# Eastman cellulose esters

## for osmotic drug delivery

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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[1] and permeability needed for osmotic drug delivery.

Eastman cellulose esters provide a wide range of film permeability with hydrophilic polymers such as cellulose acetate CA-398-10NF/EP and CA-320SNF/EP and hydrophobic polymer such as cellulose acetate butyrate CAB-171-15NF. See Table 1 for physical and chemical properties. Furthermore, the permeability of cellulose ester films can be modified by using mixtures of cellulose ester polymers, additions of plasticizers, inclusion of water as a cosolvent, and varying the coating film thickness as measured by coating weight gain. The formulation variables' effects on the permeability of a coating film and ultimately the release rate of a drug have been demonstrated with bilayer osmotic ibuprofen tablets coated with CA-398-10NF/EP.

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

| Type | Viscosity[b] cP | Acetyl | | Butyryl | | Hydroxyl | | Melting range (°C) | $T_g$[d] (°C) | MWn[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-398-10NF/EP and CAB-171-15NF) and NMP (for CA-320SNF/EP)*

## Permeability of coating films

The permeability of coating films was determined by water uptake experiments. Model tablets (250 mg per tablet) consisting of 98.5% POLYOX water-soluble resins (hydrogel) with a molecular weight of 5,000,000, 0.5% colorant, and 1.0% magnesium stearate were coated (processing conditions in Table 2) and tested in 1000 ml of deionized water at 37°C using a standard USP disintegration tester to provide gentle agitation. At selected intervals, the tablets were taken out, dried gently with a tissue, and weighed. The amount of water uptake was determined by subtracting the tablet weight before testing from the weight at the time of testing.

### Table 2. Coating processing conditions

| Factor | Condition |
| --- | --- |
| Equipment | 12" pan coater (COMPU-LAB, Thomas Engineering) |
| Nozzle | 35100-ss |
| Substrate | 250 mg tablets |
| Pan charge | 800 g |
| Inlet temperature | 25°C (bed temperature 21°C) |
| Airflow rate | 175 cfm |
| Pan rotation speed | 15 RPM |
| Atomized air pressure | 15 psi |
| Spray rate | 20 ml/min for 5 min; increased to 25 ml/min for another 5 min; and maintained at 30 ml/min for the rest of the run |

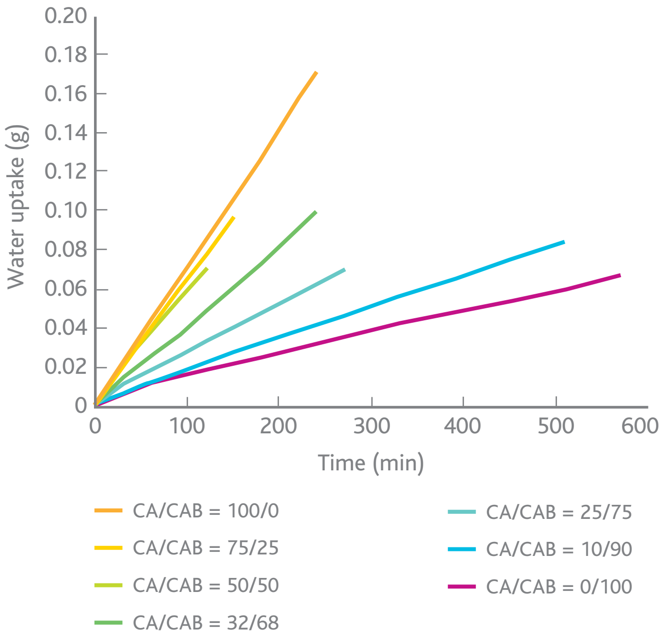
## Factors which affect the permeability of cellulose ester films

### Polymer type

#### CA-398-10NF/EP combined with CAB-171-15NF

Figure 1 shows the water uptake results with changing the ratio of CA to CAB while maintaining plasticizer level (polyethylene glycol [PEG] 3350 at 0.7%) and water level (5.0%). As can be seen for these two polymers, CAB gives the lowest permeability and CA gives the highest permeability. One can tailor the permeability of a coating film between CA and CAB by adjusting the ratio of CA to CAB in the coating formulation.

### Figure 1. CA to CAB ratio effect on permeability*




*Water uptake rate with changing the ratio of CA to CAB. Other formulation variables and processing variables were held constant. The ratio of CA to CAB is in weight percentage.

### CA-398-10NF/EP combined with CA-320SNF/EP

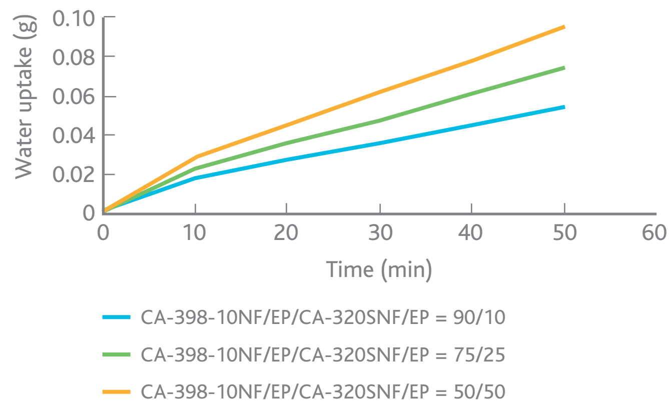
The degree of acetylation of cellulose acetate has a significant effect on the water permeability of its film. The higher acetyl content in the cellulose acetate will give lower permeability. Figure 2 demonstrates that mixtures of CA-398-10NF/EP (acetyl: 39.3%–40.3%) and CA-320SNF/EP (acetyl: 32.0%–34.5%) can be used to adjust the film permeability.

## Plasticizer type and amount

It is well known that a hydrophilic plasticizer in a coating film will increase the permeability of the film, and a hydrophobic plasticizer will decrease the permeability of the film[1]. The molecular weight of a plasticizer can also affect the permeability as seen in Figure 3.

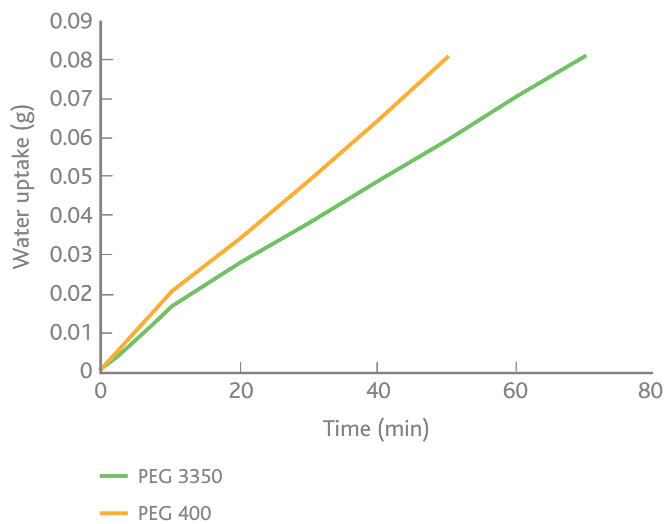
The amount of plasticizer in a coating formulation also plays a significant role in determining the permeability of the coating film. See Figure 4.

**Figure 2. CA-398-10NF/EP to CA-320SNF/EP ratio effect on permeability***



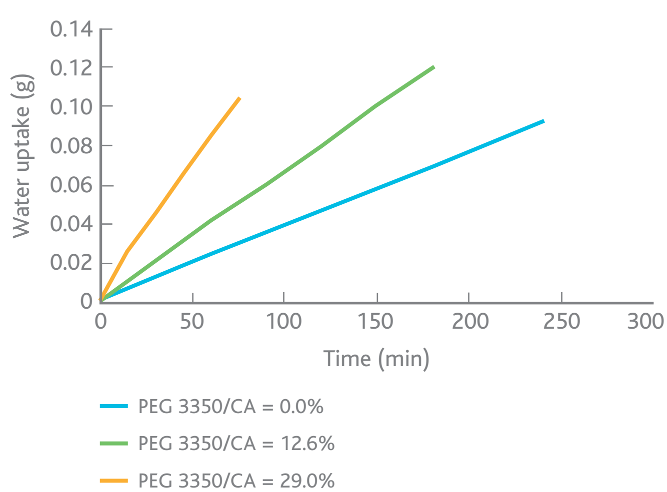

**The ratio of CA-398-10NF/EP to CA-320SNF/EP effect on the permeability of the coating films on hydrogel tablets (PEG 3350 = 11.1% in the formulations). The ratio of CA-398-10NF to CA-320SNF/EP is in weight percentage.*

**Figure 3. PEG molecular weight effect on permeability***




**Polyethylene glycol (PEG) molecular weight effect on the permeability of CA-398-10NF/EP combined with CA-320SNF/EP coating film on hydrogel tablets (the ratio of CA-398-10NF/EP to CA-320SNF/EP is 50/50). PEGs are hydrophilic plasticizers.*

**Figure 4. Plasticizer level effect on permeability***




**Plasticizer level effect on the permeability of CA-398-10NF/EP coating film on hydrogel tablets (5.0% water in the formulations). Plasticizer levels are shown as a weight percentage relative to the weight of cellulose ester in the coating solution.*

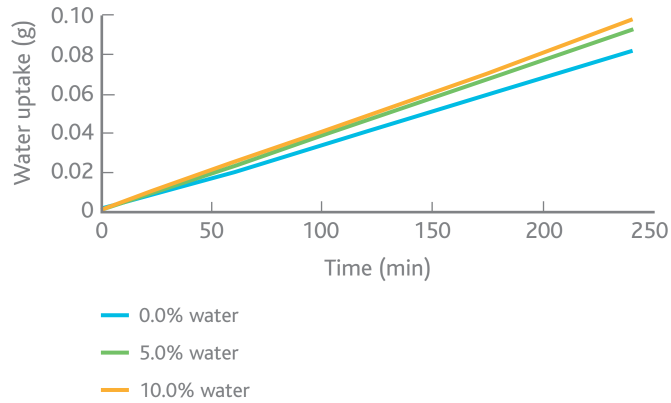
## Water as a cosolvent

Acetone is the most commonly used solvent for cellulose esters. When water is included as a cosolvent in a coating formulation, an increase in permeability of the coating film is observed.[1]

## Coating weight

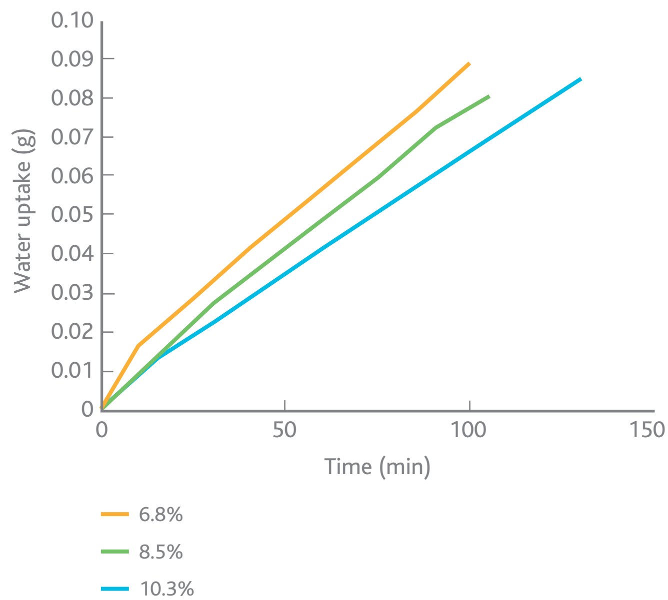
The film thickness on the tablet is a function of the weight gain during the coating process. The thicker the film, the lower the permeability. See Figure 6.

**Figure 5. Water effect on permeability***




*Effect of water as a cosolvent on the permeability of CA-398-10NF/EP coating film on hydrogel tablets (no plasticizer is present in these coating formulations)*

**Figure 6. Coating weight effect on permeability***



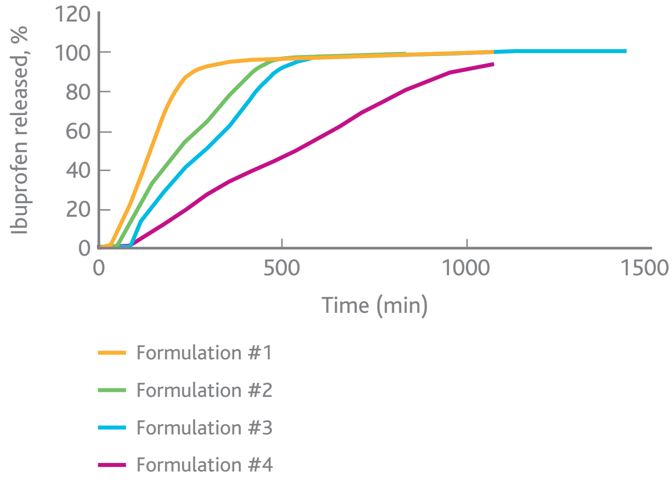

*Coating weight effect on the permeability of CA-398-10NF/EP coating film on hydrogel tablets (formulation: PEG 3350/CA = 11.1%, water = 5.0%)*

## Bilayer osmotic ibuprofen tablet

It can be demonstrated that formulation variables' effects on film permeability observed in the model tablet are also evident in a more complex drug delivery system containing an active. To investigate formulation variables' effects on the release rate of an active, CA-398-10NF/EP was coated on bilayer osmotic ibuprofen tablets.[2] Coating formulations are listed in Table 3 and release profiles are displayed in Figure 7.

These release profiles confirm that the permeability of coating films affected by varying the plasticizer level and water level in the coating formulations directly correlates with the rate of drug release from a bilayer osmotic tablet.

**Figure 7. Ibuprofen release profiles***




*Ibuprofen (model active) release profiles from CA-398-10NF/EP-coated bilayer osmotic tablets.*

**Table 3. Coating formulations for bilayer osmotic tablets**

| ID | CA-398-10 NF/EP (%) | PEG 3350 (%) | PEG 3350/CA (%) | Water (%) | Acetone (%) |
|---|---|---|---|---|---|
| 1 | 4.65 | 1.35 | 29.0 | 5.0 | 89.0 |
| 2 | 5.33 | 0.67 | 12.6 | 10.0 | 84.0 |
| 3 | 5.33 | 0.67 | 12.6 | 5.0 | 89.0 |
| 4 | 6.00 | 0.00 | 0.0 | 0.0 | 94.0 |

## Summary

Eastman cellulose esters form semipermeable membranes that are strong and have a wide range of permeability suitable for osmotic drug delivery applications. The permeability of cellulose ester film can be adjusted by using different types of cellulose esters (those with acetyl or butyryl substituent) and by using combinations of cellulose esters. The permeability of the films can be further modified with addition of plasticizers, by including water as a cosolvent, and by adjusting the coating film thickness.

## Regulatory status

### Cellulose acetate

Eastman cellulose acetate (CA-398-10NF/EP and CA-320SNF/EP) is 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 Pharmacopeia (EP), and in the Japanese Pharmacopeia (JP). It is the subject of U.S. Drug Master File 9323.

### Cellulose acetate butyrate

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

## 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-241. 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.

## References

[1]Yuan, J., Wu S., Pharmaceutical technology, 25(10), 62-74, 2001.

[2]Yuan, J., Clipse, N., and Newton R., AAPS poster, 2008 (posted on www.eastman.com).

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