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EVALUATION OF A CELLULOSE ACETATE (CA) LATEX AS COATING MATERIAL FOR CONTROLLED RELEASE PRODUCTS

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ABSTRACT

Cellulose acetate (CA) latex plasticized with 150% triacetin (TA) and 120% triethylcitrate (TEC), based on polymer weight, provided dense and homogeneous films when deposited onto propranolol HCl tablets using conventional fluid bed technology. Film permeability to the drug was low and flux/permeability enhancers were added to the CA structure during its manufacture. Films containing 40% sucrose and 10% PEG 8000 were found to provide the best release characteristics in terms of small lagtime (1 hour) and drug release profile (over 12 hours). When sucrose was added to TA or TEC plasticized films, a macroporous membrane was created during exposure to the dissolution fluid due to sucrose release from the film. These observations are consistent with the controlled porosity walls previously described for CA films deposited from organic solvents. It was postulated that drug mass transport occurs mainly within the porous CA structure and the mechanism responsible for it is a combination of molecular diffusion/osmotic pressure via water transport into the porous cellulose acetate membrane. Plasticizer loss during drying had also been demonstrated and related to the change in release profile seen with drying time.

INTRODUCTION

There is a need in the pharmaceutical industry for membrane-coated tablets whereby the water-insoluble membrane is deposited from a totally aqueous based

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system. This need for controlled release films is particularly important for drug candidates that are used clinically at doses higher than 250 mg, where it is very difficult to develop a multiparticulate extended release dosage form. Cellulose acetate (CA) membranes have been used for many years in the development of osmotic and diffusion controlled drug delivery systems. Usually, these membranes are made by dissolving CA (or a mixture of CA's)/plasticizer(s)/additive(s) in a organic solvent system, followed by their deposition onto a solid substrate using current film coating technologies. The use of a CA aqueous colloidal dispersion would eliminate the need for organic solvents in the manufacture of these delivery systems.

Latex preparations of cellulose acetate with a degree of acetylation of 39.8% have previously been reported[1]. Aqueous dispersions were prepared by dissolving the polymer in an organic solvent system followed by emulsification of the solution in an aqueous phase. The crude emulsions were passed into an homogenizer and the solvent(s) were then evaporated under vacuum. Using these latices[2], it was noticed that the level of plasticizer generally needed for conventional film coating formulations was inadequate to plasticize cellulose acetate colloidal dispersions. Plasticizer levels from 160 to 320% by weight of CA (diacetin, diethyltartrate, ethylene glycol mono and diacetate and trimethylphosphate) were needed to provide strong films comparable to those obtained from organic solutions. It was also reported that the major part of the plasticizer evaporates from the film at 60°C and that high boiling point additives such as diacetin and diethyltartrate gave weaker membranes because they were more retained in the film than more volatile plasticizers. The use of volatile plasticizers would be difficult to justify from an environmental point of view since it implies that large amounts of plasticizers would be expelled in the atmosphere. Furthermore, it might be difficult from a regulatory standpoint to use the previously mentioned plasticizers in an actual product since none of them are designated USP/NF. In this study TA and TEC were used as plasticizers for CA latex because they were found compatible with CA. The films were homogeneous

and well plasticized with no phase separation occuring. The plasticizers have relatively low vapor pressure due to their high boiling points (TA: 258-260°C, TEC: 294°C) and are well characterized having USP/NF designation.

Water transport accross cellulose acetate membranes produced from a cellulose acetate latex system was also reported by the same authors[3]. Water permeability of these membranes was found to be strongly dependent on the nature of the plasticizer and on the processing conditions (by a factor of about 30 between the least and the more permeable films). High boiling point plasticizers gave more permeable membranes.

Potassium chloride was also used as a model drug[4] to evaluate its release from an elementary osmotic pump[5] using a coating made from an aqueous cellulose acetate dispersion. A 250 μm aperture was drilled in the coating. As expected, the device operated as an osmotic pump and release rates were found to be controlled by the physico-chemical properties and concentration of the plasticizer, as well as processing conditions, i.e. inlet temperature, spray rate and drying time.

In a production environment, the micro-orifice in the elementary osmotic pump is generally made by a laser beam. This orifice releases the hydrostatic pressure created by the osmotically active agent and provide a port for drug delivery. Release rate is controlled by the rate of water ingress across the semi-permeable membrane and the osmotic activity of the core. More recently, controlled porosity osmotic devices have been described[6,7]. The concept is an extension of the elementary osmotic pump. The device does not require a releasing aperture since the membrane contains a water soluble agent incorporated during its manufacture. This water soluble agent is released in an aqueous medium thereby creating a macroporous membrane through which the drug can be released. The mechanism of water transport and osmotic flow in controlled porosity osmotic devices have been studied[8,9]. The challenge in the early development of such a delivery system is to be able to adjust the release rate to suit a particular application while maintaining good film mechanical properties in

order to avoid any dose dumping in the GI tract. Release rates are generally modulated by varying the amount of water soluble pore former(s)/permeability enhancer(s) in the coating and by film thickness. Once a prototype formulation is developed, scaleup becomes another challenge since process parameters must be closely monitored and controlled for the manufacture of these delivery systems.

A preliminary evaluation of a CA latex dispersion (39.8% degree of acetylation, 29% solids content, undergoing development by the FMC Corp.) was carried out in order to assess its potential use as a rate controlling polymeric membrane for drug delivery. The goals of this study were to: 1. evaluate film forming properties of a CA latex by spraying the plasticized latex onto placebo and propranolol-HCl tablets; 2. assess film functionality by measuring the release of propranolol-HCl used as the model compound; and 3. show the effect of flux enhancers (PEG 8000, HPMC 5 cP and sucrose) on release profiles.

MATERIAL AND METHODS

Placebo and Propranolol-HCl Tablets

Placebos were prepared using microcrystalline cellulose (Avicel PH101, 40% w/w), spray dried hydrous lactose (DCL 11, Mallinckrodt, 59.5% w/w) and magnesium stearate (0.5% w/w). These ingredients were blended and then compressed at 210 mg tablet weight and > 10 KP (Schleuniger) hardness using 8 mm, round plain tooling. Propranolol-HCl (Sigma) 60 mg tablets were prepared using microcrystalline cellulose (Avicel PH101, 36% w/w) and spray dried hydrous lactose (DCL 11, Mallinckrodt, 34.9% w/w). These materials were sieved through a 30 mesh (590 μm) screen, lubricated with 0.5% magnesium stearate and compressed at 210 mg tablet weight and 7-9 KP hardness using 8 mm round plain tooling. Punches had two radii of curvature, 14.7 and 1.81 mm.

CA Latex Coating Dispersion

Lot #X9481 was refrigerated at 5°C upon receipt, as recommended by the FMC Corp. The CA latex contains:

27.6% CA 398-10 (39.8% degree of acetylation)

1.4% Sodium Lauryl Sulphate

71.0% Water

The solids content was tested and found in agreement with the supplier value, i.e. 29%. Scanning Electron Microscopic (SEM) evaluation on the dried latex showed the particles to be less than 1 μm.

Triethylcitrate (TEC, Pfizer, b.p.: 294°C) and triacetin (TA, Anachemia, 99%, b.p.: 258-260°C) were used as is and were added to the latex at various levels (60-150% based on polymer weight) to evaluate their ability to plasticize the film. HPMC 5 cP (Methocel E-5, Dow Chemical Corp.), Sucrose and polyethylene glycol (PEG 8000, Carbowax, Union Carbide Corp.) were used as permeability enhancers and were added at 10-50% levels (based on polymer weight). Silicon Dioxide (Syloid 74FP, Davison Chemical) was used to decrease film tackiness during coating and was dispersed with flux enhancer(s) solutions prior to its addition to the plasticized latex. Percentages are expressed as % by weight. The latex was first allowed to equilibrate at 20-22°C, then water was added to dilute the dispersion to 20% solids content. Plasticizers were slowly poured into the diluted latex and the mixture agitated for 30 minutes prior to any other addition. Flux/permeability enhancers were dissolved in sufficient water to make the final dispersion 15% solids content upon to their addition to the plasticized latex. All dispersions were sprayed at 15% solids content. The plasticized latex was agitated for 30 minutes, filtered through a 60 mesh (250 μm) screen and sprayed (with mild agitation to avoid any coagulation) onto tablets.

Coating Trials

Tablets were coated in a 10 cm diameter fluidized bed Wurster column equipped with a bottom spray pneumatic nozzle. Process parameters were as follows:

Load: 750 g, 8 mm diameter tablets

Pre-Heat Time: 2 min.

Atomizing Air Pressure: 2 bars (30 psi)

Inlet Temperature: 55°C

Outlet Temperature: from 31-45°C

Spray Rate: 9-13 g/min

Theoretical Weight Gain: 15%

Drying: 55-60°C for 2 to 24 hours in a Colton air stream oven

Film Evaluation

Films were evaluated for physical appearance and functionality by SEM (Jeol 820) and drug release (USP-2/water/50 rpm, 290 nm UV detection) using a Hewlett-Packard 89024B dissolution testing system equipped with a HP 8450A diode array spectrophotometer. All films had a thickness of about 50 to 60 μm.

Assessment of Plasticizer Volatility

Approximately 10 g of TA, TA plasticized latex (150%), TEC and CA latex were poured into tared glass petri dishes (n=4) having 63 cm^2 surface area. Petri dishes were then introduced in a Colton air stream oven at 60°C and weight losses were monitored over a 24 hour period of time.

Effect of Curing/Drying Time on Drug Release

A batch of tablets were coated with a film containing 40% sucrose, 10% PEG and 120% TEC as the plasticizer, based on polymer weight. Tablets were dried/cured in a Colton air stream oven at 60°C. Samples were taken periodically over 24 hours and tested for drug release.

RESULTS

TA as a Plasticizer/Without Permeability Enhancer(s)

The level of TA needed to provide film formation at reasonable temperatures (<70°C) was found to be between 120 to 150%, based on polymer

weight. Scanning electron micrographs showed these films to be dense, homogeneous and free from defects at tablet edges. Below this plasticizer level, films deposited onto placebos showed severe cracking after drying for 16 hours at 55°C, indicating underplasticization. TA was therefore used at 150% level in all subsequent experiments. Figure 1 shows scanning electron micrographs of a CA latex/triacetin plasticized film deposited onto propranolol HCl 60 mg cores. A dense, non-porous and homogeneous structure, free of defects at tablet edges was produced. Figure 2 shows % Propranolol HCl released as a function of time from coated tablets. Uncoated tablets released 95% of the drug after 30 minutes. For the coated tablets, no drug was released for the first 8 hours, altough water had penetrated through the membrane causing tablet swelling. These findings indicate that the membrane has low permeability to the drug, even though the theoretical TA content is high. In order to permit the release of the hydrostatic pressure and provide a port for drug release, an elementary osmotic pump was created by drilling a 250 μm diameter aperture in the coating with a high precision electric drilling machine. In this case, propranolol HCl was released at a rate of about 3% per hour with a 2 hour lagtime.

TA as a Plasticizer/With Permeability Enhancer(s)

Means of increasing membrane permeability were investigated by the addition of HPMC 5 cP or sucrose to the TA plasticized CA latex (Figure 3A). When HPMC was added to the film, release profiles were characterized by approximately the same lagtime, i.e. 3 hours and by release rates that increased with increasing HMPC content in the membrane. At 15% HPMC level, tablets had a tendency to swell and the film to rupture, showing insufficient porosity and/or film strenght.

Sucrose was added to TA plasticized films at 10, 15 and 20% levels, based on polymer weight. Films containing sucrose showed a decrease in lagtime with an increase in sucrose content (Figure 3B). However, release rates were not significantly affected by sucrose content. SEM showed all films to have a dense,

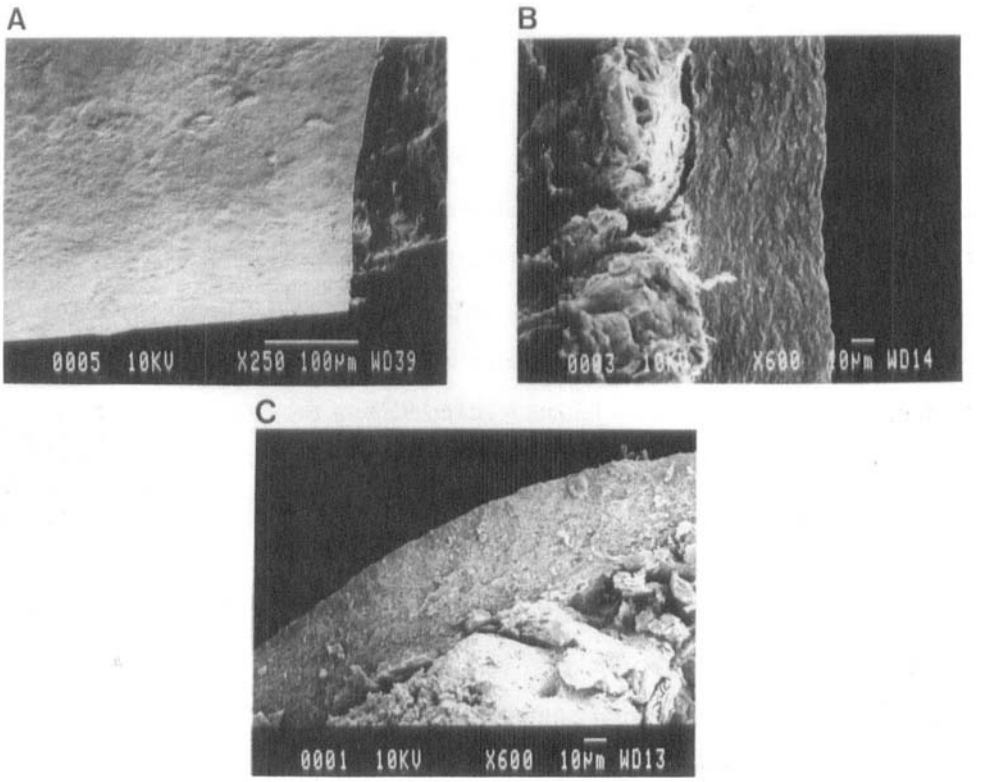

FIGURE 1

Scanning electron micrographs of CA latex/TA plasticized film deposited onto propranolol HCl 60 mg tablets; (A) outer surface at tablet edges (X250); (B) cross-section (X600) and (C) cross-section at tablet edges (X600).

homogeneous structure of about 60 µm thickness. CA/sucrose films evaluated after drug release (Figure 4) showed a highly porous structure by SEM presumably due to sucrose leached out. The same evaluation done before exposure to the aqueous medium showed no porous network. Films without sucrose did not show any porous CA network either before or after exposure to aqueous test fluids. When sucrose was added at levels higher than 20%, films did not withstand the dissolution procedure, i.e. they ruptured.

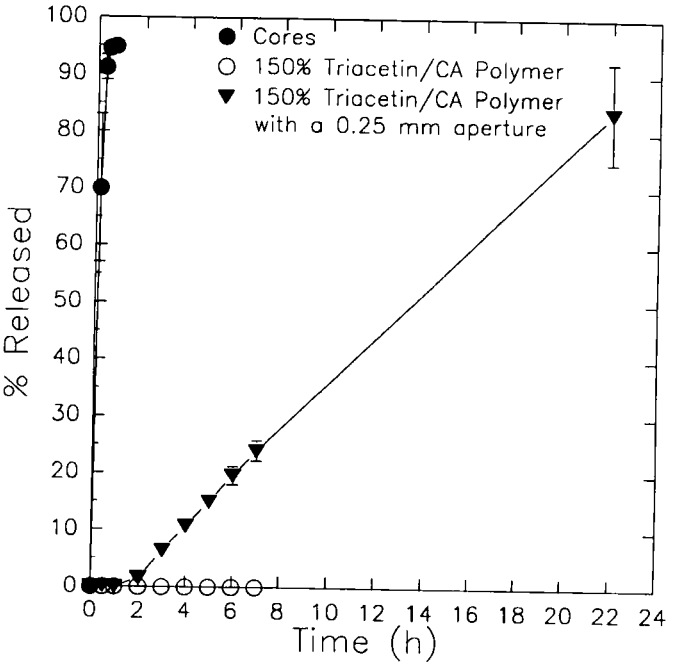

FIGURE 2

% Propranolol HCl released as a function of time from cores; CA latex plasticized with 150% TA coated tablets; and coated tablets where the coating was perforated with a 0.25 mm aperture. Mean (s.d., n=6).

Tables 1 and 2 show formulae and process parameters for CA coating dispersions plasticized with TA and sprayed onto propranolol HCl tablets.

TEC as a Plasticizer/Without Permeability Enhancers

The level of TEC needed to provide film formation at reasonable temperatures (<70°C) was found to be between 60-120%, based on polymer weight. Films that contained 60, 70 and 80% TEC were weak when introduced in the dissolution medium and ruptured. Films plasticized with 120% TEC were strong and as in the case of TA, did not release any drug after 8 hours, even though water had penetrated the membrane causing tablet swelling.

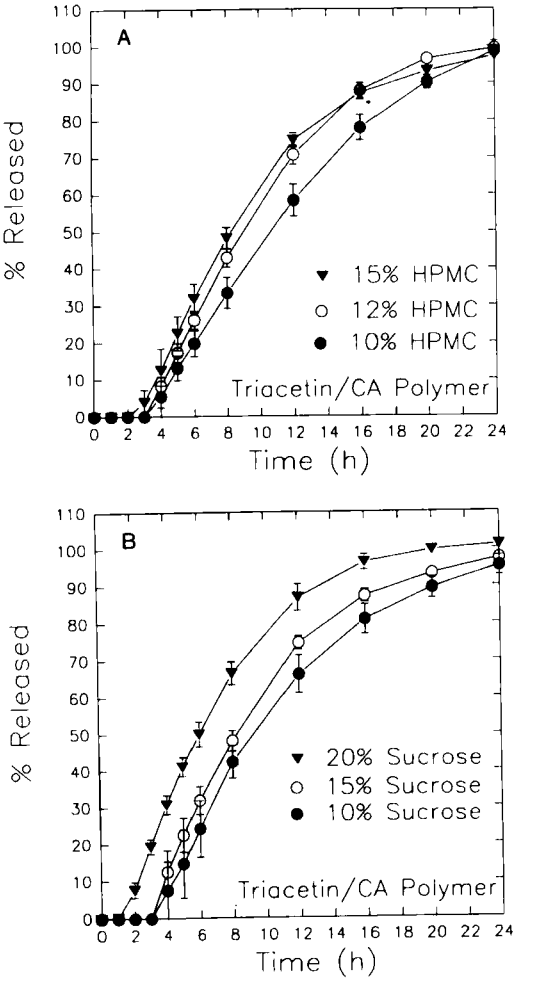

FIGURE 3

% Propranolol HCl released from tablets coated with TA plasticized CA latex containing; (A) 10,12 and 15% HPMC 5 cP; and (B) 10,15 and 20% sucrose; as permeability/flux enhancers. Mean (s.d., n=6).

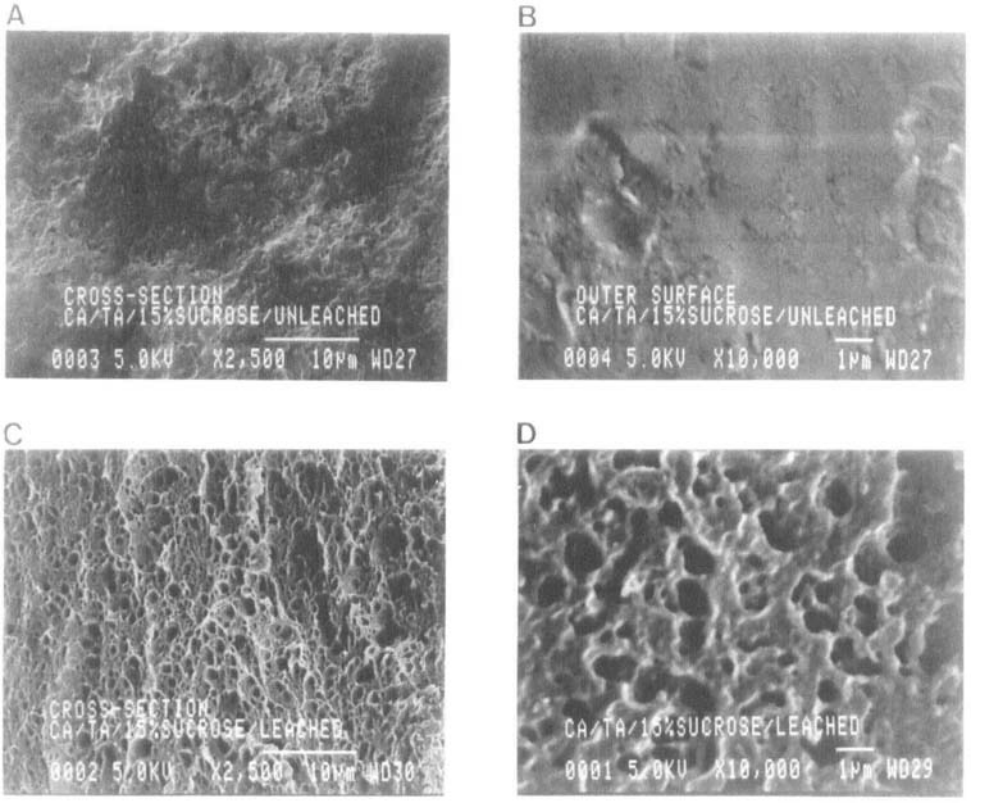

FIGURE 4

Scanning electron micrographs of CA latex/15% sucrose films; before (A) cross-section (X2,500); (B) outer surface (X10,000); and after exposure to aqueous medium (C) cross-section (X2,500); (D) outer surface (X10,000).

TEC as a Plasticizer/With Permeability Enhancers

Sucrose was added to 120% TEC plasticized films at 20, 40 and 50% levels, based on polymer weight. Sucrose had a significant impact on the release profile. As shown in figure 5A, membrane permeability to the drug increased with sucrose concentration in the film. Above 50% sucrose level, films ruptured in the dissolution medium. At the 40 and 50% levels, the tablets were tacky

TABLE 1
Formulae of CA Coating Dispersions Plasticized with TA
(amounts are expressed as g/100g formulation)

Additive	TA 150%	Sucrose 10%	Sucrose 15%	Sucrose 20%	HPMC 5cP 10%	HPMC 5cP 12%	HPMC 5cP 15%
CA Latex	20.7	19.9	19.5	19.2	19.9	19.7	19.5
TA	9.0	8.7	8.5	8.4	8.7	8.6	8.5
Sucrose	-----	0.573	0.853	1.08	-----	-----	-----
HPMC 5cP	-----	-----	-----	-----	0.57	0.69	0.85
Water	70.3	70.9	71.1	71.4	70.9	71.0	71.1

TABLE 2
Process Parameters for CA Coating Dispersions Plasticized with TA

Additive	TA 150%	Sucrose 10%	Sucrose 15%	Sucrose 20%	HPMC 5cP 10%	HPMC 5cP 12%	HPMC 5cP 15%
Spray Rate (g/min)	9-11	10-12	11-13	10-12	11-13	11-13	8-10
Inlet T (^{o}C)	55	55	55	55	55	55	55
Outlet T (^{o}C)	31-33	40-43	39-42	39-42	42-44	42-44	42-44
Drying/ Curing at 55^{o}C (hrs)	16-20	5	22	16-20	16-20	16-20	16-20

scfm between 85-100 for all trials. See other process parameters in Material and Methods.

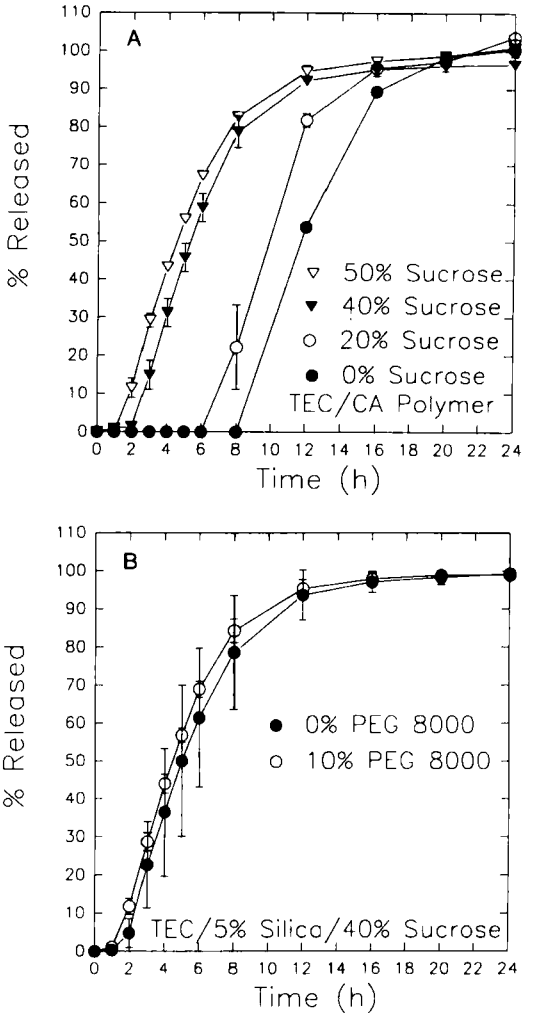

FIGURE 5

% Propranolol HCl released from tablets coated with TEC plasticized CA latex containing; (A) 0,20,40 and 50% sucrose; and (B) 0 and 10% PEG 8000. Mean (s.d., n=6).

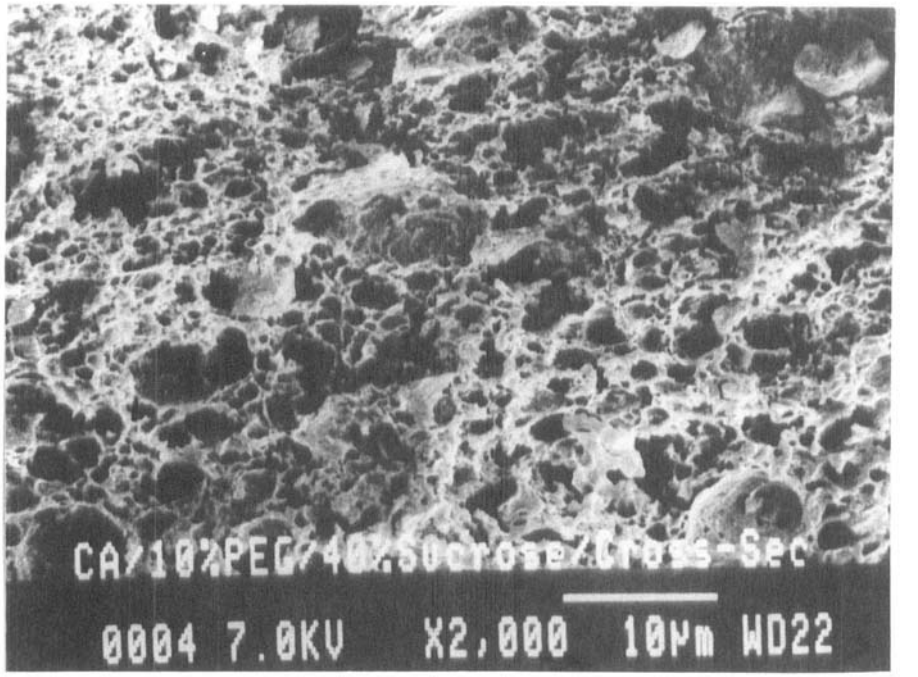

FIGURE 6

Scanning electron micrographs (X2,000) showing a cross-section of a TEC plasticized CA latex film after exposure to aqueous medium.

during coating. Micron-sized silica was added at a 5% level in all subsequent trials in order to decrease tackiness. Since these membranes already contain high levels of additives, higher silica levels were found to produce weak membranes.

PEG 8000 was also added as a flux enhancer to evaluate its effect when combined with sucrose. Figure 5B shows the effect of 10% PEG 8000 on the release of propranolol HCl from tablets coated with CA membranes containing 40% sucrose and 5% silicon dioxide. The onset of release was faster for films containing PEG, however, release rates did not appear to be higher. CA/sucrose/PEG films evaluated after drug release (Figure 6) showed a highly porous structure, as observed for TA/sucrose films.

Tables 3 and 4 show formulae and process parameters for CA coating dispersions plasticized with TEC and sprayed onto propranolol HCl tablets.

TABLE 3
Formulae of CA Coating Dispersions Plasticized with TEC (amounts are expressed as g/100g formulation)

Additive(s)	TEC 120%	Sucrose 20%	Sucrose 40%	Sucrose 50%	PEG10%/ Suc.40%	PEG0%/ Suc.40%
CA Latex	23.5	21.6	19.9	19.2	18.8	19.5
TEC	8.2	7.5	6.9	6.7	6.5	6.8
Sucrose	-----	1.2	2.3	2.8	2.2	2.3
PEG 8000	-----	-----	-----	-----	0.55	-----
SiO_2					0.27	0.27
Water	68.3	69.7	70.9	71.4	71.6	71.1

TABLE 4
Process Parameters for CA Coating Dispersions Plasticized with TEC

Additive(s)	TEC 120%	Sucrose 20%	Sucrose 40%	Sucrose 50%	PEG10%/ Suc.40%	PEG0%/ Suc.40%
Spray Rate g/min	11-13	11-13	11-13	9-11	11-13	8-10
Inlet T (^{o}C)	55	55	55	55	55	55
Outlet T (^{o}C)	42-44	41-43	43-45	42-44	42-44	42-44
Drying/ Curing at 60^{o}C,(hrs)	8	16	4	2	2	2

scfm between 85-100 for all trials. See other process parameters in Material and Methods.

Assessment of Plasticizer Volatility

Sprayed films plasticized with TA appeared to be less well plasticized than cast films. This would indicate that the actual level of triacetin in sprayed films could potentially be less than the theoretical amount. Plasticizer losses during the spraying process had previously been reported[2]. Figure 7 shows weight loss ($mg/hr/cm^2$) data for TA and TEC alone, TA plasticized and non-plasticized latex. These data clearly show that TA is more volatile than TEC and that its level in the plasticized films decreases with curing time at 60°C, althougth the curing temperature is considerably below that of the boiling point for both plasticizers. TA weight loss due to decomposition must be ruled out since the literature states that it is heat stable, i.e. only 0.11% acid generated after heating at 205°C for 2 hours.

Effect of Curing/Drying Time on Propranolol HCl Release

Figure 8 shows the effect of curing time on the release of propranolol HCl from films plasticized with 120% TEC and containing 40% sucrose/10% PEG as hours, whereafter no further decrease was observed.

DISCUSSION

Films Without Permeability Enhancers

TA and TEC plasticized CA membranes were found to have very low permeability to the drug (Figures 2 and 5). This is surprising since high amounts of water soluble plasticizers were added. However, membranes were permeable to water since tablet swelling was evident after 2-3 hours. An elementary osmotic pump (with a core having a low osmotic activity) was therefore created by drilling an aperture through the coating to allow for the drug to be released. The osmotic pump took 2 hours before any drug release occurred. This is also unexpected considering the film thickness, which was only about 60 μm. This 2 hour lagtime is too long for oral administration. In order to reduce the lagtime, pore former/flux enhancers were incorporated into the film.

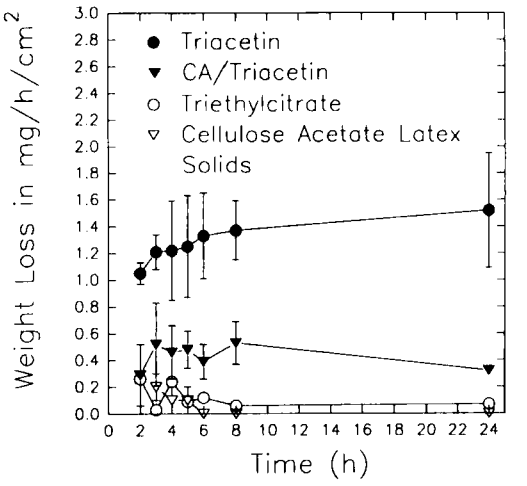

FIGURE 7

Weight losses data for TA and TEC, TA plasticized and non-plasticized latex, mean (s.d., n=4).

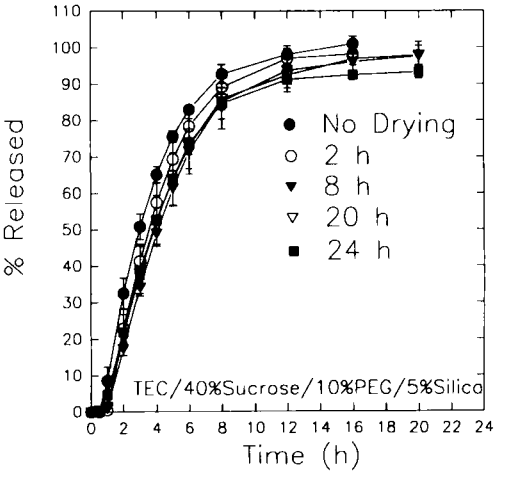

FIGURE 8

Effect of curing/drying time on the release of propranolol HCl from coated tablets, mean (s.d., n=6).

Films With Permeability Enhancers

When sucrose was added to TA plasticized films, a macroporous membrane was created after exposure to the dissolution fluid. This porous CA network, left by leached out sucrose, does not require any releasing aperture for drug release. These observations are consistent with the controlled porosity walls previously described[7] for CA films deposited from organic solvents. It is therefore postulated that drug mass transport occurs through the porous structure and that the mechanism responsible for it is probably a combination of molecular diffusion/osmotic pressure via water transport into the porous cellulose acetate membrane[8].

When 40% sucrose was added to TEC plasticized CA films, release rates were extended over a 12 hour period of time with a 2 hour lagtime. At 50% level, the lagtime was reduced by 0.5-1 hour but films were not as strong as at the 40% level. The addition of 10% PEG 8000 to TEC plasticized films containing 40% sucrose decreased the lagtime to 1 hour. This appeared to be the optimum formulation in terms of lagtime and release profile.

Assessment of Plasticizer Loss

Results have clearly indicated that plasticizer losses do happen during the drying/curing period. During spraying, where a large specific surface area is created, large amounts of plasticizers are also probably volatilized and removed in the outlet duct work. The plasticizer level (and therefore the polymer glass transition temperature) in the dried film will be a function of process parameters, drying/curing time and temperature. This phenomenon has also been reported for diacetin, diethyltartrate, ethylene glycol mono and diacetate and trimethyl-phosphate, when used at 160 to 320% levels in CA films[2,3]. Loss of volatile plasticizer (including water) should be a variable of interest during the development of controlled release film coatings, particularly with respect to film permeability after manufacturing and aging. The addition of 0.5-1% HPMC overcoat might minimize losses that occur during the drying/curing phase.

Effect of Curing/Drying Time on Propranolol HCl Release

Propranolol HCl % released as a function of time decreased with increasing drying/curing time at 60°C. However, after 8 hours of drying, no further decrease was observed. It is postulated that the film glass transition temperature (T_g) increases with drying time due to plasticizer (including moisture) volatilization. CA particles gradually coalesce during curing due to viscous flow until T_g reaches a value where the polymer viscosity is such that no further significant changes in permeability are seen.

CONCLUSIONS

TA or TEC plasticized CA latex provided dense and homogeneous films when deposited onto propranolol HCl tablets using conventional fluid bed technology. Film permeability to the drug was found to be low and flux/permeability enhancers were added to the CA structure during its manufacture. Films containing 40% sucrose and 10% PEG 8000 were found to provide the best release characteristics in terms of small lagtime (1 hour) and extended drug release profile (i.e. over 12 hours). When sucrose was added to TA and TEC plasticized films, a macroporous membrane was created during exposure to the dissolution fluid due to sucrose release from the film. These observations are consistent with the controlled porosity walls previously described for CA films deposited from organic solvents. It is postulated that drug mass transport occurs mainly in the porous CA structure and the mechanism responsible for it is a combination of molecular diffusion/osmotic pressure via water transport into the porous cellulose acetate membrane. Plasticizer loss during drying has also been demonstrated and related to the change in release profile seen with drying time.

Several questions remain to be answered; they pertain to physical stability of the film, mechanical strength to avoid dose dumping and flexibility in the use of the pore former in order to provide films having a wide range of permeabilities to low and high molecular weight organic compounds.

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