Pharmaceutical Research, Vol. 6, No. 8, 1989

Report

Evaluation of Drug-Containing Polymer Films Prepared from Aqueous Latexes

Roland Bodmeier[1,2] and Ornlaksana Paeratakul[1]

Received December 29, 1988; accepted March 28, 1989

Polymeric films containing salicylic acid or propranolol HCl were prepared by casting and drying a drug-containing, aqueous colloidal polymer dispersion (Eudragit NE 30D) as an alternative to films cast from organic polymer solutions. The drug was either dissolved (salicylic acid) or dissolved/dispersed (propranolol HCl) in the polymeric matrix. Incompatibilities (flocculation or coagulation) between salts of basic drugs and two ethylcellulose latexes were overcome by substituting the anionic surfactants with a nonionic surfactant (Pluronic P103). The drug release was studied as a function of drug loading, film thickness, amount of hydrophilic additive (hydroxypropyl methylcellulose), and storage humidity. The release of propranolol HCl (monolithic dispersion) was a combination of diffusion through the polymer and pores or channels; the extent of each release mechanism depended on the drug loading. On DSC thermograms, melting transitions were obtained with monolithic dispersions but not with monolithic solutions. The heat of fusion was linearly correlated to the amount of drug in the films. The amount of drug remaining in the film after the dissolution study was not detectable and corresponded to the drug dissolved in the polymer. The drug release increased with increased drug loading and increased amount of hydroxypropyl methylcellulose but was independent of film thickness and relatively insensitive to different storage humidities.

KEY WORDS: aqueous colloidal polymer dispersions; latexes; film casting; polymeric films; controlled release.

INTRODUCTION

Numerous controlled or sustained-release delivery systems have been described in the literature whereby the active ingredient has been dissolved or dispersed within polymeric materials (1). Drugs have been incorporated into polymeric films to achieve sustained release by casting and drying organic drug–polymer solutions or suspensions. The release properties of the solvent-cast films have been extensively studied (2–5). In recent years, however, concerns about environmental pollution, residual solvents, and fire or explosion hazards made the use of organic solvents undesirable. Commercially available aqueous colloidal dispersions (latexes) of water-insoluble acrylic or cellulosic polymers have been developed in order to circumvent the restrictions imposed on the use of organic solvents. These latexes have been used extensively to develop controlled-release delivery systems in the form of coated beads or tablets (6–8). Other pharmaceutical applications of latexes include the preparation of drug-containing latex particles for topical (9) or parenteral drug delivery (10) or of sustained-release matrix tablets by wet granulation of the powder with the polymer dispersion (11).

The objective of this study was to evaluate drug-containing matrix films prepared from aqueous colloidal polymer dispersions. The latex, Eudragit NE 30D, investigated in this study, is widely used in aqueous film coating technology and is based on neutral poly(ethylacrylate-methylmethacrylate) copolymers and prepared by emulsion polymerization (12).

MATERIALS AND METHODS

The following chemicals were obtained from commercial suppliers and were used as received: propranolol HCl, chlorpheniramine maleate (Sigma Chemical Co., St. Louis, Mo.), salicylic acid (Mallinckrodt Chemical Works, St. Louis, N.Y.), dibutyl sebacate (Eastman Kodak Co., Rochester, N.Y.), Pluronic P103 (BASF Wyandotte Corporation, Parsippany, N.J.), Aquacoat (FMC Corporation, Newark, Del.), Eudragit NE 30D [poly(ethylacrylate-methylmethacrylate] (Röhm Pharma, Darmstadt, West Germany), Surelease (Colorcon Inc., West Point, Pa.), ethylcellulose (Ethocel Std. 10, Dow Chemical Co., Midland, Mich.) hydroxypropyl methylcellulose (Methocel E3 premium grade, Dow Chemical Co., Midland, Mich.), acetone (J. T. Baker Chemical Co., Phillipsburg, N.J.), methanol, and methylene chloride (Fisher Scientific Co., Fair Lawn, N.J.).

An ethylcellulose pseudolatex was prepared by dissolving the polymer (5 g), and a water-insoluble plasticizer, dibutyl sebacate (1.25 g), in methylene chloride (30 ml). This solution was emulsified in an aqueous phase (50 ml) contain-

[1] College of Pharmacy, The University of Texas at Austin, Austin, Texas 78712.

[2] To whom correspondence should be addressed.

0724-8741/89/0800-0725$06.00/0

ing Pluronic P103 (5%, w/v,), a nonionic emulsifying agent, and then processed in a Microfluidizer M-110F (operating pressure = 6000 psi, 5 cycles; Microfluidics Corporation, Newton, Mass.). After methylene chloride diffusion into the aqueous phase and evaporation at the water/air interface, a plasticized ethylcellulose pseudolatex was obtained.

The drug (salicylic acid, 2.5–12.5%, w/w, of total solid, or propranolol HCl, 2.5–20%, w/w) was dissolved either directly in the latex or in water and then added to the latex. The drug-containing latex dispersions (6 ml; total solids content = 1 g) were cast into aluminum petri dishes (6 cm in diameter, film thickness was in the range of 450 to 550 μm). The low viscosity of the latex dispersions obviated the need for a casting knife. The films were dried for 48 hr at 40°C at 30% relative humidity. Hydroxypropyl methylcellulose was dissolved in water and then added to the latex in various proportions. The film thickness of propranolol HCl–Eudragit NE 30D films was varied by diluting the latex with water. The casting volume was kept constant. The total solids content was correlated to the film thickness in a linear fashion indicating the presence of similar microstructures in films of varying thicknesses. The thickness of the films was determined in five places using a micrometer (Paul N. Gardner Company, Inc., Pompano Beach, Fla.). It did not vary by more than 5% over the film surface.

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

Thermograms of films before and after dissolution studies were obtained by using a computer-interfaced Perkin–Elmer differential scanning calorimeter, Model DSC 2. The temperature calibration was accomplished with the melting transition of indium. The samples (5–7 mg), which were stored in a desiccator prior to the analysis, were sealed in aluminum pans. The heat of fusion was calculated by the instrument. The scanning rate throughout the investigation was 20°C/min. All tests were run in a nitrogen atmosphere.

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 7 days at 22°C and 50% relative humidity). The edges of the films were sealed with a silicone lubricant (Dow Corning Corp., Midland, Mich.) to avoid drug diffusion from the edges. The samples were withdrawn at predetermined time intervals and assayed spectrophotometrically either directly or after appropriate dilution with the release medium (propranolol HCl, $\lambda = 290$ nm; salicylic acid, $\lambda = 298$ nm). The films stayed intact during the dissolution study. The residual drug content in the films after the dissolution study was determined spectrophotometrically after extraction in methanol for selected samples (propranolol HCl, $\lambda = 291$ nm; salicylic acid, $\lambda = 237$ nm). The amount of drug released and the residual drug content in the films matched the original drug content closely, within 2 to 6%. The release rate constant, k, was obtained by plotting the cumulative amount of drug released per unit area versus the square root of time. The linear portion of the curve was determined statistically by linear regression analysis. The abscissa intercept is the lag time and the slope is the rate constant.

The films were stored in desiccators containing different saturated salt solutions for maintaining different relative humidities at room temperature (13). The moisture uptake was measured periodically over a 21-day period.

RESULTS AND DISCUSSION

A latex or pseudolatex consists of colloidal polymer particles suspended in water. Latexes are obtained from water-insoluble monomers by emulsion polymerization, while pseudolatexes are prepared by emulsification of preformed thermoplastic polymers in solution or melt. The latexes have a high solids content without encountering excessive viscosity. In the film coating of solid dosage forms, the polymer can be applied more rapidly compared to organic polymer solutions (14). The film formation mechanism of colloidal polymer dispersions differs entirely from that of organic polymer solutions. Upon evaporation of water, the polymer particles are forced into a close packing, followed by deformation and coalescence of the particles into a continuous film. During aging, the films undergo further gradual coalescence and fusion by interdiffusion of the molecules of adjacent latex particles (15–17). The film formation depends primarily on the viscoelastic properties of the polymer and the drying conditions (18).

In the present study, drugs were dissolved in the latex prior to film casting and drying. Latexes are sensitive to temperature and pH changes, high shear, and in particular, the addition of electrolytes. Goodman and Banker reported a molecular drug entrapment method in which salts of basic drugs flocculated latexes prepared from anionic polymers (19). Incompatibilities between the colloidal polymer dispersions and drugs, however, would interfere with the film formation. Pharmaceutical pseudolatexes or latexes of nonionic polymers include two ethylcellulose pseudolatexes (Aquacoat or Surelease) and an acrylic latex based on poly(ethylacrylate-methylmethacrylate) copolymers (Eudragit NE 30D). The addition of salts of basic drugs such as propranolol HCl or chlorpheniramine maleate to the ethylcellulose pseudolatexes resulted in latex flocculation or coagulation. The anionic surfactants (sodium lauryl sulfate or ammonium oleate) used to stabilize the pseudolatexes interacted with the cationic drugs. Replacing the ionic surfactants with a nonionic surfactant overcame the observed incompatibilities. A plasticized ethylcellulose pseudolatex was prepared with a microfluidizer using the nonionic surfactant, Pluronic P103. The addition of the two drugs to the pseudolatex did not result in flocculation or coagulation and films could be successfully prepared.

No incompatibilities were observed between the drugs and the acrylic latex (stabilized with isononylphenylpolyoxyethylene glycol). Flexible drug-containing films prepared from combinations of salicylic acid–Eudragit NE 30D (NE) and propranolol HCl–NE were further studied. Continuous films could be prepared without plasticizers even at room temperature, since the minimum film formation temperature of the drug–latex mixture was below 20°C. The films were either transparent or opaque, depending on whether the drug was dissolved or dispersed in the dried film. Polymeric matrix systems have been classified into monolithic solutions or dispersions (20). The active ingredient is dissolved in the

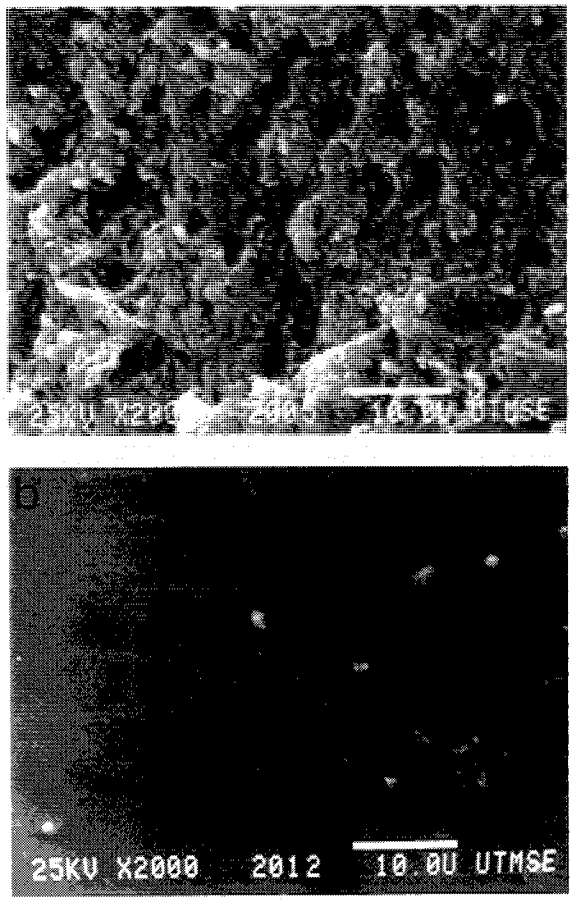

Fig. 1. Scanning electron micrographs of cross sections of (a) propranolol HCl (20%, w/w) and (b) salicylic acid (12.5%, w/w)–Eudragit NE 30D films.

polymer in a monolithic solution, while it is dissolved/dispersed in a monolithic dispersion. Salicylic acid–NE films were transparent, indicating that the drug was, at least at a microscopic level, dissolved in the polymer. Propranolol HCl–NE films, which were opaque above 50 mg drug/g film,

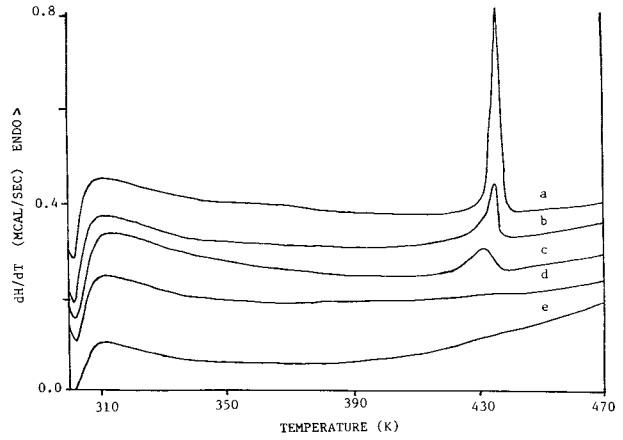

Fig. 2. DSC thermograms of propranolol HCl (%, w/w)–Eudragit NE 30D films before (a–d) and after (e) dissolution studies: (a) 20%, (b) 10%, (c) 7.5%, and (d) 5% propranolol HCl; (e) all films after dissolution studies.

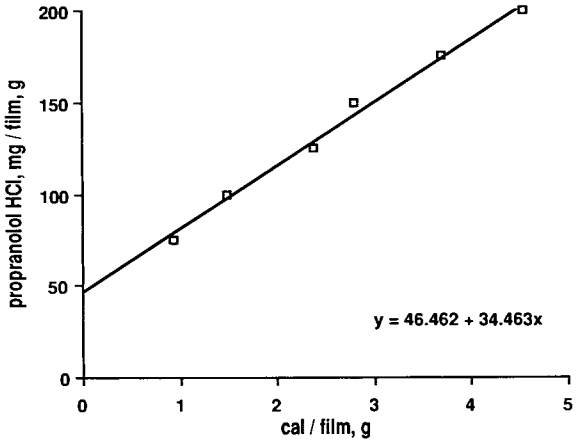

Fig. 3. Relationship of propranolol HCl loading and heat of fusion.

represented a monolithic dispersion. Propranolol HCl but not the salicylic acid crystals were visible on scanning electron micrographs of cross sections of the films (Fig. 1). In addition, DSC analysis was used in order to characterize the physical state of the drugs in the polymeric matrix (Fig. 2). Melting transitions of the drugs were absent in salicylic acid–NE films, indicating that the drug was dissolved in the polymer at its melting temperature. Propranolol HCl was dissolved and dispersed in NE films as shown by the presence of its melting transition above 5% drug content. A linear relationship existed between the heat of fusion and the amount of drug in the films (Fig. 3). The intercept of 46.5 mg propranolol HCl/g film corresponded to the solubility of the drug in the polymer at its melting temperature (21). In contrast to the homogeneous nonporous structure of the latex-cast films, the coating of pellets with latexes resulted in heterogeneous and porous films (22). The porous nature of the films was caused by uncoalesced polymer particles and depended strongly upon equipment and spraying conditions used.

The effect of drug loading on the release of propranolol HCl is shown in Fig. 4. The drug release was initially rapid but then plateaued. The drug was not released completely.

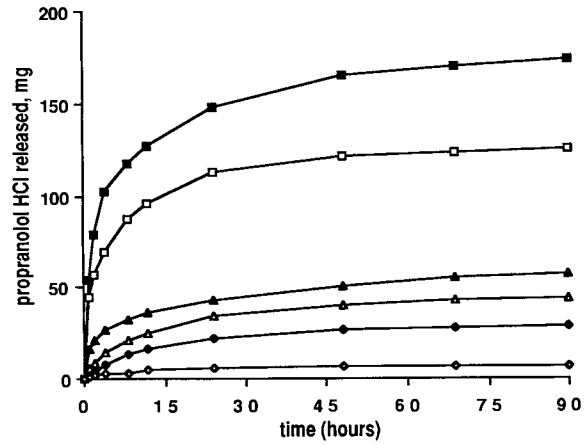

Fig. 4. Effect of propranolol HCl loading (drug, mg/film, g) on drug release: (■) 200 mg, (□) 150 mg, (▲) 100 mg, (△) 75 mg, (♦) 50 mg, and (◇) 25 mg.

Baker classified monolithic dispersions into three types depending on the volume fraction of the drug in the matrix: simple monolithic dispersions (0–5 vol%), complex monolithic dispersions (5–10 vol%), and monolithic matrix systems (above 15–20 vol%) (20). Depending on the drug loading, the drug can be released by either diffusion through the polymer, diffusion through liquid-filled pores and channels, or a combination of the two mechanisms. The initial rapid release of propranolol HCl could be explained with drug diffusion through liquid-filled pores created by the dissolution of dispersed drug crystals. The second, slow-release phase was attributed to drug diffusion through the polymer resulting from either dissolved drug or dispersed but not connected drug particles. A drug-free NE film was laminated onto the propranolol HCl-NE film by wetting the surface with acetone and pressing it onto the drug-containing layer. Propranolol HCl was not released from the laminate, which indicated that drug partitioning in and diffusion through the polymer was very slow. This verified the nonporous homogeneous structure of latex-cast films.

The amount of propranolol HCl remaining within the film after 90 hr was plotted versus the initial drug loading (Fig. 5). Three different regions could be identified and correlated to the three types of monolithic dispersions described by Baker. At a low loading (25 mg drug/g film), the drug (dissolved in the polymer) was released slowly by diffusion through the polymer. At intermediate loadings (50–100 mg/g film), drug (dissolved and dispersed) was released by diffusion through the polymer and through liquid-filled cavities left behind by the released drug. At higher loadings (150 and 200 mg/g film), the drug was released rapidly and primarily by diffusion through interconnected water-filled pores and channels. Interestingly, the melting transition for propranolol HCl was absent on DSC thermograms run on all films after dissolution studies (Fig. 2). Thus, the drug left within the film after the dissolution study was not detectable by DSC analysis and might correspond to the fraction of drug dissolved in the polymer. Propranolol HCl crystals were not visible on cross sections of films after dissolution studies.

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 (20). The release of salicylic acid from NE films could be described by these approximations as shown in Figs. 6A and B.

Higuchi derived equations which describe the drug release from monolithic dispersions as being linear with the square root of time over almost the entire release curve (23). Release rates which were determined by measuring the slopes of the linear portions of graphs of cumulative amount of drug released versus the square root of time are plotted as a function of drug loading in Figs. 7A and B. The release rate constant, k, increased in a linear fashion with increasing salicylic acid loading. The positive deviation with propranolol HCl–NE films could be explained with the leaching of drug and thus increased internal porosity at higher drug loading. Although not predicted by the Higuchi model, this linear relationship and positive deviation was also reported in other papers (2,3).

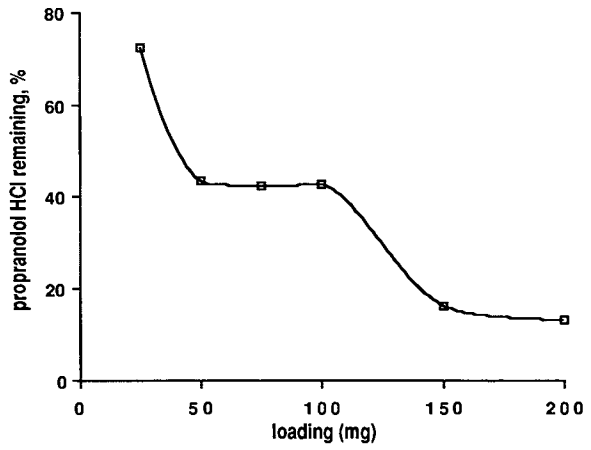

Fig. 5. Percentage propranolol HCl remaining in the films after dissolution studies (90 hr) as a function of initial loading (drug, mg/film, g).

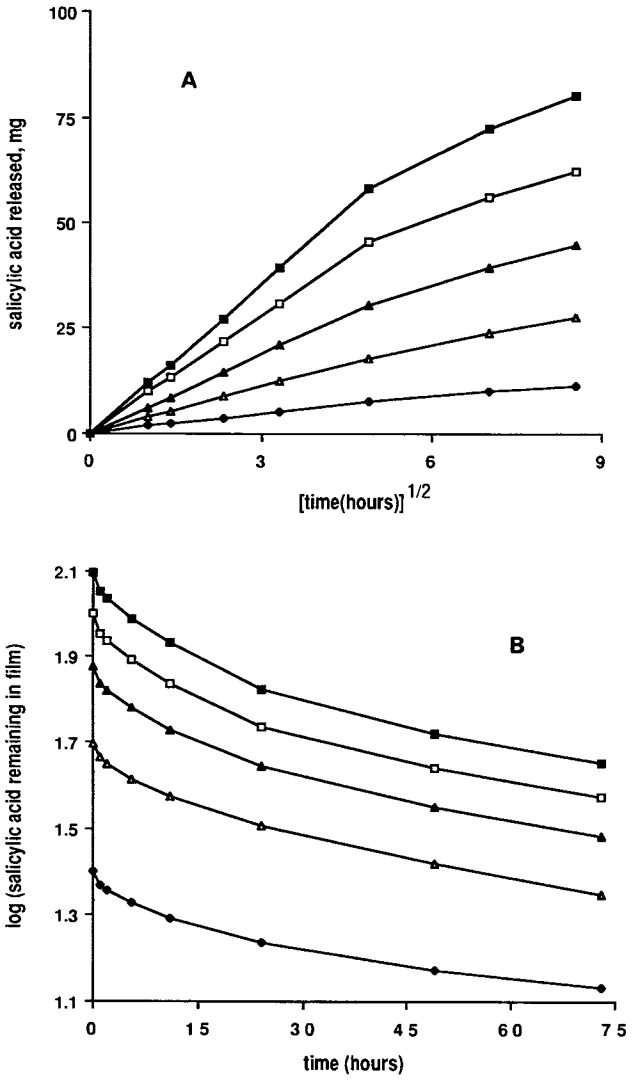

Fig. 6. Effect of salicylic acid loading on drug release: (a) salicylic acid released, mg, versus $(\text{time})^{1/2}$ and (b) log (amount of drug remaining within the film) versus time. Loading (drug, mg/film, g): (■) 125 mg, (□) 100 mg, (▲) 75 mg, (△) 50 mg, and (♦) 25 mg.

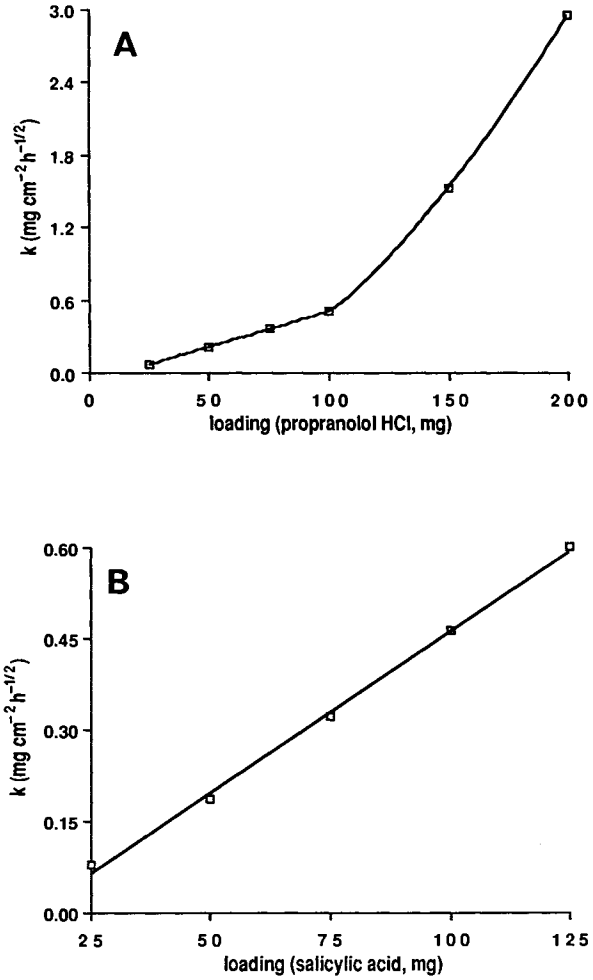

Fig. 7. Relationship of release rate constants, k, and drug loading (drug, mg/film, g): (a) propranolol HCl and (b) salicylic acid.

Except for the thinnest film, film thickness had little influence on the release rate constant as shown by the overlap of the initial portions of the release profiles (Fig. 8). The duration of drug release generally increases with increasing film thickness. In this study, however, the release profiles from thicker films were almost superimposable. This may be explained as follows. The drug release from the propranolol HCl films was complicated by the fact that the temperature of the dissolution medium was above the glass transition temperature of the polymer. The polymer was therefore in the rubbery state. Pores and channels, which formed in the upper layers of the films from dissolved drug particles, could have closed during the dissolution study. Thus, the release mechanism in thicker films may have changed from drug diffusion through pores to diffusion through the polymer, which was very slow.

The drug release from water-insoluble polymeric matrices has been modified by the addition of hydrophilic polymers such as polyethylene glycol (2) or hydroxypropyl cellulose (3). We added hydroxypropyl methylcellulose in various ratios to the latex to enhance the release of salicylic acid (Fig. 9). The increase in drug release with increasing proportions of hydroxypropyl methylcellulose in the matix could be explained with the leaching of the hydrophilic polymer.

To study the effect of storage humidity, salicylic acid–NE films were stored for 21 days in desiccators containing different saturated salt solutions. The moisture uptake and drug release as a function of relative humidity are shown in Fig. 10. The drug release was relatively insensitive to the storage humidity. Except at 97% relative humidity, only minor differences in drug release and moisture uptake were observed.

In summary, drug-containing polymeric films were prepared by casting and drying aqueous colloidal polymer dispersions or latexes. Potential pharmaceutical applications 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.

ACKNOWLEDGMENT

This research was partially supported by a faculty development award to R.B. from Merck Sharp & Dohme Research Laboratories.

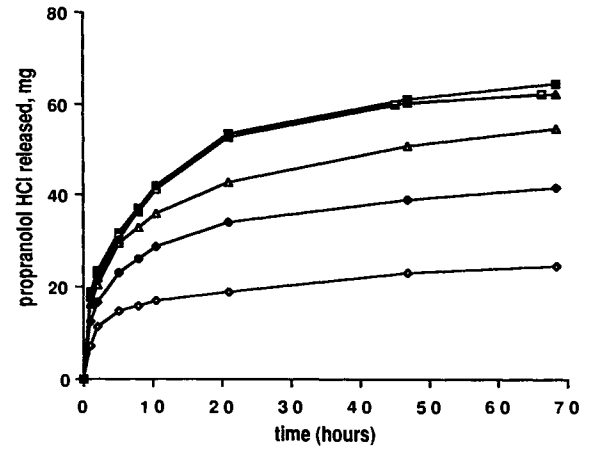

Fig. 8. Effect of film thickness on drug release from propranolol HCl (10%, w/w)–Eudragit NE 30 D films: (■) 931 μm, (□) 798 μm, (▲) 663 μm, (△) 526 μm, (♦) 387 μm, and (◇) 250 μm.

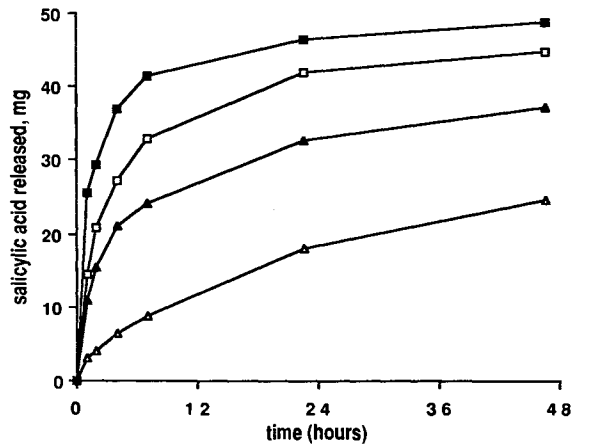

Fig. 9. Effect of the addition of hydroxypropylmethylcellulose (%, w/w) on drug release from salicylic acid (50 mg/g film)–Eudragit NE 30D films: (■) 20%, (□) 10%, (▲) 5%, and (△) 0%.

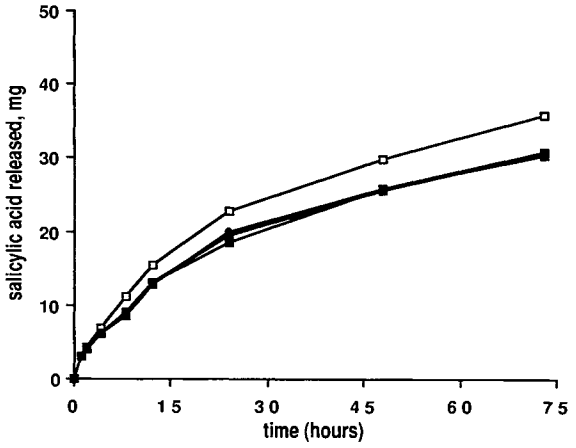

Fig. 10. Effect of storage humidity (21 days, 22°C) on drug release from salicylic acid (50 mg/g film)–Eudragit NE 30D films; relative humidity/moisture uptake (%, w/w): (□) 97%/11.54, (■) 75%/1.43, (▲) 54%/0.52, (△ 33%/0.14, and (♦) 11%/−0.40.

REFERENCES

1. R. Baker. *Controlled Release of Biologically Active Agents*, John Wiley & Sons, New York, 1987.
2. Y. Samuelov, M. Donbrow, and M. Friedman. *J. Pharm. Sci.* 68(3):325–329 (1979).
3. S. Borodkin and F. E. Tucker. *J. Pharm. Sci.* 63(9):1359–1364 (1974).
4. M. Donbrow and M. Friedman. *J. Pharm. Sci.* 64(1):76–80 (1975).
5. M. Donbrow and M. Friedman. *J. Pharm. Pharmacol.* 26:148–150 (1974).
6. I. Ghebre-Sellassie, R. H. Gordon, R. U. Nesbitt, and M. B. Fawzi. *Int. J. Pharm.* 37:211–218 (1987).
7. F. W. Goodhart, M. R. Harris, K. S. Murthy, and R. U. Nesbitt. *Pharm. Tech.* 4:64–71 (1984).
8. G. S. Banker and G. E. Peck. *Pharm. Tech.* 4:55–61 (1981).
9. S. Büyükyaylaci, Y. M. Joshi, G. E. Peck, and G. S. Banker. In J. M. Anderson and S. W. Kim (eds.), *Recent Advances in Drug Delivery Systems*, Plenum Press, New York, 1984, pp. 291–307.
10. R. Gurny, N. A. Peppas, D. D. Harrington, and G. S. Banker. *Drug Dev. Indust. Pharm.* 7(1):1–25 (1981).
11. Y. Kawashima, H. Takeuchi, T. Handa, W. J. Thiele, D. P. Deen, and J. W. McGinity. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Marcel Dekker, New York, 1989, pp. 363–397.
12. K. O. R. Lehmann. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Marcel Dekker, New York, 1989, pp. 153–245.
13. H. Nyqvist. *Int. J. Pharm. Tech. Prod. Mfr.* 4(2):47–48 (1983).
14. C. R. Steuernagel. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Marcel Dekker, New York, 1989, pp. 1–61.
15. H. Kast. *Makromol. Chem. Suppl.* 10/11:447–461 (1985).
16. J. W. Vanderhoff. *J. Polymer Sci. Symp. No.* 41:155–174 (1973).
17. D. P. Sheetz. *J. Appl. Polymer Sci.* 9:3759–3773 (1965).
18. J. Lampert. *Colloid Polymer Sci.* 258:960–967 (1980).
19. H. Goodman and G. S. Banker. *J. Pharm. Sci.* 59(8):1131–1137).
20. R. Baker. *Controlled Release of Biologically Active Agents*, John Wiley & Sons, New York, 1987, pp. 39–83.
21. F. Theeuwes, A. Hussain, and T. Higuchi. *J. Pharm. Sci.* 63(3):427–429 (1974).
22. A. M. Mehta and D. M. Jones. *Pharm. Technol.* 6:52–60 (1985).
23. T. Higuchi. *J. Pharm. Sci.* 52(12):1145–1149 (1963).