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Propranolol HCl release from acrylic films prepared from aqueous latexes

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Summary

Polymeric films containing propranolol HCl were prepared by dissolving the drug in the aqueous colloidal polymer dispersion, Eudragit RS 30D, before casting and drying. The release of propranolol HCl was studied as a function of drug content, Eudragit RS 30D/RL 30D ratio, plasticizer content, method of film preparation and storage humidity. The addition of the more hydrophilic Eudragit RL 30D increased the permeability of the films. The amount of water-soluble plasticizer, triethyl citrate, added had a pronounced effect on drug release. The release was rapid at low and high plasticizer concentrations because of incomplete coalescence of the latex and leaching of the plasticizer. The drug release from latex-cast films was faster when compared to that from solvent-cast films.

Introduction

The necessity to circumvent restrictions imposed on the use of organic solvents has led to the development of a variety of latexes for pharmaceutical applications. An aqueous latex or pseudolatex consists of colloidal polymer particles dispersed in water. Latexes are obtained from water-insoluble acrylic monomers by emulsion polymerization (Eudragit NE 30D, L 30D) while pseudolatexes are prepared by emulsification of ethylcellulose in solution (Aquacoat) or melt (Surelease) into an aqueous phase. Eudragit RS 30D or RL 30D are pseudolatexes based on poly(ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) copolymers with ratios of 1:2:0.1 and 1:2:0.2. They are prepared by direct emulsification of the solid polymer (prepared by bulk polymerization) in hot water without the use of emulsifying agents. The colloidal dispersions are stabilized by the quaternary ammonium groups.

These latexes have been used extensively to formulate oral controlled release drug delivery systems in the form of coated small particles, beads, or tablets (Lehmann and Dreher, 1981; Goodhart et al., 1984; Gumowski et al., 1987). Drug-containing latex particles for topical (Büyükyaylaci et al., 1984), ophthalmic (Gurny et al., 1985), or parenteral drug delivery (Gurny et al., 1981; Krause et al., 1985) were prepared by dissolving the drug in the polymer solution before

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emulsification and pseudolatex formation. Other pharmaceutical applications include a molecular scale drug entrapment technique in which the addition of drug solutions to colloidal polymer dispersions resulted in latex flocculation and drug entrapment (Larson and Banker, 1976), and the preparation of sustained release matrix tablets by wet granulation of the powder with the polymer dispersion (Klinger et al., 1986; Kawashima et al., 1989).

Drug-containing films of water-insoluble polymers are generally prepared by casting and drying organic drug-polymer solutions or suspensions. Several studies characterized the permeability and physicochemical properties of these films (Borodkin and Tucker, 1974; Donbrow and Friedman, 1975; Samuelov et al., 1979; Rosilio et al., 1988). The objective of this study was to evaluate the release properties of propranolol HCl-containing polymeric films which were prepared from the aqueous colloidal polymer dispersions, Eudragit RS and RL 30D, as an alternative to solvent-cast films. Potential pharmaceutical applications of drug-containing latex films could include topical drug delivery systems in the form of films or drug-containing latexes which transform into continuous films after administration, or oral systems in the form of free films or coatings.

Materials and Methods

Materials

The following chemicals were obtained from commercial suppliers and used as received: propranolol HCl (Sigma, St. Louis, MO), Eudragit RS 30D, RL 30D or NE 30D (Röhm Pharma, Darmstadt), Aquacoat (FMC Corp., Newark, DE), Surelease (Colorcon, West Point, PA), dibutyl sebacate (Eastman Kodak, Rochester, NY), triethyl citrate (Citroflex 2; Morflex, Greensburo, NC), methanol (Fisher, Fair Lawn, NJ).

Methods

Propranolol HCl (2.5–12.5% w/w of total solids; film weight, 1 g) and triethyl citrate (25% w/w of polymer) were dissolved either directly in the latex or in water and then added to the latex. The drug-containing latexes (6 ml) were cast into aluminum petri dishes (6 cm in diameter). The low viscosity of the latexes obviated the need for a casting knife. The films were dried for 48 h at 40 °C and 30% relative humidity. The thickness of the films was determined in 5 places using a micrometer (P.N. Gardner Co., Pompano Beach, FL). The thickness of the films studied was between 400 and 500 μm. It did not vary by more than 5% over the film surface.

The USP XXI rotating paddle method (37 °C, 30 rpm, 500 ml deionized water, $n = 2$ or 3, coefficient of variation $< 5\%$) was used to study the drug release from the films (stored for 3 days at 22 °C and 50% relative humidity). The edges of the films were sealed with a silicone lubricant (Dow Corning, Midland, MI) to avoid penetration of the dissolution medium along and drug diffusion from the edges. The films stayed within the aluminum dishes at the bottom of the dissolution vessel during the dissolution study. The samples were withdrawn at predetermined intervals and assayed spectrophotometrically either directly or after proper dilution with the release medium ($\lambda = 290$ nm). The residual drug content in the films after the dissolution study was determined spectrophotometrically after extraction in methanol for selected samples ($\lambda = 291$ nm). The amount of drug released and the residual drug content in the films matched the original drug content closely. The release rate constant, k, was obtained by plotting the cumulative amount of drug released per unit area vs. the square root of time. The linear portion of the curve was determined statistically by linear regression analysis. The slope represented the release rate constant.

The surface morphology and cross-sections of the films were examined by scanning electron microscopy (SEM). The dried films were coated for 70 s under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and then observed with a scanning electron microscope (Jeol JSM 35C).

The solids content of the latexes was determined by freeze-drying. To determine the drying pattern of the colloidal dispersions, the latexes were adjusted to the same solids content by dilution with water, then placed into aluminum dishes

($n = 2$) and dried in an oven at fixed temperatures (20, 30, 40, 50, and 60 ° C) and a relative humidity of 30%. The samples were removed at predetermined intervals and weighed. The cumulative water loss was plotted vs. time. The evaporation of the plasticizers used was negligible.

The films were stored in desiccators containing different saturated salt solutions for maintaining different relative humidities at room temperature (Nygvist, 1983). The moisture uptake was measured periodically over 21 days.

Results and Discussion

The favorable solids content-viscosity relationship of latexes allows the processing of more concentrated systems when compared to polymer solutions. The viscosity of polymer solutions increases with increasing polymer concentration or polymer molecular weight while the viscosity of latexes is independent of molecular weight and increases only slightly with increasing solids content. With polymer solutions, the polymer concentration and the viscosity increase significantly during the drying process, thus reducing the rate of evaporation. The drying curves of different pharmaceutical latexes are shown in Fig. 1. In latexes, water is not a solvent but a dispersion medium. With the exception of Eudragit RS 30D plasticized with triethyl citrate, no major differences were observed in the drying patterns of different latexes and water. The water loss was initially linear with time followed by a drop off in drying rate in the late stages. As shown previously (Vanderhoff, 1973), the presence of latex particles had little influence on the rate of evaporation of water from the latex surface. Unplasticized Aquacoat and Eudragit RS 30D did not form continuous and flexible films upon drying. They required the addition of plasticizer for film formation because the minimum film formation temperature was above the drying temperature. The initial drying rates were very similar in each case. The difference in drying rate of plasticized Eudragit RS 30D appeared at higher polymer contents at which Eudragit RS 30D dried at a slower rate than the other latexes. With plasticized

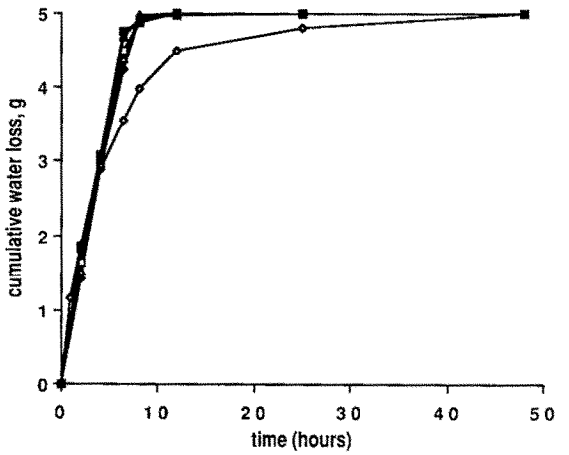


Fig. 1. Drying curves of different pharmaceutical latexes at 50 ° C: (●) water; (□) Aquacoat; (■) Aquacoat, plasticized with dibutyl sebacate; (△) Surelease; (▲) Eudragit NE 30D; (◇) Eudragit RS 30D, plasticized with triethyl citrate; (◆) Eudragit RS 30D.

Eudragit RS 30D, a visible film was formed with large amounts of water not yet evaporated when compared to other latexes. At later drying stages, water was lost at slower rates by diffusion through the polymeric RS film either through the polymer itself or through channels between uncoalesced polymer particles. This can be explained with the more hydrophilic character of the acrylic latex because of the presence of quaternary ammonium groups. The higher affinity for water resulted in film formation at higher water contents. Water may also act as a plasticizer for the polymer. The films became more brittle upon drying and storage in a desiccator. The effect of drying temperature on water loss from plasticized and unplasticized RS films is shown in Fig. 2. The latexes dried faster at higher temperatures and plasticized latexes dried significantly slower than the unplasticized latexes.

The objective of this study was to prepare drug-containing films from aqueous latexes. To prepare uniform films, the addition of the drug should not cause latex flocculation or coagulation. Depending on the solubility characteristics of the drug, it should be either dissolved or dispersed in the latex. Liquid lipophilic drugs have been emulsified directly into latexes in the preparation of films for transdermal applications (Lichten-

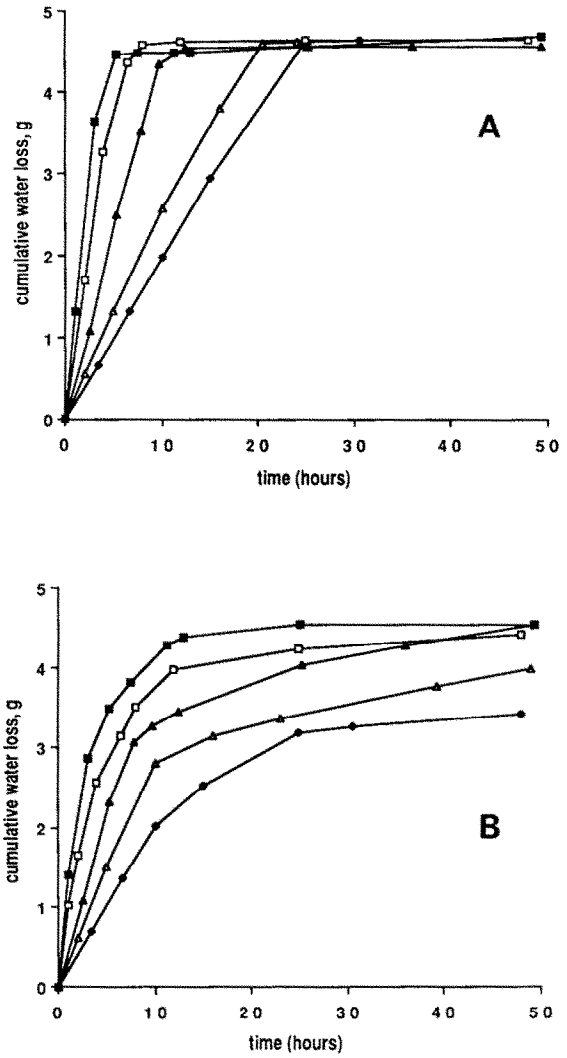


Fig. 2. Drying curves of unplasticized (A) and plasticized Eudragit RS 30D (B) at different temperatures: (◆) 20 °C; (△) 30 °C; (▲) 40 °C; (□) 50 °C; (■) 60 °C.

berger et al., 1988). Insoluble, solid drugs must be dispersed prior to latex casting and drying. In the present study, propranolol base was dispersed in an ethylcellulose latex (Surelease). The drug settled during the drying process resulting in a non-homogeneous drug distribution in the polymer film as indicated by visible drug crystals. A more homogeneous distribution was obtained by first dissolving the drug in a water-insoluble plasticizer. Propranolol base was dissolved in dibutyl sebacate, emulsified in water, and then added to Surelease before film casting. No drug crystals were visible and a melting transition was absent on DSC thermograms, indicating that the drug was dissolved in the polymeric film.

Monolithic or matrix films were prepared by dissolving propranolol HCl in Eudragit RS or RL 30D before film casting and drying. Upon drying, the colloidal polymer particles are forced together, deformed and coalesced into a continuous, pore-free film (Bradford and Vanderhoff, 1966; Kast, 1985). The drug may dissolve (monolithic solution) or precipitate in the polymeric matrix (matrix suspension) during film formation (Bodmeier and Paeratakul, 1989). Propranolol HCl-Eudragit RS or RL 30D films represented a monolithic solution. The films were clear and the melting transition of the drug was absent on DSC thermograms. This indicated that the drug was dissolved in the polymer at its melting point. Scanning electron micrographs of cross-sections of the films showed a non-porous, crystal-free structure.

The release properties of the films were studied with respect to drug loading, latex composition, plasticizer concentration, and storage humidity. As expected, the drug release increased with increasing drug loading as shown in Fig. 3. The duration of drug release was inversely correlated to the drug loading.

Eudragit RS 30D and RL 30D require the addition of plasticizers to reduce the minimum

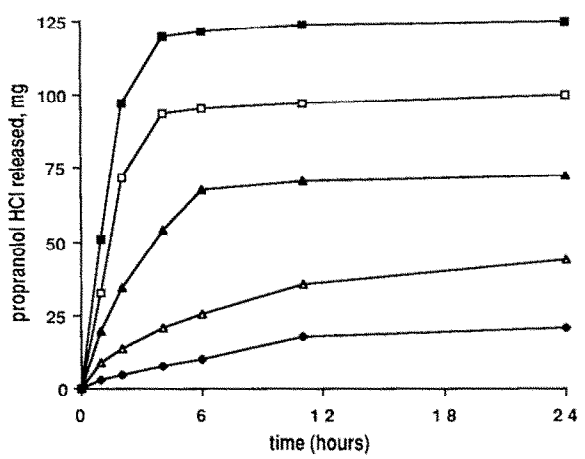


Fig. 3. Effect of propranolol HCl loading (drug, mg/film, g) on drug release from Eudragit RS films: (◆) 25 mg; (△) 50 mg; (▲) 75 mg; (□) 100 mg; (■) 125 mg.

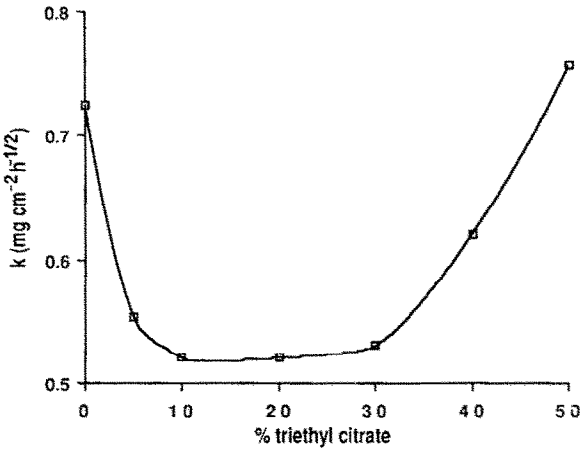
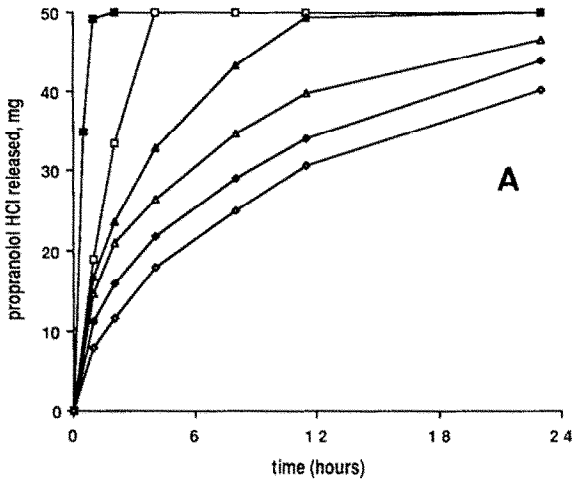


Fig. 4. Effect of triethyl citrate concentration on release rate constant of propranolol HCl (50 mg)-Eudragit RS films.

film formation temperature of the dispersions (between 40 and 50 °C) below 20 °C. Triethyl citrate, a water-soluble plasticizer, was chosen in this study. The plasticizer diffuses into and softens the polymer particles. This softening promotes latex coalescence and film formation. The permeability of the films was dependent on the presence of water-soluble or insoluble plasticizers in the dried films. The effect of the triethyl citrate concentration on the release rate constant is shown in Fig. 4. With monolithic solutions, the amount of drug released over time can be linearly described by a square-root of time relationship during the early time approximation and by a first-order equation during the late time approximation (Baker, 1987). Release rates were determined by measuring the slopes of the linear portions of graphs of cumulative amount of drug released vs. square root of time. The release rate constant was high at low plasticizer concentrations, then went through a minimum plateau, and increased at higher plasticizer concentrations. The cup-shaped curve could be explained as follows. At low plasticizer concentrations, the latex particles were insufficiently plasticized. This interfered with the coalescence or fusion of the latex particles. Incomplete fusion into a continuous polymer film explained the faster release at low plasticizer levels. The polymer particles resisted deformation and water evaporated without complete particle fusion resulting in brittle films. The release rate constant did not vary in the 10–30% plasticizer range. The triethyl citrate concentration recommended by the supplier and necessary for good film formation is between 10 and 20% (Lehmann, 1989). The increase in release rate constant at high triethyl citrate concentration could be explained with the leaching out of the water-soluble plasticizer. The leaching became more pronounced at higher plasticizer levels. Goodhart et al. (1984) coated phenylpropanolamine HCl pellets with Aquacoat, an ethylcellulose latex. Increasing amounts of the water-soluble plasticizer, triethyl citrate, in Aquacoat films resulted in a decreased drug release in the plasticizer range investigated. In contrast, the solute diffusivity in ethylcellulose films cast from solution increased with increasing amounts of triethyl citrate because of leaching of the plasticizer.

Beads containing chlorpheniramine maleate were coated with organic solutions of Eudragit RS/RL mixtures. The drug release increased with increasing amount of the more hydrophilic Eudragit RL (Jambhekar et al., 1987). Eudragit RS and RL 30D are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The ammonium groups are responsible for the permeability and swelling of these water-insoluble films. The two latexes were mixed in various proportions to study the drug release from mixed films as a function of Eudragit RS/RL ratio (Fig. 5). The amount of drug released vs. square root of time relationship remained valid up to about 80% drug release (Fig. 5B). The mixed films had intermediate release patterns when compared to those of pure films. Propranolol HCl-Eudragit RL 30D formed films which swelled rapidly and later disintegrated in the dissolution medium. The higher proportion of quaternary ammonium groups in Eudragit RL films resulted in rapid hydration and drug release. The other films imbibed water, swelled, but stayed intact during the drug release phase.

The release of propranolol HCl from latex-cast films was compared to the release from films prepared from a redispersed latex powder or from an organic polymer solution (Fig. 6). All films had the same composition. Latex powder was obtained by freeze-drying the polymer dispersion. The re-



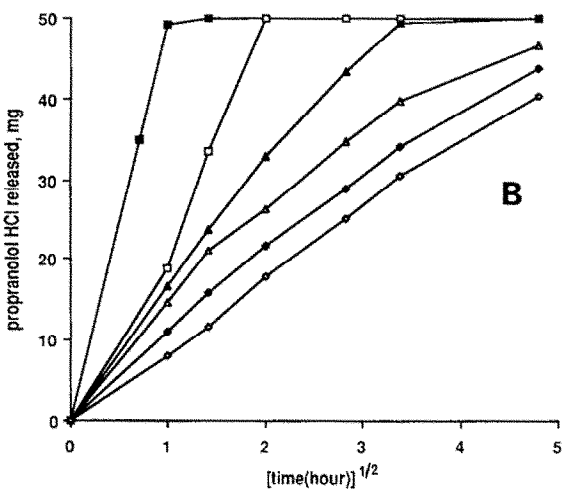


Fig. 5. Effect of Eudragit RL/RS ratio on propranolol HCl (50 mg) release: A, % drug released vs. time; B, % drug released vs. square root of time: (■) 10:0; (□) 8:2; (▲) 6:4; (△) 4:6; (◆) 2:8; (◇) 0:10.

dispersed latex was prepared by dispersing the loose agglomerates in water without the addition of surfactants. Films cast from organic solutions were prepared by dissolving the freeze-dried latex and drug in a methylene chloride/methanol solvent blend (2:1 v/v). The release of drug was fastest from films prepared from the redispersed latex followed by films prepared from the original latex and from the organic solution. This release behavior could be explained with the different densities of the films. At the same solids content,

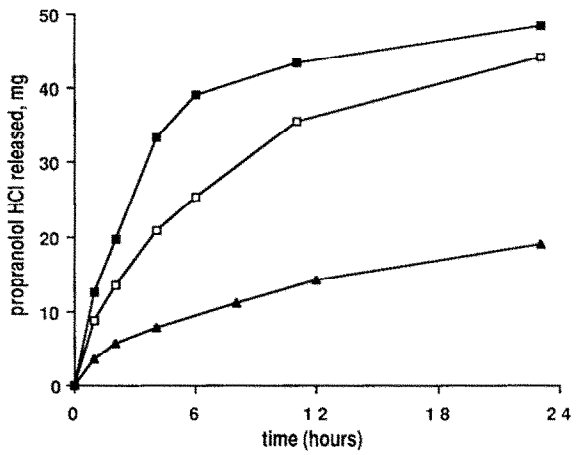


Fig. 6. Effect of film preparation on propranolol HCl (50 mg) release from Eudragit RS films: (■) redispersed latex – film thickness, 478 μm; (□) latex, 449 μm; (▲) organic solution, 375 μm.

the thickness of the films depended on the method of film preparation. Films cast from the organic drug-polymer solution resulted in the thinnest film. This film was therefore denser or less porous than the latex-cast films as confirmed by scanning electron micrographs (Fig. 7). The porous nature of films prepared from redispersed latexes indicated incomplete coalescence and fusion of the polymer particles possibly because of incomplete redispersion and hence, larger agglomerates of polymer particles. In addition to density, the slower drug release from organic solvent-cast films when compared to latex-cast films, could possibly be explained with different microstructures of the films. The microstructure depends strongly on processing and formulation variables such as drying condi-

TABLE 1

Moisture uptake during storage of propranolol HCl (50 mg)-Eudragit RS films at different relative humidities (21 days, 22 °C)

Relative humidity (%)	Moisture uptake (%)
97	22.93
75	3.50
54	1.24
33	0.25
11	−0.50

tions and solvent composition. At the same plasticizer level, cellulose acetate membranes prepared from latexes were more permeable to water and swelled to a greater extent than those prepared from organic solutions (Bindschaedler et al., 1986). Other groups, however, reported that organic films were more permeable than latex films (Banker and Peck, 1981).

The films were stored at different humidities. The data on moisture uptake and drug release as a function of storage humidity are shown in Table 1 and Fig. 8. Except at a relative humidity of 97%, the moisture uptake was marginal. The drug release, which was initiated by the hydration of the films, increased with increasing humidity or water uptake.

In conclusion, polymeric films containing propranolol HCl were successfully prepared from acrylic colloidal polymer dispersions. The propranolol HCl-Eudragit RS films represented homogeneous monolithic solution systems. The release properties could be varied by adjusting the film compositions. The prepared latex films were aqueous-based, solvent-free, and could offer an alternative to the conventional solvent-cast films.

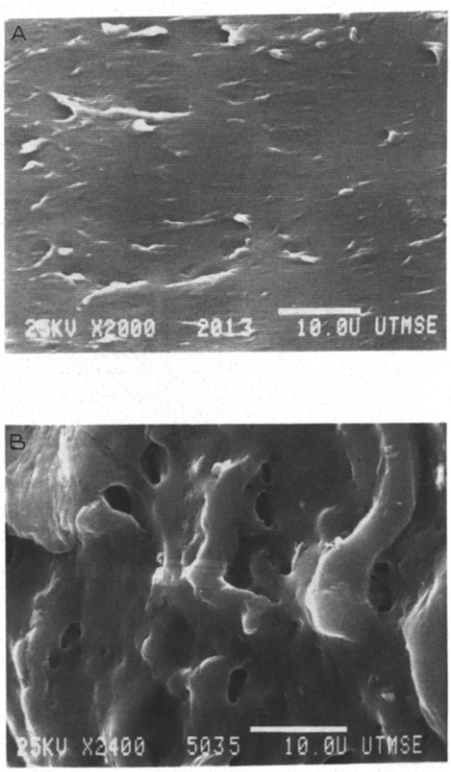


Fig. 7. Scanning electron micrographs of propranolol HCl (50 mg)-Eudragit RS films cast from (A) organic solution, and (B) redispersed latex.

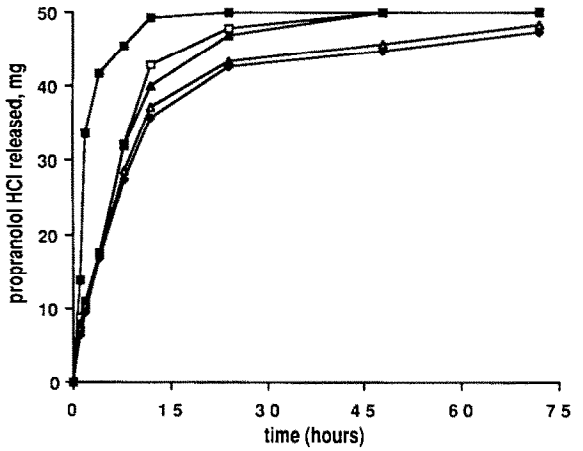


Fig. 8. Effect of relative humidity on propranolol HCl (50 mg) release from Eudragit RS films (storage time = 21 days, 22° C): (■) 97%; (□) 75%; (▲) 54%; (△) 33%; (◆) 11%.

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