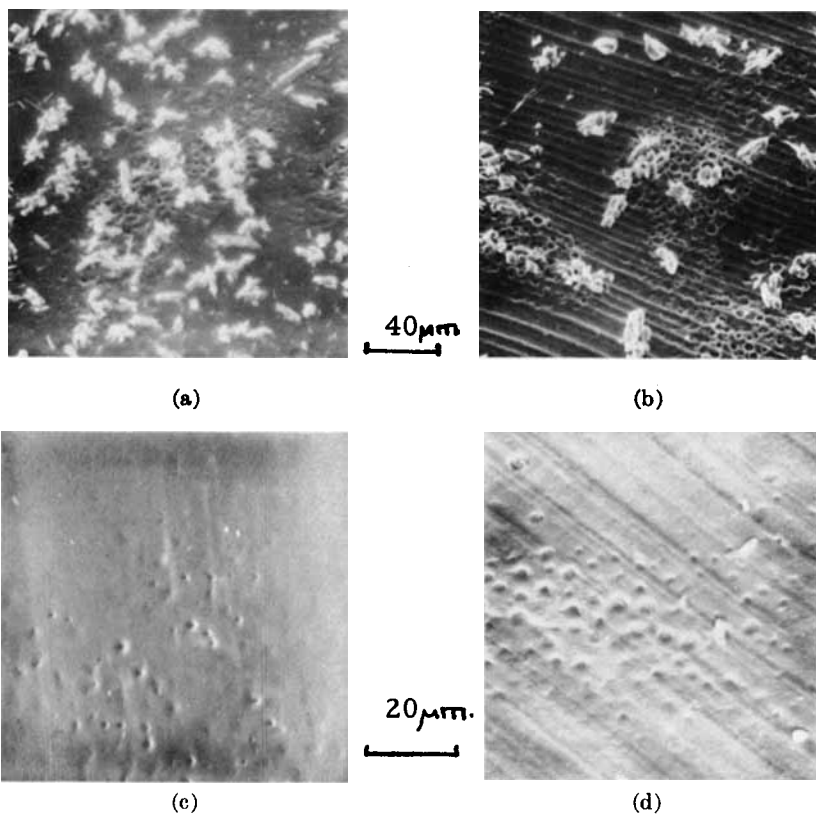


Fig. 5. Eudragit RL100 after 5 hr urea dialysis: (a) upper surface when lower side has been exposed to urea; (b) lower surface when lower side has been exposed to urea; (c) upper surface when upper side has been exposed to urea; (d) lower surface when upper side has been exposed to urea.

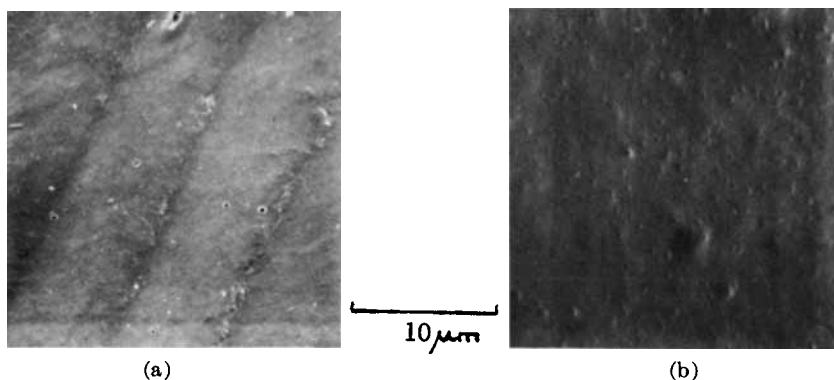


Fig. 6. Eudragit RS100 after 5 hr urea dialysis: (a) lower surface when upper side has been exposed to urea; (b) upper surface when lower side has been exposed to urea.

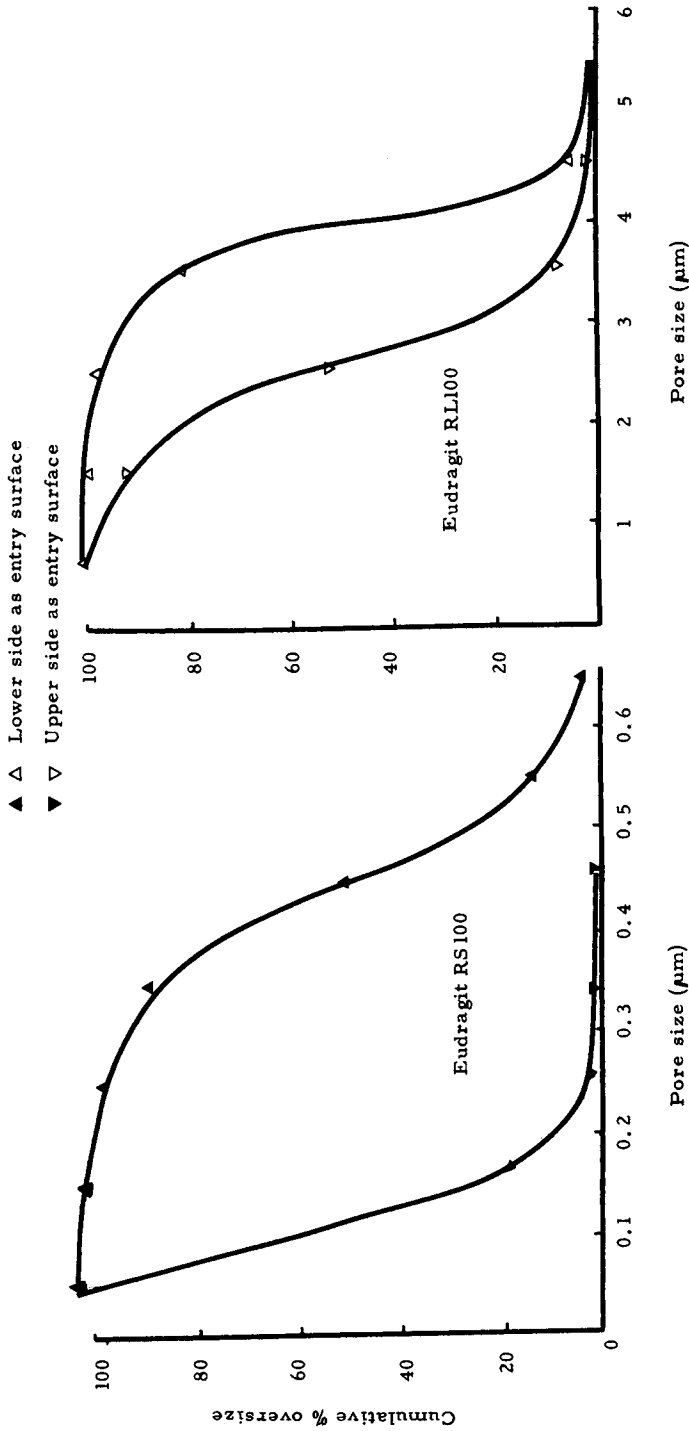


Fig. 7. Pore size distribution of lower surface of Eudragit RS100 and RL100 after 5 hr dialysis with urea.

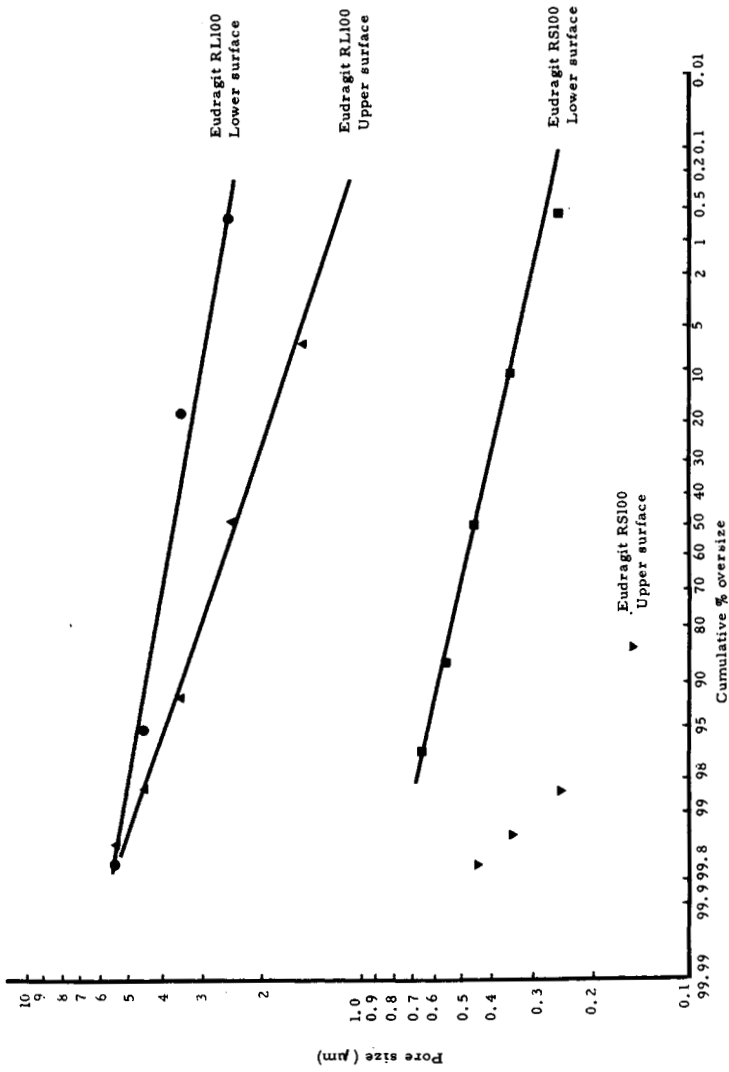


Fig. 8. Cumulative per cent oversize vs. pore size for Eudragit polymers.

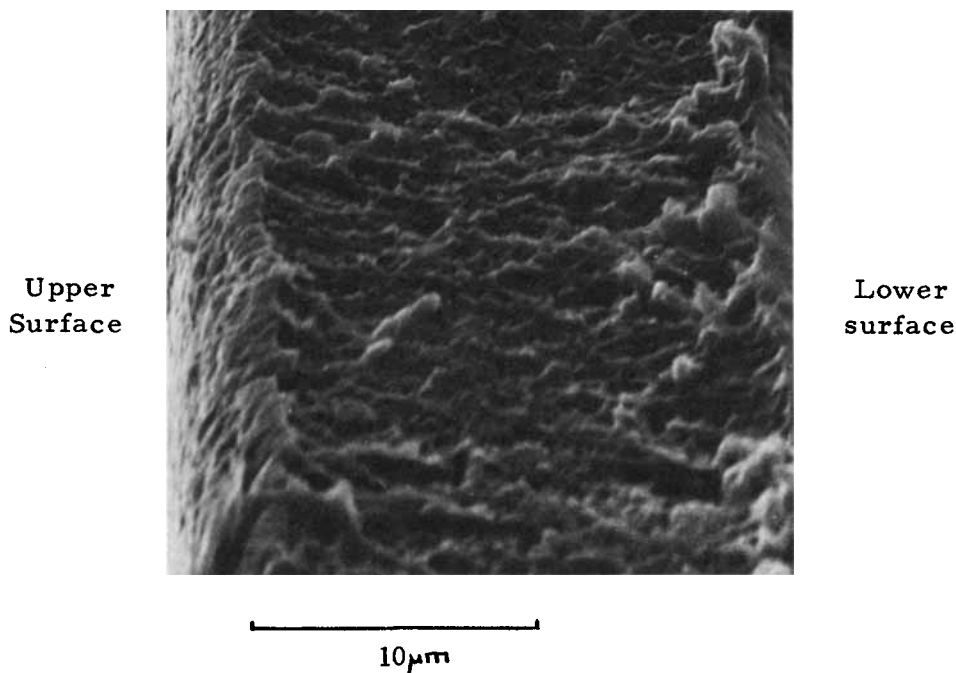


Fig. 9. Cross section of Eudragit RL100 showing internal pores.

one surface, reveal a sponge-like structure within the film (Fig. 9) and suggest that the pores, while not clearly showing any instances of patent channels extending directly between both surfaces, are probably not seriously misnamed and could easily provide direct fluid access to at least the central region of the film with accessibility to and from the other surface.

It is clear that, in some cases (Fig. 5), the pores appear as random clusters and are therefore unlikely to be artefacts related to the machining pattern left on the PTFE mold. The casting mold striations of the lower surface which slightly increase its area are an unlikely cause of higher permeability rate, because, were permeability characteristics of both surfaces similar, the one of slightly lesser area would be expected to be rate limiting for overall permeability, and no such marked difference as we find would be likely.

In the present work the aqueous solution may be able to penetrate the upper surface of the film when it comes from the direction of the lower surface, perhaps causing swelling with consequent increase in permeability to urea, whereas this sequence may not be so easily accomplished when the upper surface of the film is approached directly by the urea solution.

Clustering of the pores seen in the present work, or a similar phenomenon, has been noted by Shah and Sheth¹² who used ethylcellulose films in which hydroxypropylmethylcellulose has been dispersed as a hydrophilic polymer in a hydrophobic polymer matrix. These workers found that a wide variation in uniformity of dispersion of soluble agent within the matrix could occur, the resulting films tending to show the soluble agent either uniformly dispersed or as clusters. They

observed that films which had been prepared using slower drying conditions showed more uniformity in the distribution of these pores. Earlier still, Riley, Gardner, and Merten¹³ had postulated that a water-soluble agent could be dispersed inhomogeneously throughout a film and that this could have been related to drying conditions.

At present, inhomogeneous distribution cannot satisfactorily be explained and the mechanism whereby pores are formed is not yet known, but the films which have not been exposed to urea (Fig. 4) appear substantially homogeneous. This could be due either to the pores being below the resolution of the microscope, or perhaps to their formation during the experiment as a result of removal of water-soluble plasticizer (glycerol triacetate), by film swelling or by uneven swelling of inhomogeneous film.

While care was taken to standardize the drying conditions, eddy currents of acetone vapor within the funnel could have created variations in the partial pressure of acetone thereby altering vaporization rate and resulting in nonuniform localized evaporation of solvent together with localized precipitation of both polymer and plasticizer. This would be in accord with the clustering aspect of the pores, particularly if leaching of plasticizer was involved.

Overall it appears that permeability rate for urea depends upon surface of exposure with which size and number of pores appearing at the end of the experiment and hydrophilic character could be linked.

In certain other studies, Lachman and Drubulis¹ using cellulose acetate phthalate films, noticed development of different textures on casting but said there was no difference in water vapor permeation properties of the films. Kuriyama and others² also studied water vapor transmission using multiple films and found that despite the increase in thickness of the complete film, permeability to water vapor was sometimes greater than that of either film composing the mixed film and sometimes less than the individual films. Again, no explanation was advanced but in the light of our findings it could now be suggested that orientation of the film surfaces during earlier experiments may have determined the results, the greater permeation perhaps occurring when the surface nearest the casting substrate had been exposed to the vapor.

The pictorial evidence (Figs. 5 and 9) now clearly reveals structural inhomogeneity. Inhomogeneity has also been observed by Kesting, Barsh, and Vincent¹⁴ using cellulose acetate films in which the polymer was desolvated rapidly from organic solution by quenching in iced water, the resultant film showing a dense surface layer and a more porous underlying layer. Riley and others¹³ studied the same type of film and found that those films which had been prepared by air drying showed uniform compact film throughout. These authors postulated that the air-dried film would show smaller permeability properties than the rapidly precipitated film, which showed a spongy underlying texture. Our film structure seems to bear a closer resemblance to their rapidly precipitated films. It could be that a sequence of drying similar to that envisaged by Kesting and others¹⁴ could occur but that a capsule-like upper layer may prevent evaporation occurring at a uniform rate throughout film production.

Studies presently being undertaken are intended to elucidate the sequence in the production of pores.

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