Eastman cellulose esters

Pharmaceutical applications and drug delivery

Cellulose esters are part of a large family of cellulose derivatives that have a long history of use in pharmaceutical applications. Cellulose esters fall into two categories: enteric and nonenteric. Enteric esters, such as cellulose acetate phthalate (C-A-P), are insoluble in acidic conditions (e.g., in the stomach) but soluble in mildly acidic to slightly alkaline conditions. Nonenteric esters, such as cellulose acetate (CA) and cellulose acetate butyrate (CAB), do not show pH-dependent solubility characteristics.

Nonenteric cellulose esters have found extensive use in solid dosage forms. Typical technologies that employ cellulose esters include semipermeable membranes for osmotic drug delivery systems, sustained release from cellulose ester-based matrix formulations and coating applications, microencapsulation, and taste masking.

Eastman cellulose esters

Eastman esterifies cellulose to produce cellulose acetate and cellulose acetate butyrate. See Figure 1 for structural formula. The structure of cellulose consists of repeating anhydroglucose units. Each anhydroglucose unit (AGU) 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. Because DS is a statistical mean value, a value of 1 does not assure that every AGU has a single substituent. In some cases, there can be unsubstituted anhydroglucose units with two or three substituents. More often than not, the value will be a non-integer.

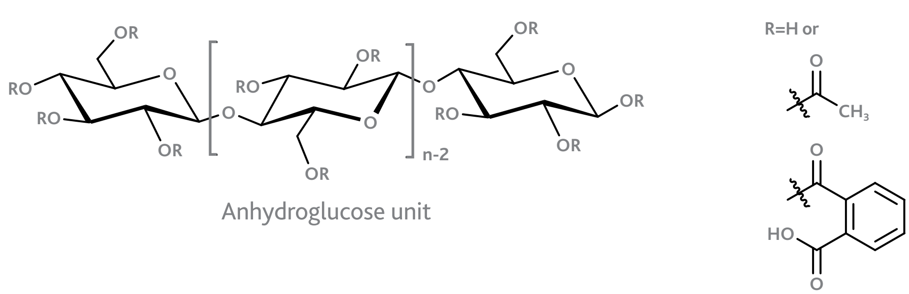
Eastman cellulose esters for controlled drug delivery

- Semipermeable membranes for osmotic drug delivery
  (CA-398-10 NF/EP, CA-320S NF/EP, CAB-171-15 NF)
- Sustained drug release
  (CA-398-10 NF/EP, CAB-171-15 NF)
- Taste masking
  (CA-398-10 NF/EP, CA-320S NF/EP, CAB-171-15 NF)
- Binder to make tablets for sustained release via direct compression
  (CA-398-10 NF/EP, CAB-171-15 NF)

Key attributes of cellulose esters

- Coatings: semipermeable, excellent film former, strong, flexible
- Characteristics of coating (permeability, mechanical strength, flexibility) can be modified through blending two CAs or CA and CAB.
- Tunable hydrophilicity/hydrophobicity for targeted release rates

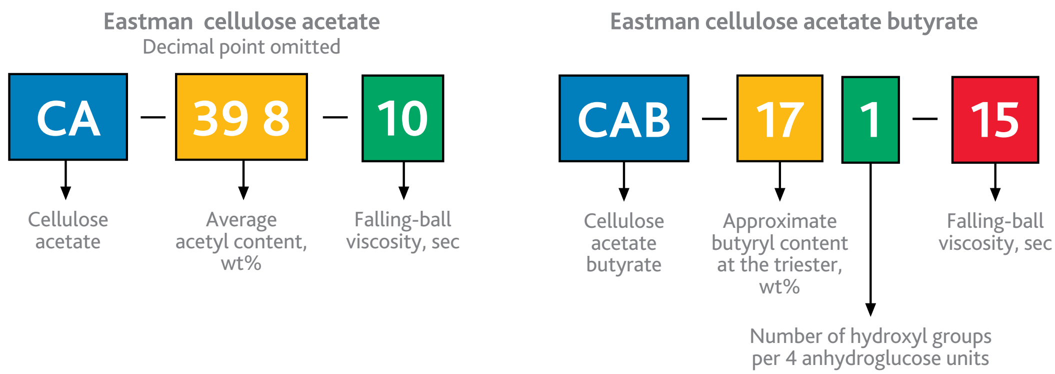
Figure 1. Structural formula of cellulose esters



Nomenclature

See Figure 2 for an easy-to-use nomenclature system designating Eastman cellulose esters. The designation consists of three parts. The first part identifies the ester type—CA for cellulose acetate and CAB for cellulose acetate butyrate. For CA, the three digits following the letter prefix indicate the acetyl content by weight, omitting the decimal point between the second and third digit. For CAB, the first two digits following the letter prefix indicate the butyryl content at the triester stage; the third digit gives the number of hydroxyl units per four anhydroglucose units. The suffix of the name indicates the falling-ball viscosity of the ester in a designated solvent system, which is related to the degree of polymerization or molecular weight.

Figure 2. Eastman cellulose ester nomenclature



Cellulose ester properties

Physical and chemical properties

In general, the physical properties of cellulose esters depend on the cellulose chain length and the type and amount of ester groups attached to the chain. Table 1 lists the physical and chemical properties of Eastman nonenteric cellulose esters that are commercially available for pharmaceutical applications.

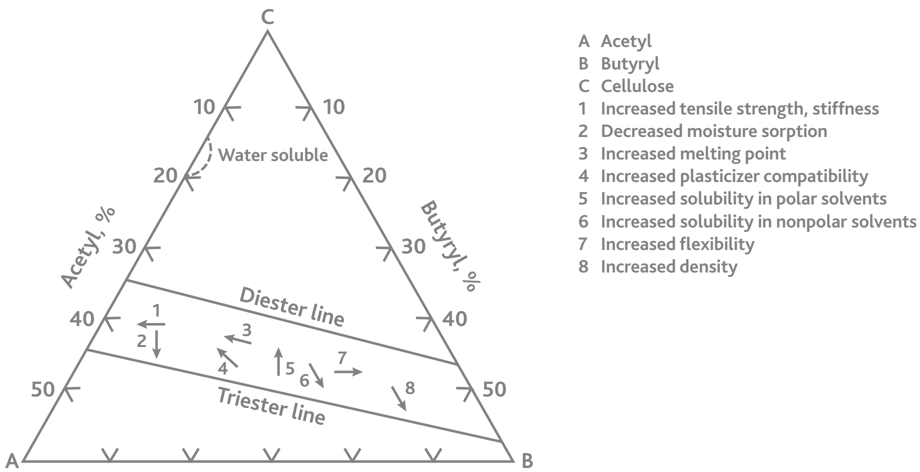
Table 1. Physical and chemical properties of Eastman cellulose esters[a]

Type	Viscosity[b] poise	Acetyl		Butyryl		Hydroxyl		Melting range, °C	T_g,[d] °C	M_n,[e] k
		%	DS[c]	%	DS	%	DS			
CA-320S NF/EP	2.1	32.0	1.8	—	—	8.7	1.2	230–250	180	20
CA-398-10 NF/EP	38.0	39.8	2.4	—	—	3.5	0.6	230–250	186	40
CAB-171-15 NF	57.0	29.6	2.0	17	0.8	1.0	0.2	230–240	161	65

[a]Properties 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. [b]ASTM D817 and D1343 [c]Degree of substitution [d]Second heating run of DSC [e]Number-average molecular weight in THF (for CA-398-10 NF/EP and CAB-171-15 NF) and NMP (for CA-320S NF/EP)

As shown in Figure 3, the physical properties of cellulose esters depend on the amount and type of acylation on the cellulose backbone. For CA, as the amount of acetyl increases, the permeability decreases and solvent resistance increases. CAB is more hydrophobic than CA.

Figure 3. Effects of composition on physical properties



Solubility

Table 2 shows the solubility of Eastman cellulose esters in commonly used pharmaceutical solvents.

Table 2. Solubility of Eastman cellulose esters in selected solvents[a]

Solvent	CA-398-10 NF/EP	CA-320S NF/EP	CAB-171-15 NF
Acetone	S	I	S
Acetone/water (90/10 wt%)	S	PS	S
Acetone/water (80/20 wt%)	S	S	PS
Ethyl acetate (EA)	PS	I	S
Isopropyl alcohol (IPA)	I	I	I
Acetone/IPA (50/50 wt%)	I	I	PS
Acetone/IPA (60/40 wt%)	S	I	S
Ethanol	I	I	I
Acetone/ethanol (50/50 wt%)	I	I	PS
Ethanol/EA (50/50 wt%)	I	I	I
Methylene chloride[b]	S	I	S
IPA/methylene chloride[b] (10/90 wt%)	S	I	PS

[a]Polymer concentration is 10 wt%. *[b]Polymer concentration is 5 wt%.*
S = soluble; PS = partially soluble; I = insoluble

Pharmaceutical applications

Eastman cellulose esters have been used in pharmaceutical applications, including as semipermeable membranes for osmotic drug delivery systems, coating material for taste masking and sustained release, and binder to make tablets.

Semipermeable membranes for osmotic drug delivery systems

An osmotic drug delivery system provides controlled release of an active by utilizing osmotic force with the advantage that the release rate of the active does not depend on physiological environment.

CA-398-10 NF/EP is one of the most suitable materials to form the semipermeable membrane for the delivery system due to its permeability and mechanical property. CAB-171-15 NF would also form a semipermeable film which has a much lower permeability compared to that of CA-398-10 NF/EP in a similar formulation. Generally, in a similar formulation with the same plasticizer and the same amount of plasticizer, CA-320S NF/EP film has the highest permeability, followed by CA-398-10 NF/EP and CAB-171-15 NF. The mechanical strength of the films will be in inverse order, with CAB-171-15 NF being the strongest and CA-320S NF/EP being the weakest. Based on the designated permeability required by a specific active, a combination of cellulose esters can be used to tailor the permeability. For example, CA-398-10 NF/EP can be combined with CA-320S NF/EP and CA-398-10 NF/EP can be combined with CAB-171-15 NF.

Many factors could affect the properties of the semipermeable film. Formulation variables, such as polymer type, solvent system, type and amount of plasticizer used, and coating processing conditions, need to be considered to develop a robust product formulation.

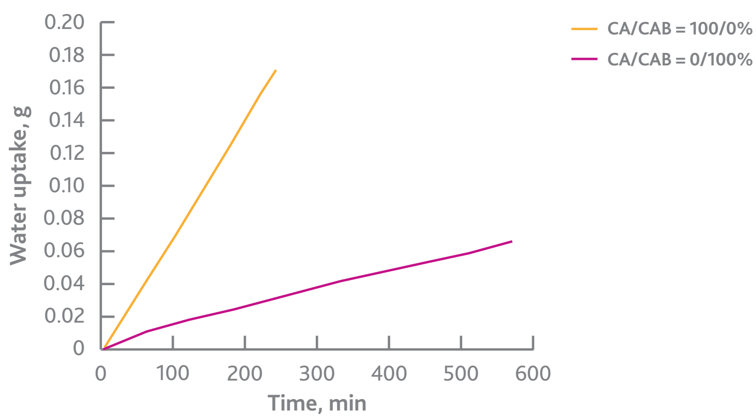
Formulation variable effect on the permeability of a coating film is discussed in following sections.

Effect of cellulose ester type

CA-398-10 NF/EP or CAB-171-15 NF was applied to coat the same model tablets in the same formulation under the same processing conditions. Figure 4 shows CA-398-10 NF/EP coating film has much higher permeability.

Cellulose esters can be combined in order to tailor the permeability of a coating film. For example, CA-398-10 NF/EP can be combined with CA-320S NF/EP and CA-398-10 NF/EP with CAB-171-15 NF. In the combination of CA-398-10 NF/EP with CA-320S NF/EP, the permeability of a coating formulation increases with the amount of CA-320S NF/EP in the formulation.[1] In the combination of CA-398-10 NF/EP with CAB-171-15 NF, the permeability of a coating film increases with the amount of CA-398-10 NF/EP and will be in the range between that of CA-398-10 NF/EP and CAB-171-15 NF.

Figure 4. Permeability comparison of CA-398-10 NF/EP and CAB-171-15 NF coating film



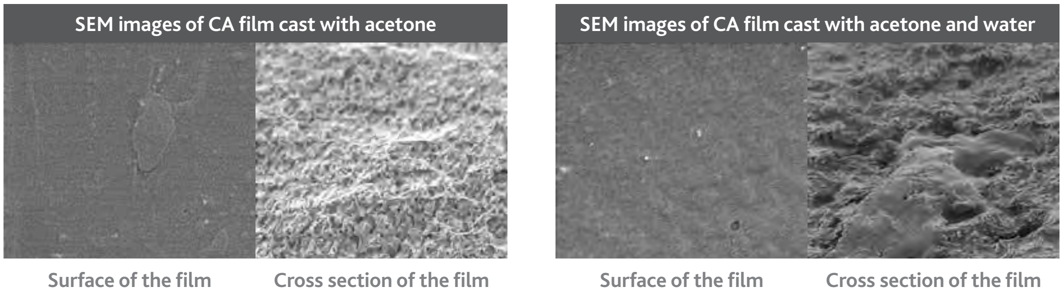
Effect of plasticizer

Plasticizers are commonly used in conjunction with cellulose esters to modify the physical properties of films. In general, for plasticized cellulose ester films, as the plasticizer level increases, the glass transition temperature decreases, film strength decreases, and film flexibility increases. Water vapor transmission rate (WVTR) depends on the type of plasticizer used. Water-soluble plasticizers increase WVTR; water-insoluble plasticizers decrease WVTR.[2]

Effect of solvent system

Acetone and acetone/water (94/6 wt%) were investigated as solvent systems. The nonplasticized cellulose ester films were transparent when acetone was the solvent system but hazy when acetone/water was the solvent system. Scanning electron microscopy (SEM) revealed that the films cast with acetone had smoother surfaces and smaller pinholes in the cross sections than the films cast with acetone/water. See Figure 5. The films prepared with acetone were stronger, tougher, and less permeable to water vapor.[3]

Figure 5. SEM images of cast cellulose acetate films



Effect of acetyl content in CA-398-10 NF/EP polymer

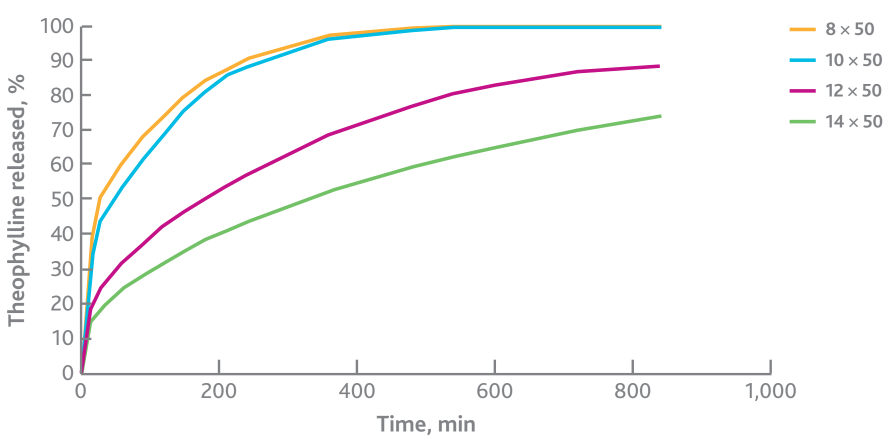
The acetyl content in CA-398-10 NF/EP polymer is in the range of 39.3%–40.3%. The permeability of coating films increases with decreasing acetyl content in CA polymers. The acetyl content over a range of about 1.0% affects permeability of coating films at some degree, and the effects were largely dependent on the formulation. With higher plasticizer level and water level in the formulation, the acetyl content only slightly affected the permeability of the coating film.[4]

Coating material for taste masking and sustained release

Cellulose esters can be used to coat tablets, granules, and small particles for taste masking. CA-398-10 NF/EP has been used commercially for this purpose.

CAB-171-15 NF can be formulated for use in sustained-release applications. Preliminary lab work demonstrated that CAB can be used for tableting as the matrix material to achieve sustained release.[5] See Figure 6.

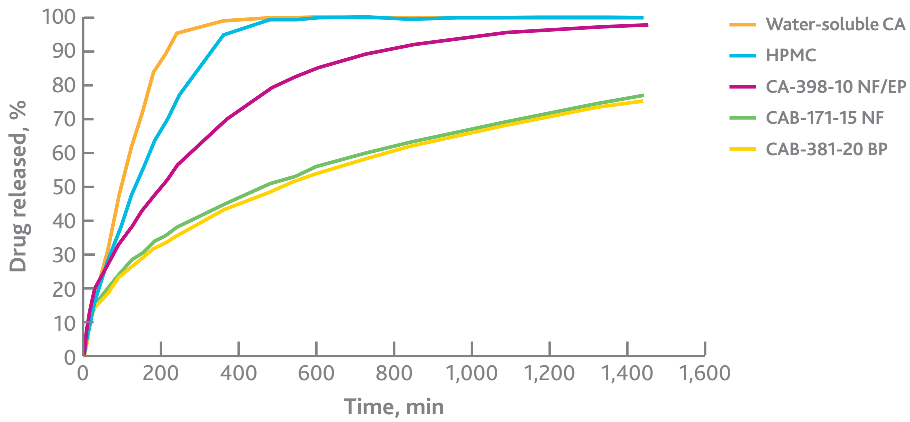
Figure 6. Theophylline release profile from CAB-171-15 NF tablets—release profiles from 4 different compression forces in the same formulation[5]



Binder for tableting

It has been demonstrated that CA and CAB can be used as binders when formulating tablets via direct compression. The tablet formulated with CAB-171-15 NF exhibited a slower release rate compared with tablets using CA-398-10 NF/EP. See Figure 7.

Figure 7. Release profile of theophylline in pH 1.2 buffer solution



Cellulose esters can be selected or tailored to give targeted release profiles.

Regulatory status

Eastman cellulose acetates (CA-398-10 NF/EP and CA-320S NF/EP) are manufactured in accordance with Current Good Manufacturing Practices as provided for in the *Joint International Pharmaceutical Excipient Council—Pharmaceutical Quality Group Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006* and meet specifications listed in the current product sales specification. Cellulose acetate is listed in the U.S. Pharmacopeia (USP) and the European Pharmacopeia (EP).

Eastman cellulose acetate butyrate (CAB-171-15 NF) is manufactured in accordance with Current Good Manufacturing Practices as provided for in the *Joint International Pharmaceutical Excipient Council—Pharmaceutical Quality Group Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006* and meets specifications listed in the current product sales specification. This product is listed as cellaburate in the USP.

Please contact your Eastman representative for information about the U.S. FDA Drug Master Files for these products.

Packaging

Eastman cellulose esters are packed and sealed in fiber drums equipped with a polyethylene inner liner and reusable metal closure. These containers should be sealed and 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-241C. Safety data sheets providing safety precautions for handling and storing Eastman products are available at **www.eastman.com/Markets/medical/Pages/Pharmaceutical_Excipients.aspx**. These publications should be obtained and reviewed before handling any of these products.

References

[1] Jinghua Yuan, Doug Dunn, Nancy Clipse, Ray Newton, "Permeability Study on the Coating Film Consisting of CA-398-10 NF/EP & CA- 320S NF/EP", Drug Development & Delivery, March (2011).

[2] Jinghua Yuan, Peter Shang, Stephen Wu, "Effects of Polyethylene Glycol on Morphology, Thermomechanical Properties, and Water Vapor Permeability of Cellulose Acetate-Free Films", Pharmaceutical Technology, Vol. (25), NO. (10), 62-74 (2001).

[3] Jinghua Yuan, Doug Dunn, Nancy Clipse, Ray Newton, "Formulation Effects on the Thermomechanical Properties and Permeability of Free Films and Coating Films: Characterization of Cellulose Acetate Films", Pharmaceutical Technology, Vol. (33), NO.(3), 88-100 (2009).

[4] Jinghua Yuan, Andy Singleton, "Cellulose Acetate Butyrate for Sustained Release via Direct Compression", poster presented at AAPS (American Association of Pharmaceutical Scientists) annual meeting, 2010.

[5] Jinghua Yuan, Stephen Wu, "Sustained-Release Tablets via Direct Compression: A Feasibility Study Using Cellulose Acetate and Cellulose Acetate Butyrate", Pharmaceutical Technology, Vol. (24), NO. (10), (2000)

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