

Effect of Curing on Water Diffusivities in Acrylate Free Films as Measured via a Sorption Technique

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ABSTRACT

Studies were performed to investigate the effect of curing on the diffusion coefficients of water, as measured via the sorption technique, in acrylate polymeric films. The mathematical model selected for obtaining diffusion constants from the vapor-phase sorption studies was derived from the long-time Fourier equation used for diffusion into a planar sheet. For Eudragit NE films, the diffusion coefficients of water decreased continuously until a constant minimum value was reached. Diffusion coefficients in Eudragit RS films decreased initially but increased beyond 4 hours of curing at 70°C and 90°C. This latter result suggested the possible evaporation of plasticizer, which also results in a more dramatic increase in glass transition temperature with curing for the Eudragit RS free film in comparison to the Eudragit NE free film. Such loss of plasticizer could also lead to the formation of molecular-scale channels within the films, which would result in increased film permeability. To verify this proposed explanation, the amounts of triethyl citrate plasticizer in Eudragit RS free films were determined using Fourier-transform infrared spectrophotometry. An optimal curing condition was predicted for Eudragit NE and Eudragit RS films based upon the curing conditions at which a minimum value of the diffusion coefficient was reached.

KEYWORDS: Curing, acrylate coating, sorption, diffusion coefficient, glass transition temperature.

INTRODUCTION

When polymeric free films are subjected to storage at temperatures above their glass transition temperatures (T_g), polymer particles undergo coalescence and interdiffusion of polymer chains occurs. This process is often referred to as further gradual coalescence or curing.¹ Interdiffusion of polymer chains during the curing process is characterized by seg-

mental movement and intertwining of the macromolecules in adjacent particles. This process can, ultimately, lead to a loss of particle identity and a completely homogeneous film. The time required to obtain a physically stable film in which further aging does not change the physical characteristics of the film is dependent on several factors, including the type and concentration of plasticizer² and the storage temperature.³ During the curing stage, the microstructure of the polymer film is altered,⁴ resulting in changes in the water diffusivity and the mechanical properties of the film. The dissolution characteristics of the film-coated dosage form also change.^{1,5,6} Furthermore, curing has been shown to promote the homogeneous distribution of the plasticizer within the film.⁷

In this study, sorption techniques have been used to determine the diffusion coefficients of small molecules in Eudragit NE and Eudragit RS polymeric free films as a function of the curing conditions.⁸⁻¹⁰ When the polymeric free films are cured at temperatures above their glass transition temperatures, the polymer chains become more flexible and rearrange themselves so as to result in greater ordering of the chains and densification of the films. This ordering and densification of film should, in turn, decrease the diffusion rate of the penetrant.

The diffusion of water into polymeric films is more specifically described by the general expression for the steady-state flux of molecules through a membrane. Fick's first law of diffusion states that the rate of diffusion across any plane that is at right angles to the direction of diffusion has a simple linear relationship to the concentration gradient across the plane.¹¹ This relationship may be quantitatively defined by a constant called the diffusion coefficient. The study of diffusion into films is started from time zero and continued until a constant rate of transport is attained. For experiments, the sample membranes must be completely dried so that they are initially at zero permeant concentration.¹²

In this study, the long-time Fourier model for diffusion into a planar sheet under non-steady-state conditions¹³ was selected for obtaining diffusion coefficients. This model is based on the following assumptions:

1. The initial concentration of the permeant in the polymer is known and uniform. Hence, the samples must be completely dried so that they are free of any moisture.

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This condition can be satisfied by purging the film prior to introducing it into the stream of water vapor.

- The surfaces of the planar sheet are kept at constant concentration. This is satisfied by maintaining the total fractional uptake at a negligible fraction of the amount of vapor in the environment, or by maintaining the vapor pressure of the permeant in the environment at a constant value.
- Total fractional uptake in the sheet is small.

The equation describing this sorption process is shown below:

$$\frac{M_t}{M_{eq}} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\{-D(2n+1)^2 \pi^2 t/h^2\} \quad (1)$$

For the diffusional process, M_t is the total amount of permeant that has diffused into the polymer strip at time t , and M_{eq} is the total amount of permeant that diffuses into the polymer upon reaching equilibrium or at infinite time. The summation sign in Equation 1 indicates the summation of a series. The term “ n ,” which can range from 0 to ∞ , is the number of the term in the series. D is the diffusion coefficient for the permeant in the polymer in square centimeters per second, t is the time in seconds, and h is the thickness of the film in centimeters.

For long periods of time, the total uptake of vapor by the polymeric free films can be well approximated by the following equation:

$$\frac{M_t}{M_{eq}} = 1 - \frac{8}{\pi^2} \exp\left(\frac{-D\pi^2 t}{h^2}\right) \quad (2)$$

An alternative form of Equation 2 is shown below. This form is obtained by taking the natural logarithm of both sides of Equation 2:

$$\ln\left(1 - \frac{M_t}{M_{eq}}\right) = \ln \frac{8}{\pi^2} - \frac{D\pi^2 t}{h^2} \quad (3)$$

A plot of $\ln(1 - M_t/M_{eq})$ vs t (seconds) will have a linear portion with a negative slope of $D\pi^2/h^2$, from which the value of D can be calculated. Ln represents natural Logarithm and log represents base 10 logarithm, natural log was used for this equation.

In addition to the water diffusivity, the effect of curing on the glass transition temperatures of the Eudragit NE and Eudragit RS free films was investigated. Eudragit RS free films were also characterized for loss of plasticizer as a function of curing condition. Triethyl citrate (TEC) was chosen as a plasticizer for the Eudragit RS system because TEC has been shown to act as an effective plasticizer in reducing the

minimum film-forming temperature and glass transition temperatures of polymeric free films.¹⁴

MATERIALS AND METHODS

Materials

The materials used for the present investigations were all obtained from commercial sources. Eudragit NE and Eudragit RS polymers were both generously donated by Röhm America Inc (Piscataway, NJ). The plasticizer used for preparing the Eudragit RS free films was TEC, which was supplied by Morflex Inc (Greensboro, NC).

Methods

Preparation of Polymeric Free Films

Eudragit NE 30D and Eudragit RS 30D are commercially available as 30% aqueous colloidal dispersions. Both Eudragit NE 30D and Eudragit RS 30D dispersions were separately weighed (50 g each) into glass beakers. Fifteen grams of dry polymer is present in each 50 g of aqueous dispersion. A 1.5-g amount, or 10% wt/wt TEC/polymer, was added separately to the beaker that contained the RS coating dispersion. Sufficient water was added to both beakers to make the total weight equal to 100 g. The coating dispersions were then agitated with magnetic stirrers for at least 8 hours to ensure proper dispersion of the polymer and complete partitioning of the plasticizer into the polymer (Eudragit RS).

Fifteen milliliter portions of both dispersions were pipetted separately into 12, 6-cm diameter, Teflon-coated plates. The contents of the plates were then dried overnight under ambient conditions to allow film formation. Upon drying, the films were removed from the Teflon-coated plates and were cut into square pieces. Each piece of film was measured in 3 different places with a 6-inch electronic digital caliper (NM9560A, Nesco, Amazon, www.amazon.com). The 3 measurements were averaged to obtain each film's thickness. The free films were then cured at 50°C, 70°C, and 90°C for 2, 4, 6, 8, 11, and 24 hours.

Measurement of Diffusion Coefficient of Water

Water vapor sorption studies were performed for all uncured and cured Eudragit NE and RS free film samples using the symmetrical vapor sorption analyzer (SGA-100, VTI Corp, Hialeah, FL). The instrument is designed for obtaining water sorption data at relative humidities between 2% and 98% and at temperatures ranging from 5°C to 60°C. Identical conditions, with respect to temperature and relative humidity, for both the sample and the reference cells are achieved by using a symmetrical 2-chamber aluminum block. Changes in sample weight are determined using a Cahn D-200 microbalance

(supplied by VTI Corp, Hialeah, FL). The microbalance was calibrated before each run using a 20-mg standard weight and glass pans that were supplied by VTI Corp. The relative humidity is determined by measuring the dew point of the process stream. The film samples initially weighed ~50 mg each. After being placed in the VTI chamber, all samples were dried at 25°C for a maximum drying time of 60 minutes, or until they reached a 0.01% weight change over a time period of at least 5 minutes. During the 60-minute drying period, the samples were also purged with dry nitrogen at a back pressure of 20 to 30 psi. After the drying process was completed, the sample was kept at 37°C inside the VTI chamber until the sample weight reading stabilized. The sorption studies were performed at 37°C and at relative humidities ranging from 30% to 90% (in increments of 10%). The criterion for equilibrium for the sorption studies at all relative humidity values was a 0.01% weight change over at least 5 minutes. The sorption data at 30% relative humidity were selected for calculating the water diffusivities in the free films. At 30% relative humidity, the total water uptake is maintained at a limit that fulfills the conditions of the Fourier-series solution without changing the properties of the film samples. A minimum of 3 film samples treated to a particular curing condition were used to calculate the average value for the diffusion coefficient.

To verify that the abbreviated Fourier-series solution (Equation 3) was a good approximation of the original Fourier-series solution (Equation 1), TK solver software (Universal Technical Systems, Rockford, IL) was used to simulate the data that would result from each of the 2 equations. In other words, each equation was assumed, in turn, to be the technically correct equation, and the data were simulated on that basis. Since the 2 data sets were found to overlap each other (Figure 1), it could be concluded that Equation 3 was a good approximation of Equation 1 over the experimental times used in this work. Hence, Equation 3 was fitted to the sorp-

tion data and D was calculated from the slope of the plot of $\ln(1 - M_t/M_{eq})$ vs t . The calculated values for D were plotted vs the curing times (for all curing temperatures) for both Eudragit NE and Eudragit RS free films.

Determination of Glass Transition Temperature by Differential Scanning Calorimetry

The glass transition temperatures (T_g) of the Eudragit NE and RS free film samples cured at 50°C, 70°C, and 90°C were measured using a differential scanning calorimeter (PerkinElmer DSC-7 system with TAC 7/DX thermal analysis controller, PerkinElmer, Waltham, MA). The apparatus was calibrated using the melting transition of indium. The cured and uncured film samples were cut into small pieces, with each piece weighing approximately 8 to 10 mg. The pieces were individually placed inside aluminum sample pans, which were sealed by crimping. Thermal analyses for the free film samples were performed under a nitrogen purge over a temperature range of -20°C to 100°C. A scan rate of 10°C per minute was used. The T_g was calculated from the midpoint of the endothermic curve. There was no replication of the T_g measurement for each condition, as the authors were more interested in the shape of the plot than the absolute value of each T_g .

Determination of Plasticizer Loss Upon Curing by Fourier-Transform Infrared Spectrophotometry

A Nicolet model 210 Fourier-transform infrared (FTIR) spectrophotometer (ThermoElectron Corp, Madison, WI) was used to determine the loss of plasticizer from Eudragit RS free films at different stages of curing. Film samples were cured at 50°C, 70°C, and 90°C in an oven. For each curing temperature, the same film sample was removed from the oven after 2, 4, 6, or 8 hours and was mounted on a V-shaped sample holder inside the FTIR sample chamber. The uncured film samples without plasticizer and the uncured film samples containing 10% wt/wt (plasticizer/polymer) TEC were scanned from 4000 to 400 cm^{-1} before measurement of the cured samples. The instrument operating conditions were as follows: resolution, 2.0 cm^{-1} ; sample scans, 16; gain, 1; aperture, 65; and velocity, 1.583. The peak used for the analysis of TEC (1730 cm^{-1}) was identified by comparing the spectra of the film samples without any TEC to the spectra of uncured film samples containing 10% TEC. The peak at 1150 cm^{-1} was identified in the spectra of the pure polymeric film and was used as the reference peak while the changing TEC peak in the polymer-TEC system was measured. For each film, the peak at 1150 cm^{-1} remained constant over time and over TEC loss. The peak absorbances were used to calculate the amount of plasticizer remaining in the film samples after curing. The peak absorbance reading for the TEC in an uncured film specimen was considered to

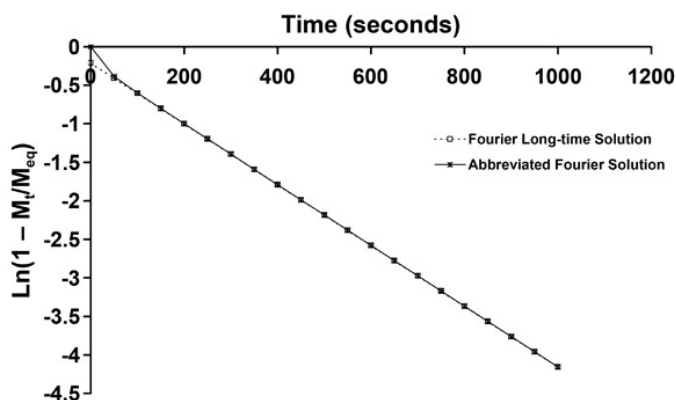


Figure 1. Overlapping of simulated data generated using the original long-time Fourier solution (Equation 1) and the abbreviated Fourier solution (Equation 3).

result from the presence of 100% of the initial amount of plasticizer. The amount of plasticizer remaining in each film was calculated from the peak absorbance reading for that sample. The amount of plasticizer remaining was then plotted vs the curing time for all 3 curing temperatures.

RESULTS AND DISCUSSION

In this study, the diffusion coefficients of water in the Eudragit NE and Eudragit RS free films were determined as a function of curing by carrying out sorption studies at a relative humidity of 30% and a temperature of 37°C using a VTI sorption apparatus. In this method, all variables—sorbed mass, vapor pressure, and temperature—are measured independently and simultaneously. The long-time Fourier equation (Equation 3) was fit to the sorption data to calculate the diffusion coefficients of water in the free films. Two of these plots are shown in Figure 2. Water diffusivities for both Eudragit NE and Eudragit RS free films were calculated at 3 different curing temperatures (50°C, 70°C, and 90°C). Samples were tested in triplicate, and the average diffusion

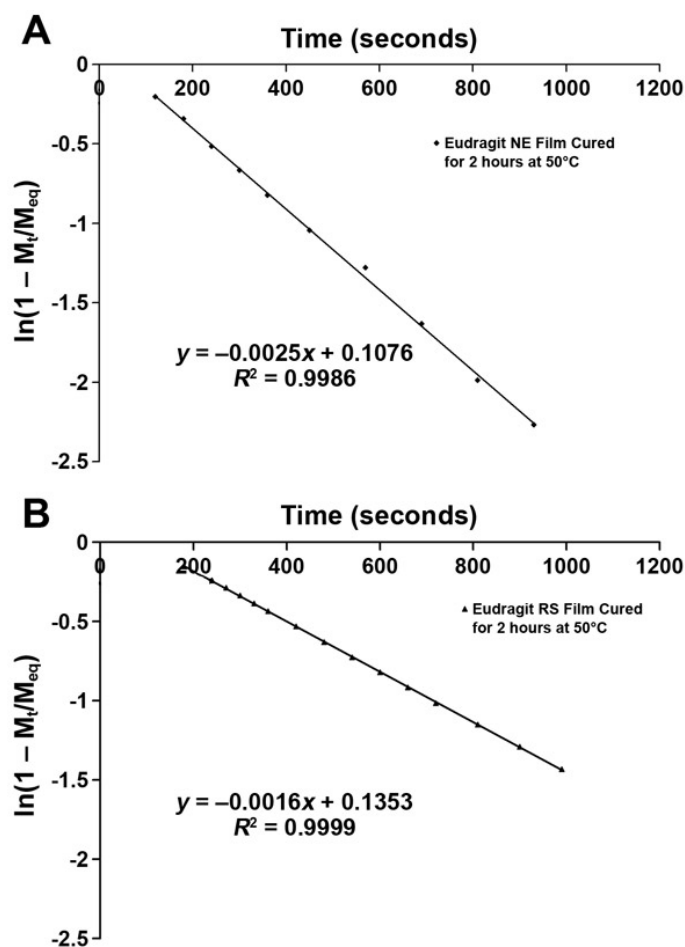


Figure 2. Fitting of the diffusion model (Equation 3) to the water sorption data for (A) Eudragit NE and (B) Eudragit RS free films cured for 2 hours at 50°C.

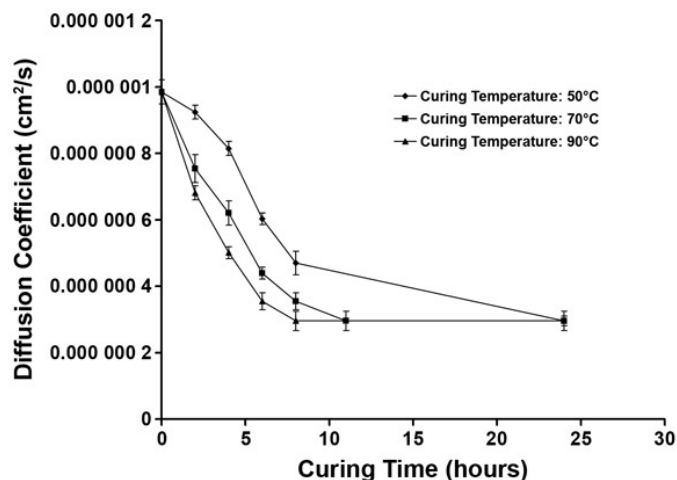


Figure 3. Effect of curing times and temperatures on the diffusion coefficient of water in Eudragit NE free films.

coefficients were plotted vs the various curing times. The error bars in the plots (Figures 3 and 4) represent the standard deviations for 3 samples. Figure 3 shows the effect of curing time and temperature on the diffusion coefficient of water in Eudragit NE free films. For these films, a continuous decrease in the diffusion coefficient of water was observed until a minimum value was reached. This finding is reasonable because longer curing times at a particular curing temperature cause greater polymer particle coalescence and greater film densification. Thus, the water diffusivities in the free films continually decrease with increasing curing time until maximum coalescence (densification) is reached. The minimum time required to reach maximum film densification can be identified as the optimal curing time at any curing temperature, because maximum film densification has occurred with a minimum exposure of the drug product to elevated temperature. For the Eudragit NE free films, the minimum D value is reached within 24 hours of curing

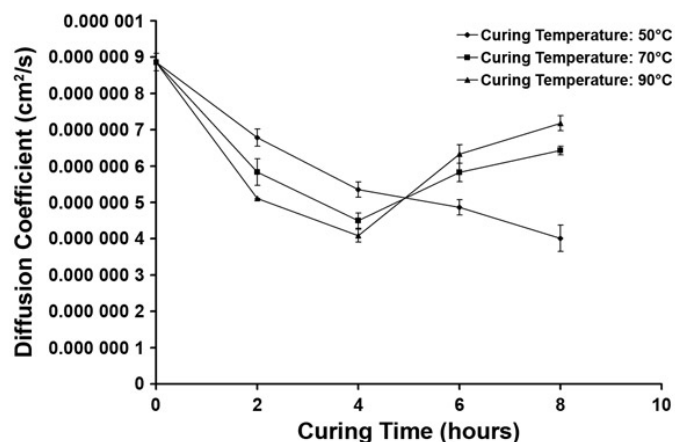


Figure 4. Effect of curing times and temperatures on the diffusion coefficient of water in Eudragit RS free films.

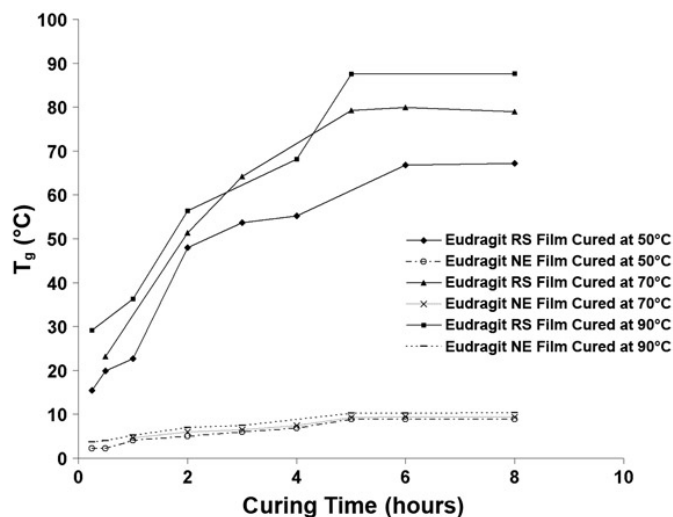


Figure 5. Effect of curing at 50°C, 70°C, and 90°C on the glass transition temperatures (T_g) of Eudragit NE and Eudragit RS free films.

at a curing temperature of 50°C, within 11 hours of curing at 70°C, and within 8 hours of curing at 90°C.

For the Eudragit RS free films (Figure 4), the diffusion coefficient of water shows a continuous decrease with an increase in curing time at 50°C. But, at curing temperatures of 70°C and 90°C, the diffusion coefficient of water vapor decreases until a curing time of 4 hours is reached. Beyond this point, the diffusion coefficient increases instead of decreasing to a plateau. The behavior of the system makes it appear that the cured film is becoming more porous as it is subjected to longer curing times. This observation will be explained later in the article.

From the results of Figure 4, it can be said that the best achievable curing time for the Eudragit RS free films containing TEC is reached within 4 hours at both 70°C and 90°C, because the minimum achievable value for D is reached within this time. Approximately the same minimum D value is reached within 8 hours of curing at 50°C.

The effect of curing at 50°C, 70°C, and 90°C on the T_g of Eudragit NE and RS free films is shown in Figure 5. Plasticizers and moisture help induce and enhance the coalescence of the colloidal polymer particles during the curing process. Plasticizers and water reduce the T_g and the minimum film-forming temperature. These effects result from the plasticizer's ability to weaken intermolecular attractions in the polymer and to increase the free volume of the polymer. It has been shown previously that water evaporation occurs during the film formation process.¹⁵ If plasticizer molecules are also lost during the curing process, both a reduction in plasticization of the polymeric film¹⁶ and an increase in the internal stresses within the coating¹⁷ are possible, and a higher T_g results. In this study, curing was found to significantly change the T_g of both Eudragit NE and Eudragit RS

free film samples. Plasticizer was not added to Eudragit NE, because that polymer forms very flexible films even at room temperature. Thus, the increase in T_g with curing for the NE films was attributed to the loss of moisture during the curing process. The increase in T_g is much more dramatic with the RS film samples when compared with the NE film samples. The difference in results is likely owing to plasticizer loss during curing for the RS free films. In addition to this, the T_g values for both NE and RS free films have been shown to reach a plateau beyond a curing time of 5 hours. This phenomenon could result from exhaustion of plasticizer and residual moisture from the system, which leads to little or no change in T_g when the films are subjected to longer curing times. At normal laboratory temperature and pressure, TEC is a liquid with a boiling point of 294°C. Further characterization of RS free films by FTIR analysis was conducted to confirm the evaporation of plasticizer and also to quantify the amount of plasticizer that was evaporated as a result of curing.

A previous study¹⁸ showed that almost 40% wt/wt of acetyl tributyl citrate plasticizer was lost from free polymeric film samples at a curing temperature of 60°C. Those authors indicated that the loss of plasticizer molecules led to the formation of microvoids in certain regions of the film, which acted as alternate passages for the diffusive loss of drug. This resulted in an increase in drug release and also an increase in permittivity of the free films, as measured using a dielectric analyzer, as a function of curing time and temperature.

In the current study, the plasticizer was TEC, which has a lower molecular weight than acetyl tributyl citrate. The foregoing information would indicate that there is an even greater potential for TEC to be lost from the Eudragit RS free films during the curing process. The carbonyl peak for TEC at 1730 cm^{-1} in the infrared spectrum was selected for analysis, and the absorbance of this peak was determined. The same Eudragit RS free film sample was used for each temperature,

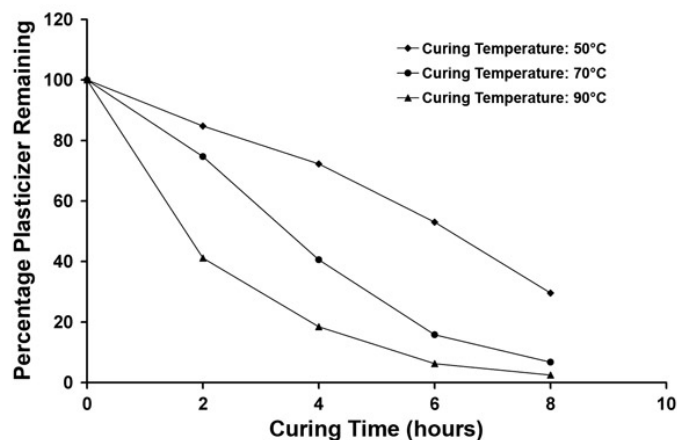


Figure 6. Effect of curing times and temperatures on percentage plasticizer loss from Eudragit RS free films.

and a spectrum was collected after 2, 4, 6, and 8 hours of curing at either 50°C, 70°C, or 90°C. The absorbance value for the uncured film sample was considered to represent 100% of the desired level of plasticizer. Based on this absorbance value, the percentage of plasticizer remaining was calculated for each cured sample. The results of these studies are shown in Figure 6. At a curing temperature of 50°C and after 8 hours of curing time, the percentage of TEC remaining fell to ~30% of the original amount. After 8 hours of curing at 70°C and 90°C, the amount of TEC remaining within the free films was reduced to ~7% and 2%, respectively. The substantial decrease in TEC content confirms the hypothesis that the observed behavior of the diffusion coefficient of water in Eudragit RS free films was caused by the extensive loss of plasticizer and the resultant formation of molecular-scale pathways within the films.

CONCLUSIONS

The curing process affects the microstructure of the polymeric film samples, thus significantly influencing their properties. The extent of the change and the direction of the change are dependent not only on the curing conditions but also on the type of polymeric coating system. An optimal curing condition can be predicted for Eudragit NE films based on the curing conditions at which a minimum D and maximum film densification were achieved.

The Eudragit RS coating system was cured beyond its optimal curing condition, which resulted in excessive loss of plasticizer. The result was a more porous and more brittle film. At higher curing temperatures of 70°C and 90°C, the optimal curing condition for the Eudragit RS/TEC coating system is reached within 4 hours of curing. However, "optimal" curing for this system may not be adequate curing. The loss of plasticizer most likely prevented the film from achieving a high degree of coalescence.

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