



Eastman Cellulose Esters
for Pharmaceutical Drug Delivery

Pharmaceutical
Ingredients

EASTMAN

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Eastman Cellulose Esters

for Pharmaceutical Drug Delivery



Introduction

Cellulose esters are part of a large family of cellulose derivatives that have a long history of use in pharmaceutical and industrial applications. Cellulose esters fall into two categories—enteric and nonenteric. Enteric esters are those, such as *C-A-P* (cellulose acetate phthalate) which are insoluble in acidic solutions but soluble in mildly acidic to slightly alkaline solutions. Nonenteric esters do not show pH-dependent solubility characteristics. With the exception of cellulose acetates with low levels of acetyl, most nonenteric esters are insoluble in water. The three groups of *Eastman* nonenteric cellulose esters and their typical applications are described herein.

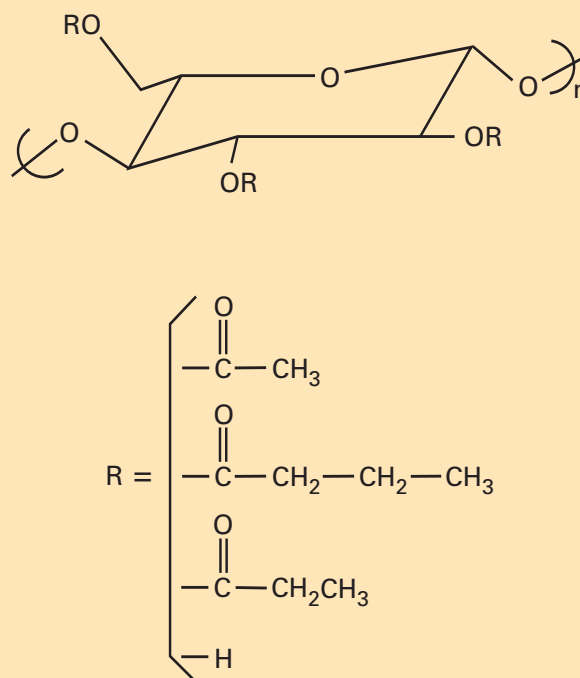
Cellulose esters have found extensive use in solid pharmaceutical dosage forms, where they are typically used for controlled drug delivery. Typical technologies that employ cellulose esters include semipermeable membranes for osmotic pump drug delivery applications, sustained release from cellulose ester-based matrix formulations, and microparticles formed from cellulose esters and drugs.

Materials listed as “technical grade” in this publication should be considered for pharmaceutical developmental use only. Technical materials are not produced under cGMP.

Eastman Cellulose Esters

Eastman esterifies cellulose to produce cellulose acetate (CA), cellulose acetate butyrate (CAB), and cellulose acetate propionate (CAP) (see Figure 1). The structure of cellulose consists of repeating anhydroglucose units. Each monomer of anhydroglucose has three hydroxyl groups that are esterified to yield cellulose esters. The amount of esterification can be expressed as weight percent of acyl group or degree of substitution (DS). DS = 3 means all three hydroxyl groups are esterified; DS = 1 means one out of three groups is esterified. The physical properties of cellulose esters depend on the cellulose chain length and on the type and amount of ester groups attached to the chain.

Figure 1
Structure of Cellulose Esters



Nomenclature

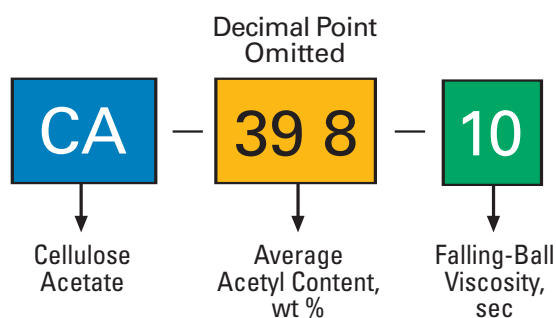
An easy-to-use nomenclature system describes and designates *Eastman* cellulose esters. The designation consists of three parts: the first identifies the ester type—CA for cellulose acetate, CAB for cellulose acetate butyrate, and CAP for cellulose acetate propionate (see Figure 2). For CA, the three digits following the letter prefix indicate the acetyl content by weight, omitting the decimal point between the

second and third digits. For CAB and CAP, the first two digits indicate the butyryl or propionyl content, respectively, at the triester stage; the third digit gives the number of hydroxyl units per four anhydroglucose units. The suffix of the name indicates the viscosity of the ester, in a designated solvent system, which is related to the degree of polymerization or molecular weight.

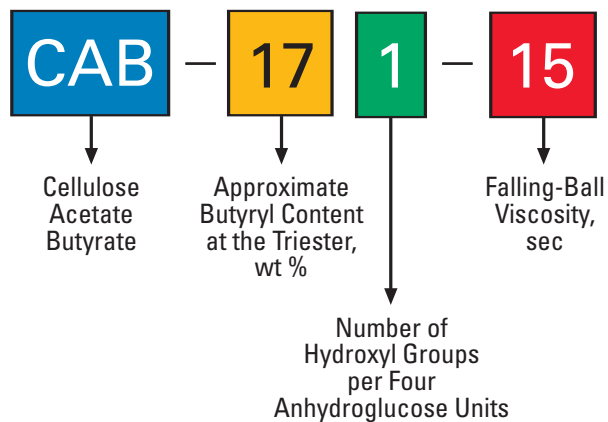
Figure 2

Cellulose Ester Nomenclature

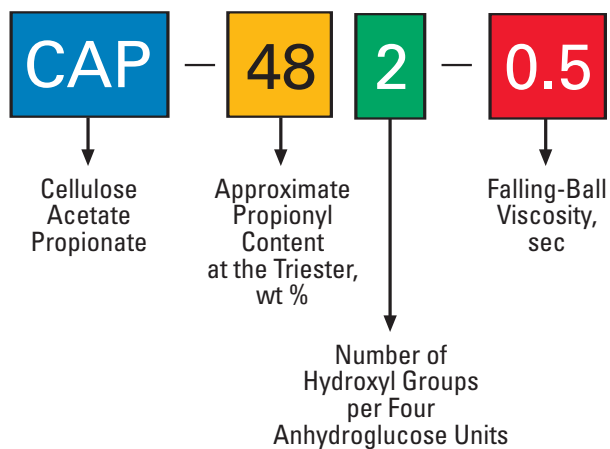
Eastman Cellulose Acetate



Eastman Cellulose Acetate Butyrate



Eastman Cellulose Acetate Propionate



Cellulose Ester Properties

Solubility

Table 1 shows the solubilities of several cellulose esters in solvents typically used in the pharmaceutical industry.

Table 1
Solubility^a of Selected Cellulose Esters

	CA- ^b		CAB- ^b						CAP- ^b		
	320S	398-10NF ^{c,d}	171-15PG ^e	321-0.1	381-0.5	381-20	500-5	551-0.2	553-0.4	482-0.5	504-0.2
Acetone	PS	S	S	S	S	S	S	S	S	S	S
Ethyl Acetate, 99%	I	PS	S	S	S	S	S	S	S	S	S
Ethyl Alcohol, 95%	I	I	I	I	I	I	I	I	S	I	S
Methylene Chloride	I	S	S	S	S	S	S	S	S	S	S
Methylene Chloride/ Isopropyl Alcohol 90/10	S	S	S	S	S	S	S	S	S	S	S
Ethyl Alcohol (anhy)/ Ethyl Acetate (99%) 70/30	I	I	I	S	S	S	S	S	S	S	S
Methyl Acetate	S	S	S	S	S	S	S	S	S	S	S
Acetone/Water 90/10	S	S	S	S	S	S	S	S	S	S	S

^aS = Soluble; PS = Partly Soluble; I = Insoluble

^bTechnical grade material, unless otherwise indicated

^cNational Formulary grade

^dAlso available as CA398-10NF/EP, a European Pharmacopoeia grade

^ePG = Pharmaceutical grade

Effect of Plasticizers on Film Properties

Plasticizers are commonly used in conjunction with cellulose esters to modify physical properties. Some physical properties that are of interest are glass transition temperature, mechanical strength and elongation, and water vapor transmission rate (WVTR). In general for plasticized cellulose ester

films, as the plasticizer level increases, the glass transition temperature decreases, film strength decreases, and film flexibility increases. The WVTR depends on the type of plasticizer used. Very water-soluble plasticizers increase WVTR; water-insoluble plasticizers decrease WVTR.

Effect of Increased Molecular Weight

No effect on the release profile was observed when the molecular weight of the CA was increased from 30,000 to 50,000 as shown in Figure 3. The data shown is for tablets coated with 2 wt % CA-398-3 and CA-398-30 coatings containing 20 wt % of a water-soluble plasticizer.

Physical Properties of Cellulose Ester Films

The physical properties of cellulose esters depend on the amount and type of esterification on the cellulose backbone. The glass transition temperature, tensile properties, and WVTR data were measured on three cellulose acetate and one cellulose acetate butyrate films and the results are shown in table 2. The CA and CAB films were prepared by dissolving the polymer in solvent at 10 and 15 wt % solids levels, respectively and casting onto a glass plate using a Gardner knife. The solvent used for the cellulose acetate films is 9:1 CH₂Cl₂:MeOH and acetone was used for the cellulose acetate butyrate film.

As is seen in Table 2, the glass transition temperature (T_g) decreases as the degree of substitution of cellulose acetate esters increase and decreases further with substitution of butyryl for acetyl. Additional data shows that as the butyryl concentration of CAB increases, the T_g continues to decline. Cellulose acetate films, while strong, do not stretch appreciably as indicated by the tensile property data.

Figure 3
Effect of Molecular Weight on Release Rate

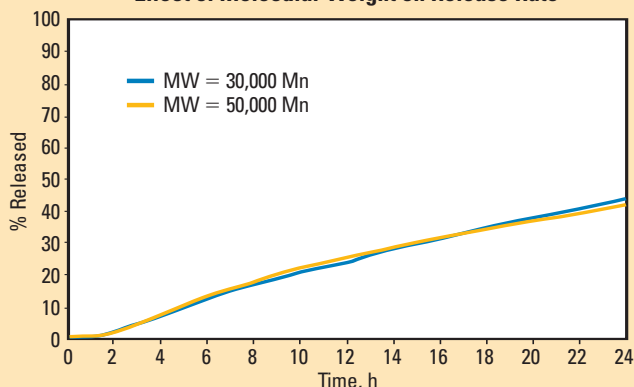


Table 2
Physical Properties of Cellulose Ester Films

	Break Stress, MPa	Elongation to Break, %	T _g °C	WVTR, g-mil/m ² /day
CA-320S	50.9	4.1	203	1,201
CA-398-10NF	61.3	5.6	187	1,404
CA-435-75S	93.3	8.5	177	837
CAB-171-15PG	44.6	6.3	166	1,091

Eastman Cellulose Acetate

Physical and Chemical Properties

Table 3 lists the various types of *Eastman* cellulose acetate that are commercially available and their physical and chemical properties.

Table 3
Physical and Chemical Properties^a of *Eastman* Cellulose Esters

Type	Viscosity, ^b Poise	Acetyl, %	Degree of Substitution	Hydroxyl, %	Melting Range, °C	T _g , °C	Bulk Density, ^c kg/L	MW _n ^d
CA-320S ^e	2.4	32.0	1.8	8.7	230–250	180	0.4	38,000
CA-398-3 ^e	11.4	39.8	2.4	3.5	230–250	180	0.4	30,000
CA-398-6 ^e	22.8	39.8	2.4	3.5	230–250	182	0.4	35,000
CA-398-10NF CA-398-10NF/EP	38.0	39.8	2.4	3.5	230–250	185	0.4	40,000
CA-398-30 ^e	114.0	39.7	2.4	3.5	230–250	189	0.4	50,000
CA-394-60S ^e	228.0	39.5	2.4	4.0	240–260	186	—	60,000
CA-435-75S ^e	—	43.5	2.9	0.9	280–300	185	0.7	122,000

^aProperties reported here are typical of average lots. Eastman makes no representation that the material in any particular shipment will conform exactly to the listed properties.

^bASTM D871 (Formula A) and D1343

^cTapped density

^dNumber-average molecular weight in polystyrene equivalents

^eTechnical grade material

Drug Delivery Applications

Sustained Release by Direct Compression

Sustained release from direct-compression matrices of CA-398-10NF has been demonstrated for both relatively water-insoluble and very water-soluble actives [data presented at 1995–96 American Association of Pharmaceutical Scientists (AAPS) meetings and published in *Pharmaceutical Technology* (October, 2000)]. These studies investigated various factors to see their effect on the drug-release profile.

The methodology employed consisted of mixing plasticizer, if any, with CA-398-10NF followed by incorporation of the active with additional mixing.

Tablets were then made on a hydraulic press using a tablet die coated with a thin film of magnesium stearate. The USP dissolution test method using Apparatus II was employed to determine the active release profiles. Dissolution data were collected using a UV/VIS spectrometer with flow cells for each dissolution vessel. At least three tablets were analyzed for each formulation. Additionally, some tablets were made using a Manesty Betapress 16-station rotary tablet press for scalability purposes.

Theophylline Release. The main factor controlling theophylline release from CA matrices was the CA:theophylline ratio (see Figure 4). Addition of triethyl citrate (TEC) plasticizer slowed drug release from the matrix (see Figure 5).

Other experiments investigating factors such as CA molecular weight and CA particle-size distribution did not significantly influence theophylline release, indicating a robust formulation working range.

A formulation based on lab data was run on a Manesty Betapress 16-station rotary tablet press to demonstrate the scalability of this technology. As Figure 6 shows, the tablets produced on the rotary press had release profiles that correlated well with tablets made on the hydraulic press.

Diphenhydramine Hydrochloride Release. A similar study was completed using the very water-soluble diphenhydramine hydrochloride as the model active. As expected, the amount of cellulose acetate needed to provide sustained release was more than for the relatively water-insoluble theophylline (see Figure 7).

As seen in the theophylline study, adding plasticizer slowed the release rate. Also, formulations with varying molecular weights and particle-size distributions of cellulose acetate did not significantly affect drug release.

Again, transferral of this technology to pilot-scale tableting equipment was demonstrated. The tableting run also provided data on the effect of compression force on the release profile. For the compression force range of 1,750–3,000 lb, no effect on the release profile was seen. Only when compression force dropped to 1,500 lb was a change in the release observed—again indicating that this system has a robust operating range.

Figure 4
Effect of Theophylline:CA-398-10NF Ratio on Release Profile

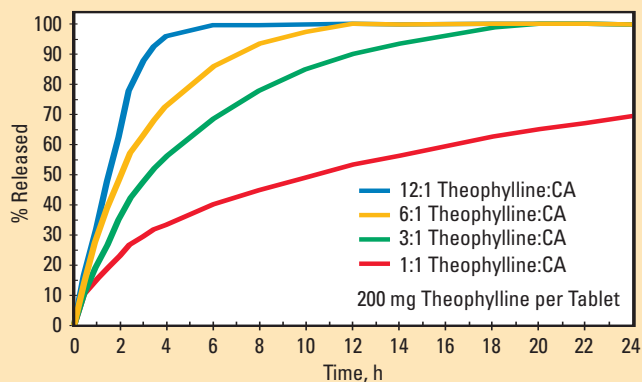


Figure 5
Effect of Plasticizer on Release Profile

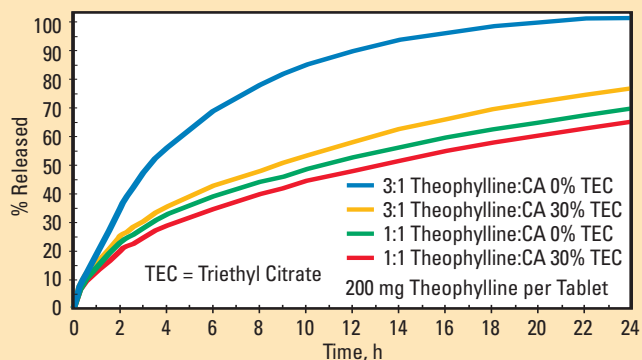
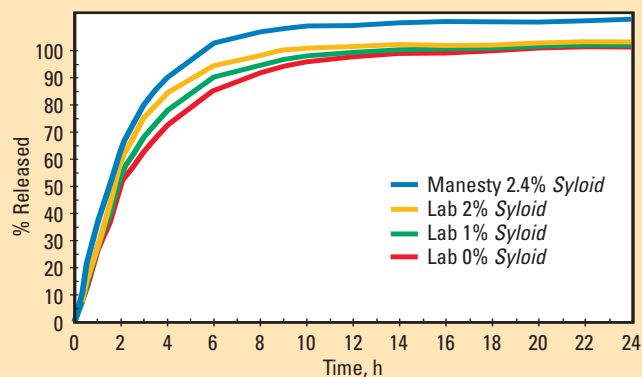
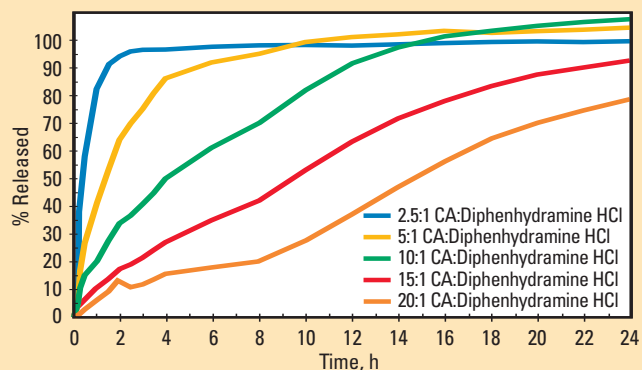


Figure 6
Comparison of Tablets Made on Rotary Press^a and Hydraulic Press^b



^aManesty Betapress 16-Station 87.4% Theophylline, 9.7% CA-398-10NF, 2.4% Syloid, 0.5% Magnesium Stearate
^b9:1 Theophylline:CA-398-10NF

Figure 7
Impact of CA:Diphenhydramine HCl Ratio
CA-398-10NF, 25-mg Dose



Sustained Release Through Permeable Membranes

The osmotic pump drug delivery technology typifies sustained release that capitalizes on the nature of CA films—insoluble yet semipermeable—to allow water to pass through a tablet coating. An osmotic agent that swells absorbs the water, forcing the active out through a hole drilled in the film.

Sustained drug release through CA films without hole-drilling can also be achieved by employing water-soluble materials in the film to increase the drug's ability to diffuse through it. This concept was demonstrated using tablets containing 18 mg of theophylline.

The factors influencing the properties of CA films investigated include acetyl content, plasticizer type and level, solvent system, and CA molecular weight.

Effect of Acetyl Content. Tablets containing theophylline were coated with CA-398-10NF and CA-320S; theophylline release through the resultant films was studied. Figure 8 shows that a film with 32% acetyl (CA-320S) allows higher, faster theophylline release than a film with 39.8% acetyl (CA-398-10NF).

Effect of Plasticizer Type and Level. CA-398-10NF films with a water-soluble plasticizer (up to 20%), PEG-400, exhibit higher water vapor transmission rates. Figure 9 reflects this finding. Figure 10 demonstrates that CA films containing water-soluble plasticizer allow faster release of active than films plasticized with relatively water-insoluble plasticizer (TEC). The higher level of water-soluble plasticizer, the faster release of active.

Also investigated was the effect of polyethylene glycol (PEG) molecular weight and level on properties of CA-398-10NF free films. The higher the level and the lower the molecular weight of PEG, the more flexible the film was. (Data were published in *Pharmaceutical Technology*, 25(10), 62–74, 2001).

Figure 8
Effect of % Acetyl on Theophylline-Release Profile^a
2% Coating of CA on Tablet

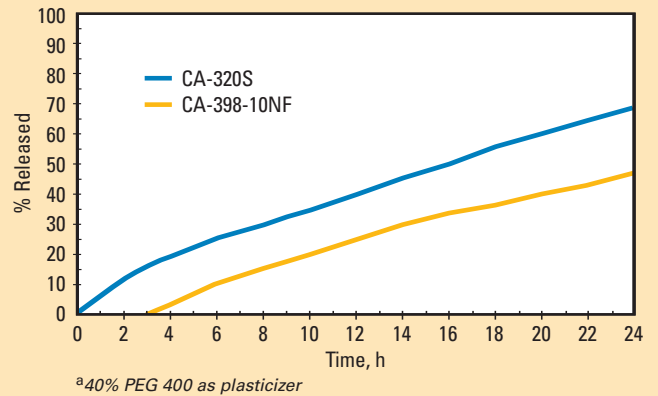


Figure 9
Effect of Plasticizer on WVTR^a
CA-398-10NF Films

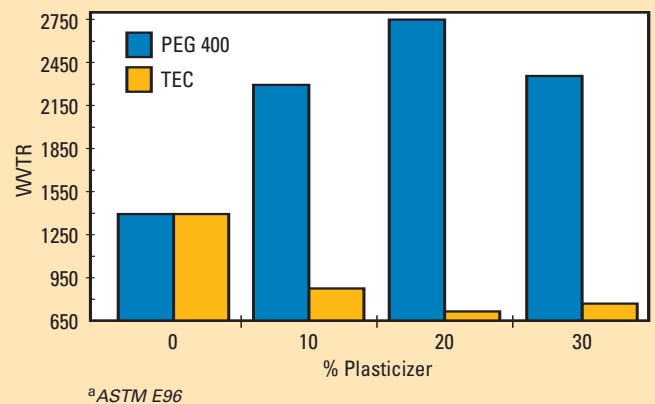
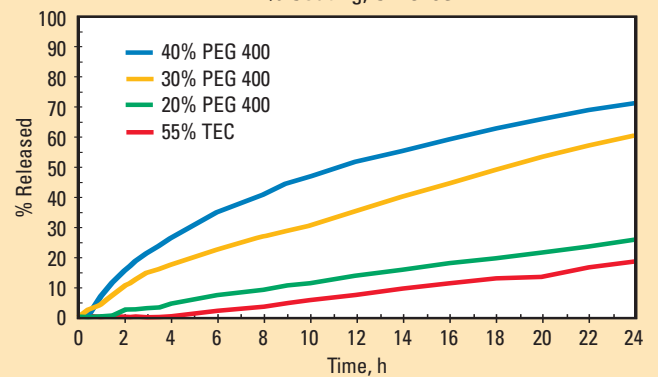


Figure 10
Effect of Film Additive on Release Rate
2% Coating, CA-320S



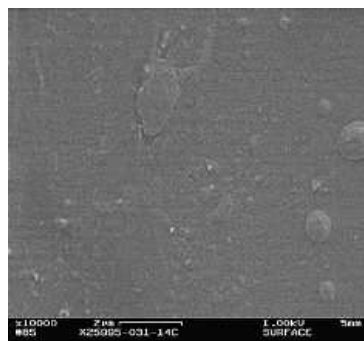
Effect of Solvent System. CA-398-10NF films were prepared by using acetone or acetone/water as solvent. Scanning electron microscopy (SEM, see Figure 11) revealed that the films cast with acetone had smoother surface and smaller pinholes in the

cross sections than the films cast with acetone/water. Therefore, the films prepared with acetone were flexible, stronger, tougher, and less permeable to water vapor.

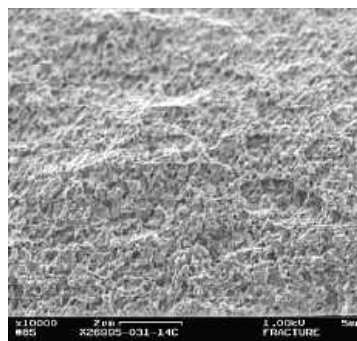
Figure 11

**Effect of Solvent System on Morphology
CA-398-10NF Films**

SEM Images of CA Film Cast With Acetone

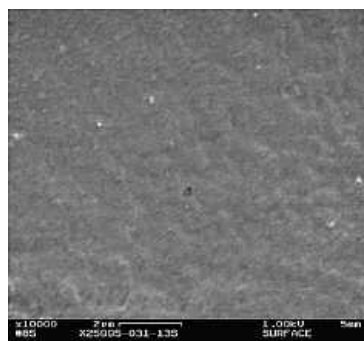


Surface of the Film

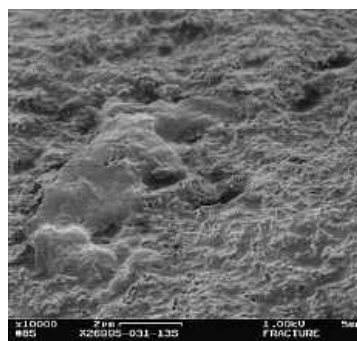


Cross Section of the Film

SEM Images of CA Film Cast With Acetone and Water



Surface of the Film



Cross Section of the Film

Eastman Cellulose Acetate Butyrate

Physical and Chemical Properties

Table 4 lists the wide variety of *Eastman* cellulose acetate butyrates, along with some of their physical and chemical properties.

Table 4
Physical and Chemical Properties^a of *Eastman* Cellulose Acetate Butyrate

Type	Viscosity, ^b Poise	Acetyl, %	DS ^c	Butyryl, %	DS	Hydroxyl, %	DS	Melting Range, °C	T _g , °C	Bulk Density, ^d kg/L	MW _n ^e
CAB-551-0.2 ^f	0.76	2.0	0.2	52	2.5	1.8	0.3	130–140	101	0.5	30,000
CAB-531-1 ^f	7.20	3.0	0.2	50	2.4	1.7	0.4	135–150	115	0.5	40,000
CAB-500-5 ^f	19.00	4.0	0.3	51	2.5	1.0	0.2	165–175	96	0.5	57,000
CAB-553-0.4 ^f	1.14	2.0	0.1	46	2.0	4.8	0.9	150–160	136	0.4	20,000
CAB-381-0.1 ^f	0.38	13.5	1.0	38	1.8	1.3	0.2	155–165	123	0.5	20,000
CAB-381-0.5 ^f	1.90	13.5	1.0	38	1.8	1.3	0.2	155–165	130	0.5	30,000
CAB-381-2 ^f	7.60	13.5	1.0	38	1.8	1.3	0.2	171–184	133	0.5	40,000
CAB-381-20 ^f	76.00	13.5	1.0	37	1.7	1.8	0.3	195–205	141	0.4	70,000
CAB-321-0.1 ^f	0.38	18.5	1.3	31.2	1.4	1.3	0.3	165–175	127	0.4	12,000
CAB-171-15 PG	57.00	29.5	2.0	17	0.7	1.1	0.3	230–240	161	—	65,000

^aProperties reported here are typical of average lots. *Eastman* makes no representation that the material in any particular shipment will conform exactly to the listed properties.

^bASTM D817 (Formula A) and D1343

^cDegree of substitution

^dTapped density

^eNumber-average molecular weight in polystyrene equivalents

^fTechnical grade material

Drug Delivery Applications

Sustained Release by Direct Compression

Eastman CABs have been used to make sustained-release vitamin C and diphenhydramine hydrochloride formulations. A methodology similar to the direct-compression cellulose acetate matrix experiments was employed. Figures 12 and 13 show some of these results.

Also investigated was CAB-171-15PG and CAB-381-20 as matrix materials to make tablets by direct compression method (Reference: *Pharmaceutical Technology*, 24(10), 92–106, 2000). Results show that tablets exhibited a slower release rate when CAB was used in the tablets matrix than when CA was used as the matrix material. This suggests that the release mechanism from CA and CAB may be different. Figure 14 represents theophylline release profiles through CAs and CABs in pH 1.2 buffer.

Sustained Release Using CAB Films

A veterinary product sold in Europe uses CAB to form a semipermeable membrane that is part of an osmotic pump mechanism. Also, the patent literature discusses several formulations that utilize CAB films for sustained drug delivery applications (see References).

CAB free films' properties were investigated and are available upon request.

Figure 12
Impact of CAB-381-2:Diphenhydramine HCl Ratio

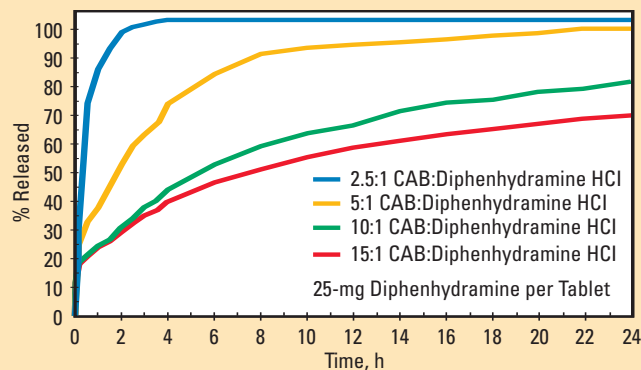


Figure 13
Vitamin C Release Profile

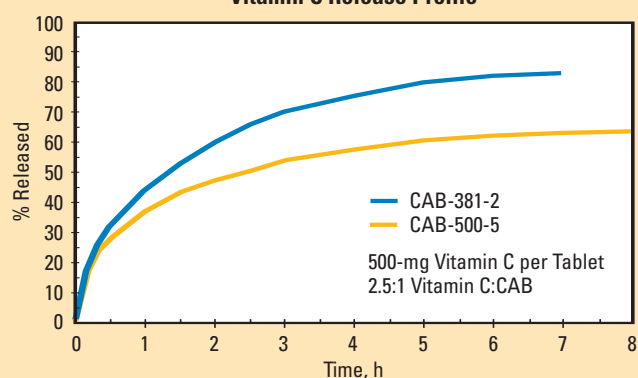
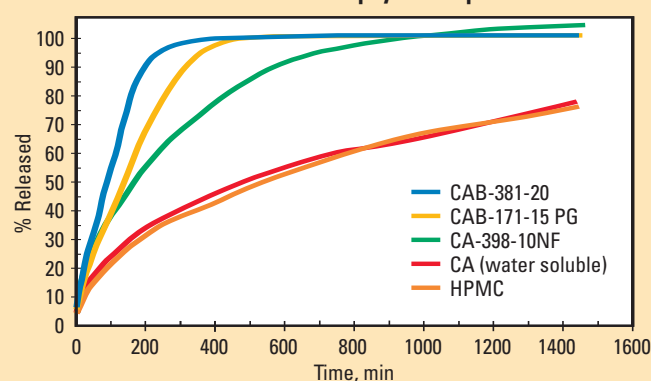


Figure 14
Release Profiles of Theophylline in pH 1.2 Buffer



Eastman Cellulose Acetate Propionate

Physical and Chemical Properties

Table 5 lists some physical and chemical properties of commercially available *Eastman* cellulose acetate propionates.

Table 5
Physical and Chemical Properties^a of *Eastman* Cellulose Acetate Propionate

Type	Viscosity, ^b Poise	Acetyl, %	DS ^c	Propionyl, %	DS	Hydroxyl, %	DS	Melting Range, °C	T _g , °C	Bulk Density, ^d kg/L	MW _n ^e
CAP-482-0.5 ^f	1.52	1.2	0.1	47.7	2.6	1.7	0.3	188–210	142	0.4	25,000
CAP-482-20 ^f	76.00	1.5	0.1	46.7	2.5	2.6	0.4	188–210	147	0.4	75,000
CAP-504-0.2 ^f	0.76	0.6	0.1	42.5	2.1	5.0	0.8	188–210	159	0.5	15,000

^aProperties reported here are typical of average lots. Eastman makes no representation that the material in any particular shipment will conform exactly to the listed properties.

^bASTM D817 (Formula A) and D1343

^cDegree of substitution

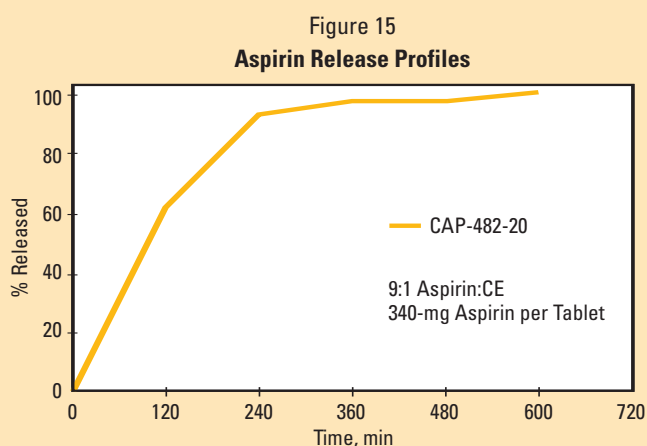
^dTapped density

^eNumber-average molecular weight in polystyrene equivalents

^fTechnical grade material

Drug Delivery Applications

Drug delivery applications for CAP are similar to those for CA and CAB. Figure 15 shows a direct-compression, sustained-release profile for aspirin using CAP.



Regulatory Status

Cellulose Acetate

Eastman CA-398-10NF and CA-398-10NF/EP is made under current good manufacturing practices (cGMP) for pharmaceutical use. Cellulose acetate is listed in USP25/NF20 of the U.S. Pharmacopoeia (USP) and in the European Pharmacopoeia. It is the subject of Drug Master File 009323.

Cellulose Acetate Butyrate

Cellulose acetate butyrate is listed in the U.S. Pharmacopoeia (USP) USP28/NF23 under the name cellaburate. It is the subject of Drug Master File 015490. CAB-171-15PG is manufactured under cGMP.

Cellulose Acetate Propionate

Acute and subchronic toxicology data are listed in the applicable Material Safety Data Sheets (MSDS).

Packaging

Eastman cellulose esters are packaged in 10-kg (22-lb) and 50-kg (110-lb) net weight fiber drums equipped with a polyethylene inner liner and reusable metal closure. These containers should be protected from moisture or high humidity for extended periods. Drums held in cool, dry storage should be brought to room temperature before opening to prevent condensation of moisture on inside surfaces.

Storage and Handling

Information on “Handling Precautions for Cellulose Esters in Formulating Coatings” is contained in *Eastman* publication E-241. Material Safety Data Sheets providing safety precautions that should be observed in handling and storing *Eastman* products are also available on request. These publications should be obtained and reviewed before handling any of these products.

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