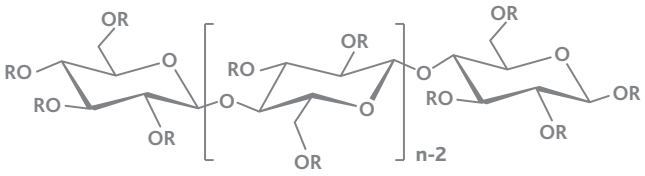
Cellulose ester blends for tunable drug delivery—
Achieving more with less

Eastman manufactures NF grade cellulose esters under cGMP that meet all the specifications of the United States Pharmacopeia. Eastman cellulose esters have unique properties to address mechanical strength and permeability needed for drug delivery applications.

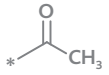
Eastman esterifies cellulose to produce cellulose acetate (CA), cellulose acetate butyrate (CAB), and cellulose acetate phthalate (C-A-P). See Figure 1 for structural formula. The structure of cellulose consists of repeating anhydroglucose units (AGU). Each AGU has three hydroxyl groups that can be esterified to yield cellulose esters. The amount of esterification can be expressed as weight percent of acyl group or degree of substitution (DS). If DS = 3, then 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.

Figure 1. Structural formula of Eastman pharma-grade cellulose esters

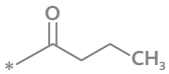


Anhydroglucose unit

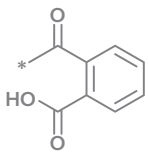
R = H or



Cellulose acetate (CA-398-10 NF/EP)
Cellulose acetate (CA-320S NF/EP)



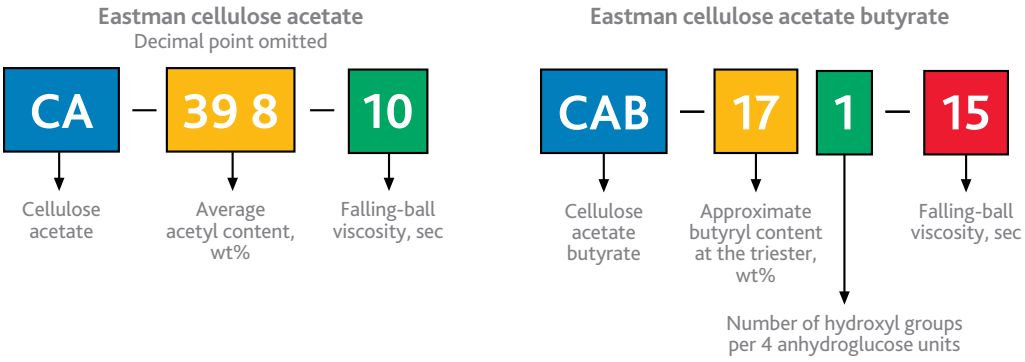
Cellulose acetate butyrate (CAB-171-15 NF)



Cellulose acetate phthalate (C-A-P)

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 approximate number of hydroxyl units per four AGU. 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. Cellulose acetate phthalate is an enteric polymer and is designated as C-A-P.

Figure 2. Eastman cellulose ester nomenclature



Eastman cellulose acetates such as CA-398-10 NF/EP and CA-320S NF/EP and hydrophobic cellulose acetate butyrate CAB-171-15 NF provide films with a wide range of water/API permeabilities. See Table 1 for physical and chemical properties of these polymers.

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

Type	Viscosity[b] cP	Acetyl		Butyryl		Hydroxyl		Melting range,°C	T_g,[d] °C	MW_n[e]
		%	DS[c]	%	DS	%	DS			
CA-398-10 NF/EP	38.0	39.8	2.4	—	—	3.5	0.6	230–250	191	35,000–37,000
CAB-171-15 NF	57.0	29.5	2.0	17	0.7	1.1	0.3	230–240	151	34,000–36,000
CA-320S NF/EP	2.1	32.0	1.8	—	—	8.7	1.2	230–250	213	18,000–19,000

[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 absolute molecular weight in THF (for CA-398-10 NF/EP and CAB-171-15 NF) and NMP (for CA-320S NF/EP)

Study describing the use of cellulose ester/enteric polymer blends for tunable drug delivery

Eastman cellulose esters are used in a variety of extended-delivery applications, such as the semipermeable membrane in osmotic pump technologies, sustained release from cellulose ester-based matrix formulations and coating applications, microencapsulation, and taste masking.

In a study described in the following section and carried out by Prof. Ziyaur Rahman's lab at Texas A&M Irma Lerma Rangel College of Pharmacy, the utility of cellulose ester blending to achieve desired dissolution profiles was investigated. The results show that cellulose ester/enteric polymer blends greatly expand the delivery profile space and offer a new tool to formulators for achieving the desired dissolution profile.

Core tablets composed of diclofenac sodium lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose (MW 100,000), croscarmellose, and magnesium stearate were prepared by wet granulation method. Refer to the following table (Table 2).

Table 2. Tablet compositions

Diclofenac sodium core tablet composition	
Ingredients	mg/tablet
Intragranular	
Diclofenac sodium	50
Lactose monohydrate	85
Microcrystalline cellulose	28
Hydroxypropyl cellulose	30
Extragranular	
Croscarmellose	5
Magnesium stearate	2
Total core tablet weight	200
Coating composition (5%)	
Polymer blend	9 (4.5%)
PEG-400	1 (0.5%)
Batch size for each coating composition	1 kg (5000 tablets)

The coating solution formulations contained polymer(s) and PEG 400 plasticizer in aqueous acetone solvent. See Table 3 for coating compositions. The core tablets were coated with coating polymer(s) at two levels (approximately 5% and 10% w/w). Core tablets and coated tablets were characterized for various quality parameters such as hardness, friability, disintegration, and dissolution (USP apparatus 2 at 50 rpm and 37°C). The two-step dissolution was performed in 0.1 N HCl and 0.2 M phosphate buffer for coated tablets. See Table 3 for coating formulations.

Table 3. Coating composition

Formulation	Cellulose ester	Enteric polymer	Ratio (cellulose ester: enteric polymer)	Plasticizer PEG 400
F1	CA-320S	C-A-P[a]	9:1	0.5%
F2	CA-320S	C-A-P	1:1	0.5%
F3	CA-398-10	C-A-P	9:1	0.5%
F4	CA-398-10	C-A-P	1:1	0.5%
F5	CAB-171-15	C-A-P	9:1	0.5%
F6	CAB-171-15	C-A-P	1:1	0.5%
F7	CA-320S	HPMCP 55[b]	9:1	0.5%
F8	CA-320S	HPMCP 55	1:1	0.5%
F9	CA-398-10	HPMCP 55	9:1	0.5%
F10	CA-398-10	HPMCP 55	1:1	0.5%
F11	CAB-171-15	HPMCP 55	9:1	0.5%
F12	CAB-171-15	HPMCP 55	1:1	0.5%
F13	CA-320S	Eudragit L100[c]	9:1	0.5%
F14	CA-320S	Eudragit L100	1:1	0.5%
F15	CA-398-10	Eudragit L100	9:1	0.5%
F16	CA-398-10	Eudragit L100	1:1	0.5%
F17	CAB-171-15	Eudragit L100	9:1	0.5%
F18	CAB-171-15	Eudragit L100	1:1	0.5%

[a]Cellulose acetate phthalate commercially available from Eastman. [b]Hydroxypropyl methylcellulose phthalate 55 commercially available from Shin-Etsu. [c]Eudragit® L100 commercially available from Evonik Industries.

Coating equipment and spray conditions for coating tablets are given in Table 4.

Table 4. Coating equipment and conditions

Equipment	8" Vector Hi-Coater, model HCT Mini
Substrate (tablet size)	8 mm x 3 mm
Pan charge	400 g
Inlet temp.	60°–80°C
Pan temp.	55°–70°C
Outlet temp.	30°–40°C
Pan rotation speed	35–40 rpm
Atomized air pressure	1.5–2.0 bar
Spray rate	1 mL/min
Tablet bed to spray gun distance	5–7 cm

Dissolution data and release profiles

Table 5. Dissolution results of diclofenac tablets (F1–F6) coated with polymer combination at approximately 5% coating weight

Formulation	F1	F2	F3	F4	F5	F6
Coating level (%)	6	7	6.75	6.60	5.40	6.20
0 min	0	0	0	0	0	0
15 min	0.3 ± 0.0	3.4 ± 2.4	1.6 ± 1.4	9.9 ± 2.7	0.6 ± 0.1	12.1 ± 2.8
30 min	1.4 ± 0.1	18.5 ± 2.3	17.0 ± 0.7	32.6 ± 3.7	5.8 ± 1.9	53.2 ± 4.1
45 min	3.3 ± 0.4	31.3 ± 3.1	36.4 ± 0.2	50.5 ± 1.7	17.3 ± 2.1	74.6 ± 3.7
60 min	5.6 ± 0.4	39.6 ± 2.9	47.5 ± 2.2	58.3 ± 1.9	34.3 ± 1.3	81.3 ± 3.0
90 min	10.9 ± 0.0	46.6 ± 2.3	51.9 ± 2.1	65.2 ± 8.0	63.7 ± 1.8	87.5 ± 2.0
120 min	16.2 ± 0.2	48.5 ± 2.5	53.7 ± 0.9	84.3 ± 2.5	67.8 ± 1.5	89.8 ± 0.5

Note: *All measurements in triplicate*

Figure 3. Dissolution profile of diclofenac tablets (F1–F6) coated with polymer combination at approximately 5% coating weight

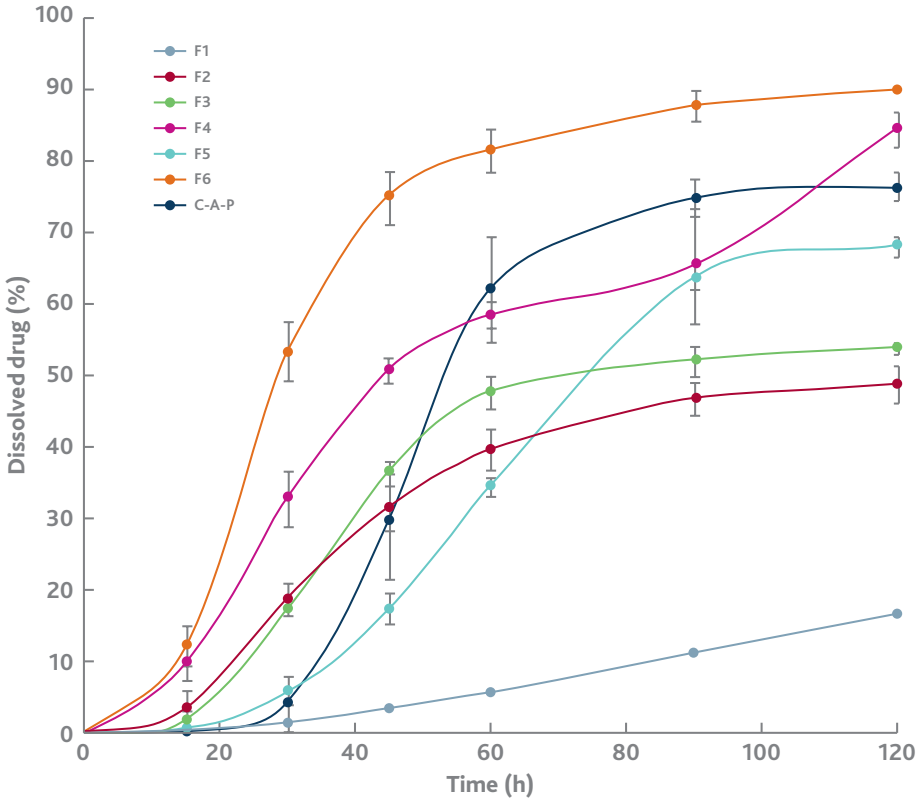
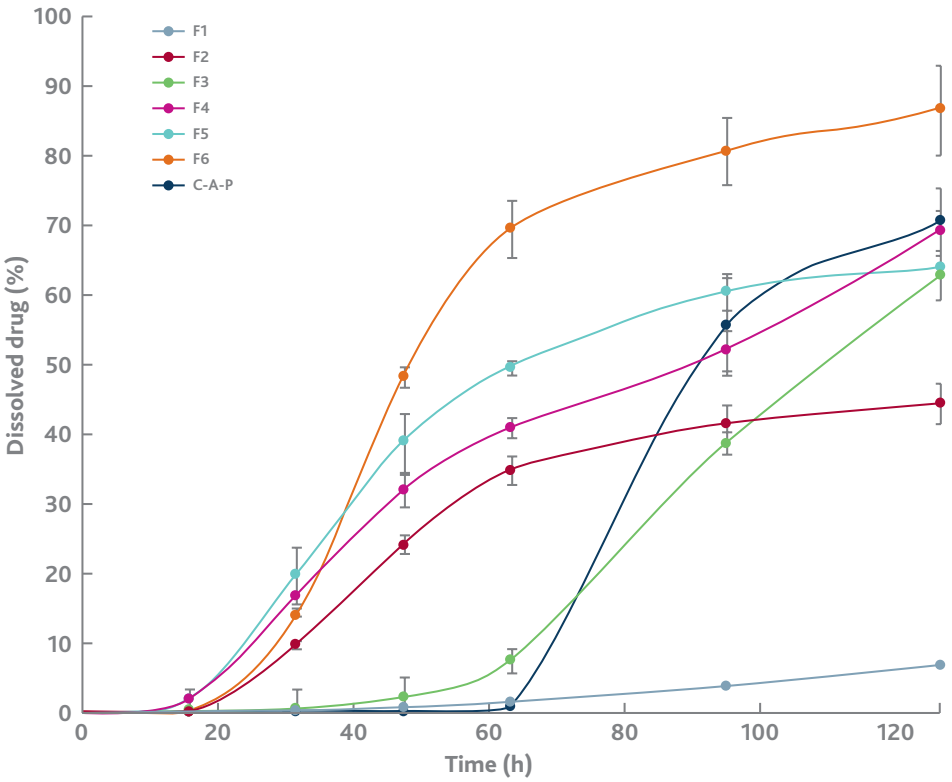


Table 8. Dissolution results of diclofenac tablets (F1–F6) coated with polymer combination at approximately 10% coating weight

Formulation	F1	F2	F3	F4	F5	F6
Coating level (%)	10	11	10.70	10.70	9.90	11.50
0 min	0	0	0	0	0	0
15 min	0.1 ± 0.1	0.1 ± 0.1	0.3 ± 0.0	2.0 ± 0.0	2.0 ± 1.5	0.0 ± 0.1
30 min	0.2 ± 0.1	9.8 ± 0.6	0.6 ± 3.0	16.8 ± 0.1	19.7 ± 4.1	14.0 ± 0.1
45 min	0.7 ± 0.1	24.2 ± 1.3	2.4 ± 2.8	32.0 ± 2.5	38.9 ± 4.2	48.2 ± 1.5
60 min	1.6 ± 0.1	35.0 ± 2.0	7.4 ± 1.8	41.0 ± 1.6	49.5 ± 1.0	69.6 ± 4.1
90 min	3.7 ± 0.1	41.5 ± 2.7	38.7 ± 1.6	52.0 ± 2.9	60.6 ± 2.7	80.6 ± 4.8
120 min	6.8 ± 0.2	44.5 ± 2.8	62.8 ± 3.6	69.3 ± 2.8	64.0 ± 0.6	86.6 ± 6.5

Note: *All measurements in triplicate*

Figure 7. Dissolution profile of diclofenac tablets (F1–F6) coated with polymer combination at approximately 10% coating weight



Note: *Additional data available on request through your Eastman representative.*

Conclusions

Cellulose esters form strong, flexible semipermeable coatings with a tunable hydrophobic/hydrophilic ratio, depending on the choice of ester type and amount. These cellulose esters have been used extensively in drug delivery applications for extended and enteric drug delivery. The present study now shows an even greater modification of a drug delivery profile that can be achieved by blending a cellulose ester with an enteric polymer. As an example, combining a cellulose ester such as CA-320S NF/EP, CA-398-10 NF/EP, or CAB-171-15 NF with an enteric polymer such as C-A-P, HPMCP 55, or Eudragit® L100 results in tunable and reproducible perturbations of the dissolution profile of coated diclofenac sodium tablets. Blending cellulose esters represents a way to achieve targeted dissolution profiles in a simple, reproducible, and flexible manner without the introduction of extraneous ingredients. Blending means achieving more with less using well-known, well-understood cellulose ester polymers.

Regulatory status

Cellulose acetate (CA-398-10 NF/EP and CA-320S NF/EP)

Eastman cellulose acetate (CA-398-10 NF/EP and CA-320S NF/EP) are produced under appropriate current good manufacturing practices (cGMP) for pharmaceutical excipients. Cellulose acetate is listed in the current United States Pharmacopeia (USP), in the European Pharmacopoeia (EP), and in the Japanese Pharmacopoeia (JP). It is the subject of U.S. Drug Master File 9323.

Cellulose acetate butyrate (CAB-171-15 NF)

Cellulose acetate butyrate is listed in the current USP under the name cellaburate. Eastman CAB-171-15 NF is the subject of U.S. Drug Master File 15490 and is manufactured under appropriate cGMP for pharmaceutical excipients.

Cellulose acetate phthalate (C-A-P NF)

C-A-P meets the National Formulary (NF) compendial specifications found in the cellacefate monograph. The JP and EP have also implemented the harmonized text of this monograph. Confidential information on C-A-P to support pharmaceutical applications is maintained in a Drug Master File 8 with the U.S. Food and Drug Administration.

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 that should be observed in handling and storing Eastman products are available online or by request. These publications should be obtained and reviewed before handling any of these products.

EASTMAN

The results of **insight**™

Eastman Corporate Headquarters
P.O. Box 431
Kingsport, TN 37662-5280 U.S.A.

U.S.A. and Canada, 800-EASTMAN (800-327-8626)
Other Locations, +(1) 423-229-2000

www.eastman.com/locations

PHMA-7889 10/18