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Drug Release From Kollicoat SR 30D-Coated Nonpareil Beads: Evaluation of Coating Level, Plasticizer Type, and Curing Condition

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ABSTRACT A newly available polyvinylacetate aqueous dispersion, Kollicoat SR 30D, was evaluated with respect to its ability to modulate the in vitro release of a highly water-soluble model compound (diphenhydramine hydrochloride) from nonpareil-based systems. Kollicoat SR 30D premixed with a selected plasticizer (10% wt/wt propylene glycol, 2.5% triethyl citrate, or 2.5% dibutyl sebacate), talc, and red #30 lake dye was coated onto the drug beads in an Aeromatic Strea I fluid-bed drier with a Wurster insert using bottom spray. With propylene glycol as the plasticizer, increases in polymer coating level retarded drug release from beads in a stepwise fashion along with apparent permeability, indicating a consistent release mechanism. Stability studies at 40°C/75% RH revealed gradual decreases in dissolution rate, and additional curing studies further confirmed the dependence of release kinetics on curing condition. Furthermore, the type of plasticizer was found to play a key role. Unplasticized formulations exhibited the fastest dissolution, followed by formulations plasticized with triethyl citrate, propylene glycol, and dibutyl sebacate. All 4 formulations (unplasticized and plasticized), nevertheless, revealed a marked difference between uncured and cured dissolution profiles. Kollicoat SR 30D has, thereby, been demonstrated to effectively retard drug release from nonpareil-based systems. However, selected plasticizer type and subsequent curing condition play important roles in controlling drug release from such a system.

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INTRODUCTION

The most widely used aqueous polymer dispersions for sustained-release coating applications are either ethylcellulose-based (Aquacoat ECD, Surelease) or acrylate-based (Eudragit NE30D and others) products. Because of ethylcellulose's relatively high glass-transition temperature (Tg) and pseudolatex nature, ethylcellulose aqueous dispersions require adequate plasticization, with the end product needing further curing steps. Although Eudragit products are true latex with low Tg's, particle coalescence at room temperature is still slow and incomplete, necessitating accelerated curing conditions and/or the incorporation of water-soluble additives [1]. Upon aging, an endogenous surfactant (nonoxynol 100) of Eudragit NE30D was recently found to be prone to gradual precipitation from the cast-free film, thereby creating pores in the film and potentially affecting product dissolution [2].

Recently, Kollicoat SR 30D, an aqueous dispersion composed of 27% polyvinyl acetate (PVAc), 2.5% povidone, and 0.3% sodium lauryl sulfate, was introduced by BASF AG (Ludwigshafen, Germany) [3, 4]. With adequate plasticizing, the formed PVAc film has been shown to possess unique physical and mechanical properties such as enormous flexibility, rendering the film-coated pellets compressible without rupture [5]. Additionally, PVAc-based matrix and film-coated products were demonstrated to release drugs in a pH-independent fashion [4, 6, 7].

An added advantage in taste-masking formulations has also been claimed when this material is used in the presence of soluble and/or swellable pore formers [8].

Although ample data have been published or presented on coated beads produced by extrusion, limited information is available on the performance of Kollicoat SR 30D-coated nonpareil systems involving aqueous layering technology. It was therefore the purpose of this study to examine, in detail, the effects of coating level, plasticizer type, and curing conditions on drug release kinetics from such nonpareil systems. Mathematical treatment and modeling of dissolution data were also attempted using a model developed for nonpareil systems that takes into consideration the bead volume change due to swelling in aqueous medium.

MATERIALS AND METHODS

Materials

Diphenhydramine hydrochloride USP was internally obtained from Pfizer Chemical Development. Kollicoat SR 30D was obtained from BASF Corporation (Mount Olive, NJ). Nonpareil beads (Sugar Spheres NF) of 16-18 mesh cut were purchased from Paulaur (Cranbury, NJ). Propylene glycol and triethyl citrate were purchased from Lyondell Chemical (Houston, TX). Dibutyl sebacate was provided by Morflex (Greensboro, NC) as a sample. Red #30 lake dye was provided as a sample by Colorcon (West Point, PA). All other excipients and reagents were sourced through internally approved vendors.

Layering of Diphenhydramine Hydrochloride onto Nonpareil Cores

Diphenhydramine hydrochloride (214.1 g) was dissolved in 125 g of water to form a concentrated drug solution. Five hundred grams of nonpareil cores were then loaded into an Aeromatic Strea I (Niro, Columbia, MD) equipped with a Wurster insert and a bottom-spray gun. Spraying of the solution was carried out at an atomization pressure of 1.0 bar, an inlet temperature of 60°C, a spray rate of 5 mL/min, and a fan speed of 7 to 9. Upon completion of spraying, the drug-loaded beads were further dried at 60°C inlet temperature for 5 minutes. The end product was then sieved on top of a 20-mesh screen to eliminate fines.

Coating of Kollicoat SR 30D Film

Talc and the lake dye were first dispersed in water, followed by the addition of Kollicoat SR 30D and a selected plasticizer. The final mixture was stirred for 30 to 60 minutes before spraying commenced. The detailed coating suspension compositions are contained in Table 1.

Drug spheres (320 g) were then loaded into the Aeromatic Strea I unit, and coating was initiated. A 0.8-mm diameter spray nozzle was used with atomization air pressure set at 1.0 bar for all runs. The inlet air temperature for batches without a plasticizer or plasticized with propylene glycol was 60°C. When either triethyl citrate or dibutyl sebacate was used, the inlet air temperature was reduced to 50°C to eliminate pellet sticking. The starting spray rate was 2 mL/min, and it was gradually increased to 5 mL/min over the first 25 minutes. Coating was continued until completion at this spray rate. Assay of drug content in the spheres before and after the film-coating process indicated a coating efficiency of ≥ 98%.

Except for the coating-level study, where the weight gain varied from 0% to 20%, all other formulations were coated to a constant weight gain of 15%.

Curing Conditions

To evaluate the effect of curing on drug release, the beads were spread on a tray and placed in a Hotpack Supermatic oven (Philadelphia, PA) preequilibrated to a set temperature (40, 50, 60, 70, or 80ºC) for 16 hours. Dissolution testing was performed after the beads were allowed to cool at room temperature for at least overnight or longer.

Table 1. Composition of Film Formulations*

Composition	No Plasticizer		Propylene Glycol		Triethyl Citrate		Dibutyl Sebacate	
	g/batch	% wt/wt*	g/batch	% wt/wt*	g/batch	% wt/wt*	g/batch	% wt/wt*
Kollicoat SR 30D	155.27	82.50	141.20	74.99	151.48	80.49	151.48	80.49
Plasticizer	0	0	4.24	7.51	1.13	2.01	1.13	2.01
Talc	9.18	16.25	9.18	16.25	9.18	16.25	9.18	16.25
Lake dye	0.71	1.25	0.71	1.25	0.71	1.25	0.71	1.25
Water	127.00	-	127.00	-	127.00	-	127.00	-

*on dry basis

Stability Testing Protocol

Film-coated beads were packaged in 20-g quantities into 90-cc high-density polyethylene bottles. One 1-g Sorb-it desiccant cartridge (United Desiccants, Belen, NM) was placed into each bottle. The bottles were then closed with 38-400 C/R caps and induction sealed using an Enercon LM3620-01 induction sealer (Enercon Industries, Menomonee Falls, WI). The bottles were then placed inside Espec humidity cabinets (Tabai Espec, Osaka, Japan) pre-equilibrated to 25ºC/60% relative humidity (RH) and 40ºC/75% RH. At predetermined timepoints, bottles were pulled from stations and tested for dissolution.

Dissolution Methodology

Dissolution testing was performed using an automated Distek 2100c apparatus (North Brunswick, NJ) with a model HP8453A diode-array spectrophotometer (Agilent Technologies, Palo Alto, CA) using a detection wavelength of 258 nm. Paddle method (USP Apparatus II) was used with 900 mL purified water as the medium, at a water bath temperature of 37ºC and a paddle speed of 100 rpm. A suitable amount of beads containing 300 mg of drug was weighed out individually for each vessel. The means of 6 determinations were reported for each run.

Drug Release Modeling

Because of a moderate swelling of the beads during dissolution (as shown in Figure 1), a mathematical treatment developed by Tang et al [9, 10] specifically for film-coated nonpareil systems was used to determine the apparent permeability of diphenhydramine hydrochloride across the Kollicoat SR 30D-coated film barriers.

$$\% \text{ drug released} = 100 - 100 \exp\left[-\frac{\bar{P}}{n} t^n\right]$$

where t is time in hours, $\bar{P}$ is the apparent permeability of the film to diphenhydramine, and n is a shape factor obtained from nonlinear regression using SigmaPlot (Jandel Scientific/SPSS, Chicago, IL).

RESULTS AND DISCUSSION

Photomicrographs of the Nonpareil System

Photomicrographs of nonpareil cores, drug-loaded cores (30% drug load), polymer-coated beads (15% weight gain), and beads recovered after dissolution are shown in Figure 1. Using optimized parameters, the bead-sticking problem was minimized and the

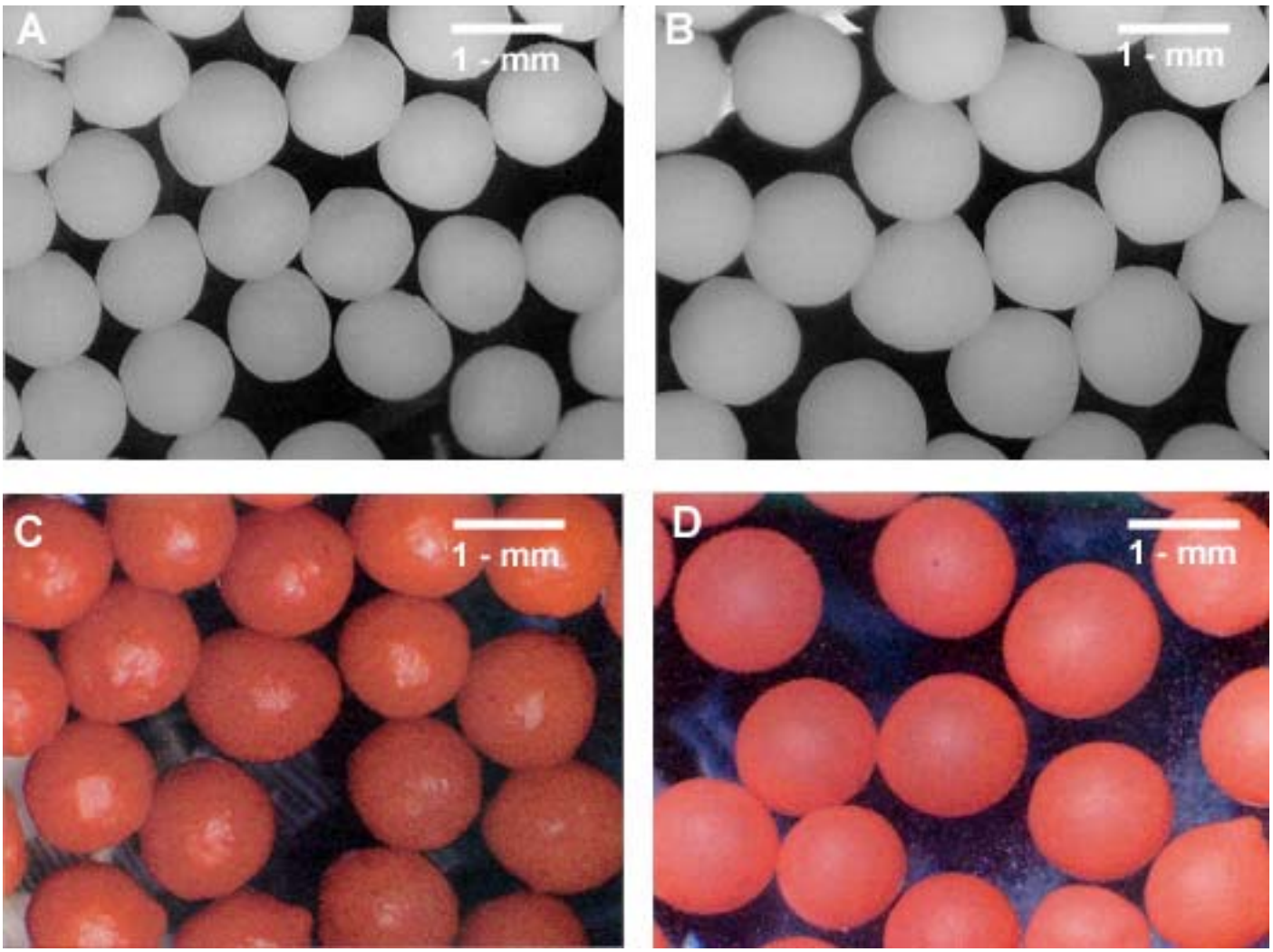

Figure 1. Photomicrographs of nonpareil cores (A), cores loaded with drug (B), polymer-coated drug beads (C), and beads recovered after dissolution run (D). Pictures were taken on a Hi-Scope at 50x and 25° angle.

end products showed few triplets and very limited twins. Size increase after drug loading and a moderate swelling effect after dissolution run are evident.

Effect of Coating Level on Drug Release

Propylene glycol was selected as the plasticizer in the coating-level study, and the drug-nonpareil beads were coated to different weight gains (0%-20%). The dissolution profiles are depicted in Figure 2. Beads without any polymer coating released the drug instantly, ie, by the first sampling point. Increases in coating level resulted in gradual reductions not only in the release rate but also in the profile shape (from asymptotic to sigmoidal at 20% weight gain). The profiles were then fitted into the equation, to determine the apparent permeability constants. The permeabilities, when plotted on a logarithmic scale as per treatment of Tang et al [9, 10], appear to be inversely related to the percent weight gain, as shown in Figure 3. Such monotonous decreases in permeability indicate the lack of a critical coating level, at which a change in the release mechanism has been observed for Surelease-based nonpareil systems [11]. The absence of the critical coating level can be explained by the povidone component in the Kollicoat SR 30D, which leaches out of the film forming a porous membrane much like that of the Surelease system in the pres-

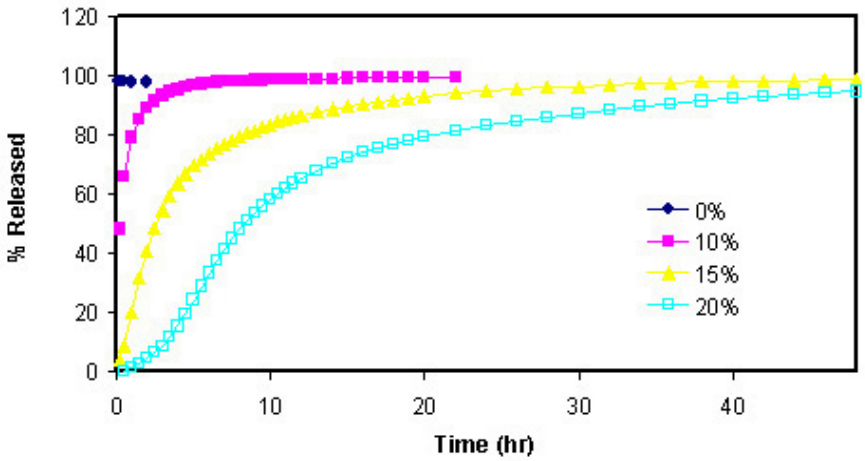

Figure 2. Effect of polymer coating level on drug release. Propylene glycol is the plasticizer.

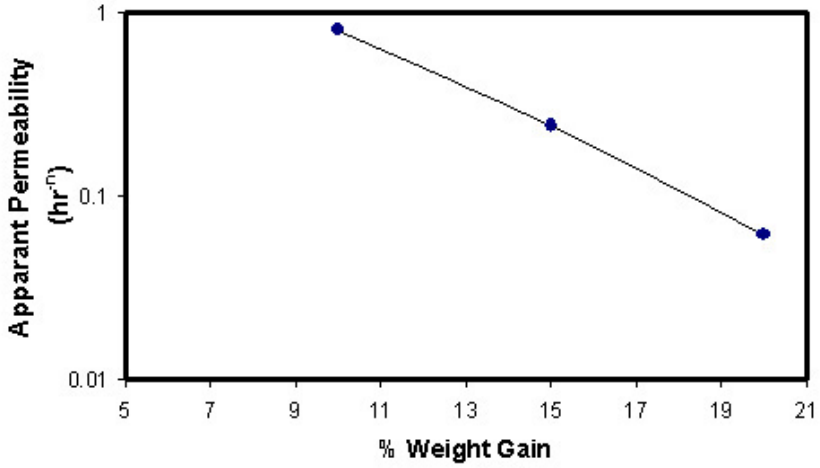

Figure 3. Dependence of apparent permeability on polymer coating level, expressed as percent weight gain.

ence of an added hydroxypropyl methylcellulose component [10].

Stability Studies

Beads coated with Kollicoat SR 30D plasticized with propylene glycol at a 15% coating level were then placed on stability. The dissolution profiles of beads pulled from stability stations are schematically illustrated in Figure 4. No significant trend was observed for samples stored at 25°C/60% RH. Testing of samples stored at 40°C/75% RH, on the other hand, revealed stepwise decreases in dissolution rate. The slowing-down effect was evident even after just a 1-day storage time.

This observation closely resembles previous findings from this laboratory involving Kollidon SR matrix tablets [12]. Such a change in dissolution profile is usually indicative of polymer structural

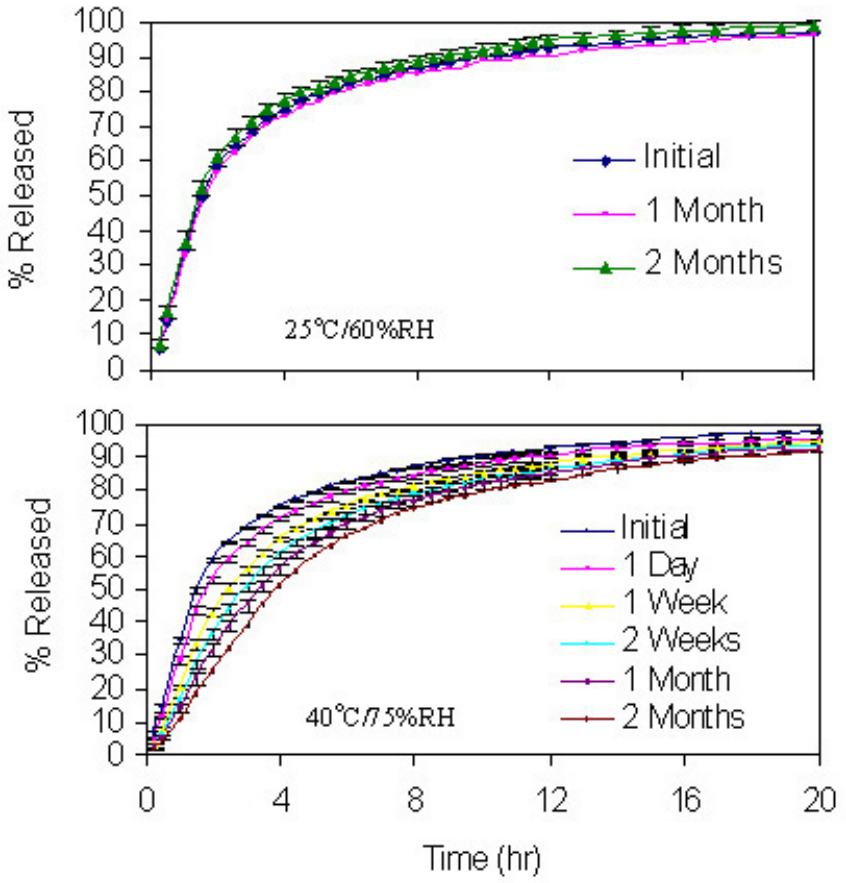

Figure 4. Diphenhydramine release from Kollicoat SR 30D-coated nonpareil beads, placed on stability at 25°C/60%RH and 40°C/75%RH (closed bottle). Coating level was 15% with propylene glycol as the plasticizer.

relaxation [13, 14, 15], necessitating a curing evaluation study. Pellets of the same formulation (but from a separate batch run) were then cured at different temperatures for 16 hours and tested for dissolution. The results are illustrated in Figure 5. Increases in curing temperature resulted in continuous decreases in dissolution, up to a temperature of as high as 80°C. Further heat treatment at a condition above 80°C was not performed. The apparent permeabilities were then plotted as a function of curing temperature (Figure 6). Increases in curing temperature resulted in decreases in permeability in a nonlinear fashion, with a bottom-out effect occurring well above 80°C.

Whether the observed stability/curing phenomena are related to a selected drug candidate or a particular pellet system (layered nonpareil vs. extruded) remains to be elucidated. Kolter and Scheiffele [16] reported little curing effects on extruded pellet systems containing caffeine, propranolol, and theophylline. Dashevsky et al [17] reported an increase in ibuprofen release following curing at 60°C for 24 hours. The authors further demonstrated that partitioning of ibuprofen into Kollicoat SR 30D coatings during storage or curing was the cause. An immediate seal coat was found to reduce the diffusion and thereby stabilize drug release.

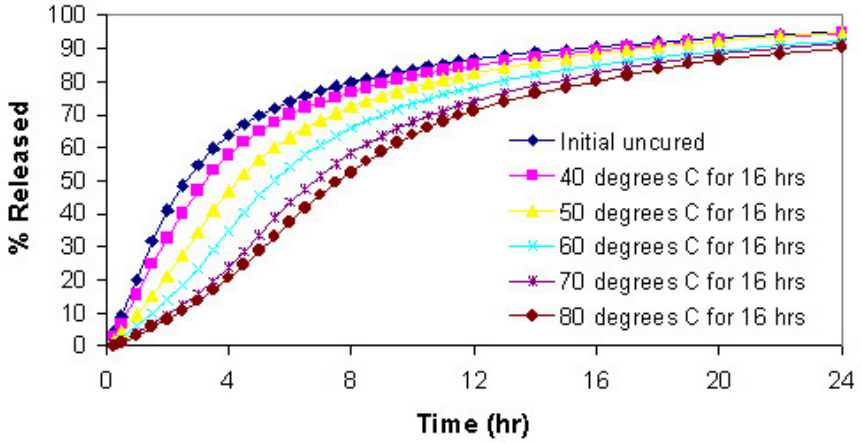

Figure 5. Dissolution profiles as a function of curing temperature. Propylene glycol is used as the plasticizer.

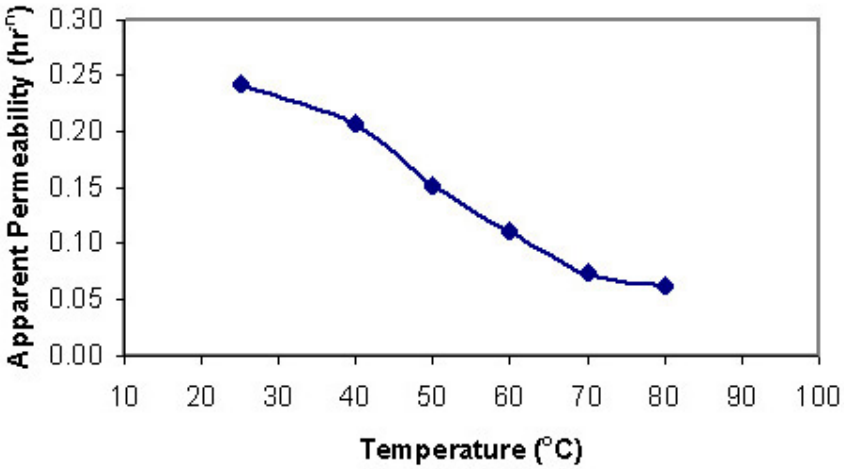

Figure 6. Effect of curing temperature on apparent permeability.

Formulations Containing Various Plasticizers

To clarify further whether the observed curing dependency is unique to the propylene glycol-Kollicoat system, batches containing no plasticizer, triethyl citrate, or dibutyl sebacate were also prepared. The dissolution profiles are schematically illustrated in Figure 7. First, the incorporation of a plasticizer in the system was found to be an important factor, without which a much faster dissolution rate was found (as shown in Figure 7A). Second, the specific type of plasticizer also played an important role, as shown in Figure 7B, C, and D. At the concentrations chosen in this study, dibutyl sebacate was found to be most effective in attenuating drug release, followed by propylene glycol and triethyl citrate. A similar study involving different plasticizer/polymer combinations on theophylline release from ethylcellulose and acrylic polymer-coated pellets has been conducted by Saettone et al [18]. The type and amount of plasticizer were found to alter membrane permeability, probably by affecting par

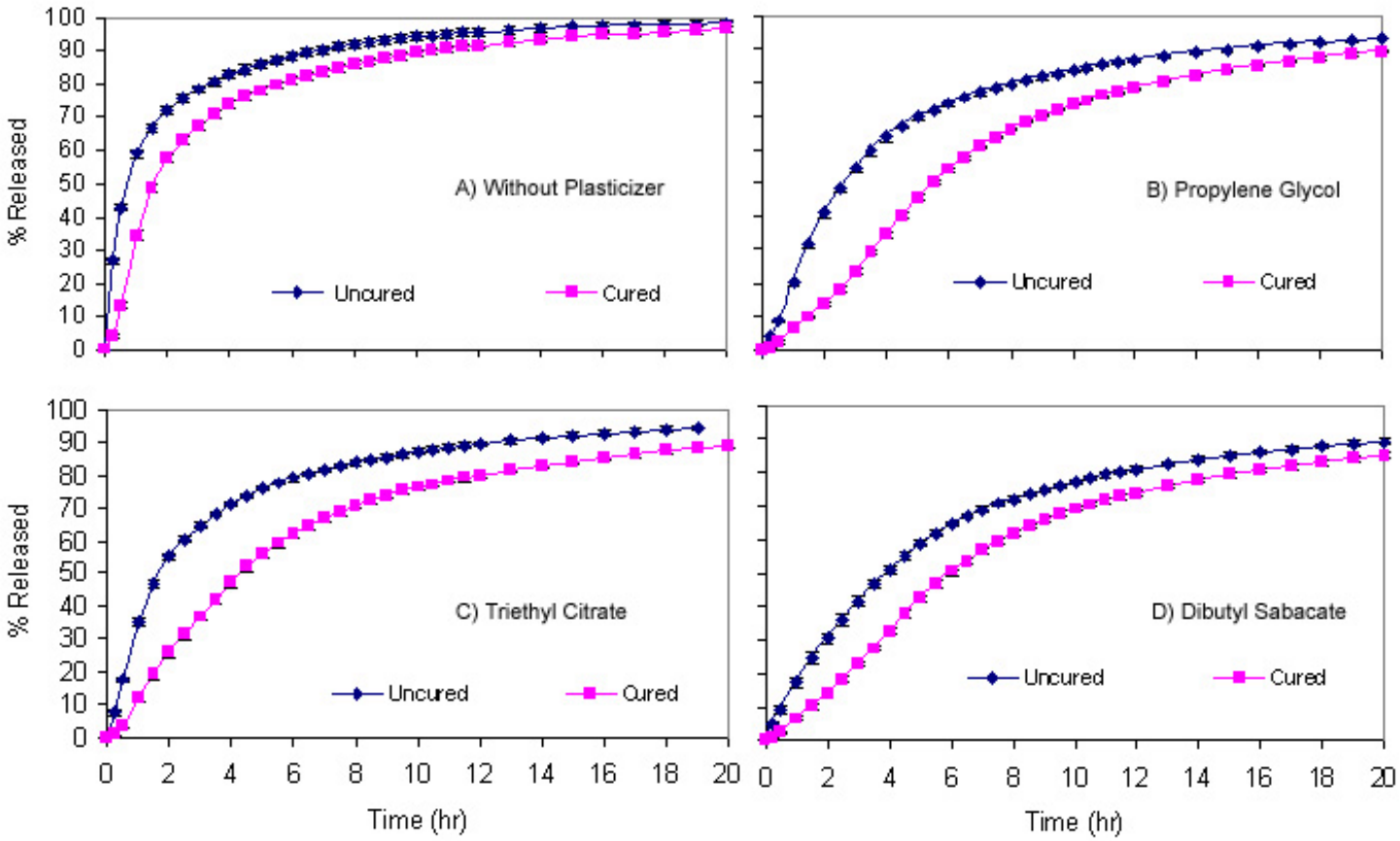

Figure 7. Dissolution profiles of diphenhydramine from Kollicoat SR 30D-coated nonpareil beads as a function of plasticizer type and curing at 60°C for 16 hours.

ticle coalescence, modifying film hydrophilicity, or the combination thereof.

The differences between the release profiles before and after curing are clearly depicted in Figure 7, in each of the 4 formulations. Nevertheless, the impact of curing on each formulation (as gauged by the gap between the cured and uncured profile) appears to be different, with the unplasticized formulation being least affected and the propylene glycol formulation being most affected at this temperature/duration (60°C/16 h).

Although quite effective as a plasticizer for Kollicoat SR 30D, dibutyl sebacate does not appear to be well dispersed in the system. Nonhomogeneous oil droplets were visible under microscope in cast films on petri dishes (photomicrographs not shown). The value of this plasticizer in the Kollicoat SR 30D system needs to be further evaluated.

CONCLUSIONS

The use of polyvinylacetate/propylene glycol–based aqueous dispersion in coating nonpareil beads resulted in effective retardation on the release kinetics of a highly water-soluble model compound, diphenhydramine hydrochloride. The release profile can be tailored by changing the coating thickness (weight gain) without altering the release mechanism. Gradual decreases in dissolution rates of beads placed on stability at 40°C were detected. Further curing studies at various temperatures proved that an additional curing step is needed for Kollicoat SR 30D-coated diphenhydramine nonpareil systems. The identification of a suitable curing condition, however, appeared to be rather challenging since a stabilizing effect occurred at above 80°C.

The observed curing dependency was also demonstrated in formulations containing (or without) other plasticizers, although the curing-induced changes varied significantly depending on the nature of the particular plasticizer. This observation, therefore, underscores the importance of proper plasticizer selection for a given system.

Current findings and previous observations involving Kollidon SR matrices [12] suggest the dependence of polyvinylacetate-based dosage forms on additional curing. Comparing available data generated from Aquacoat-, Surelease-, and Eudragit-based systems, one would be prudent to conclude that a curing step needs to be evaluated early on during formulation development for aqueous polymer-coated products.

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