Cost-effective approach to formulate controlled-release osmotic drug delivery tablets without need for laser-drilled orifice using cellulose acetate polymers in designing CPOP (controlled porosity osmotic pumps) delivery systems

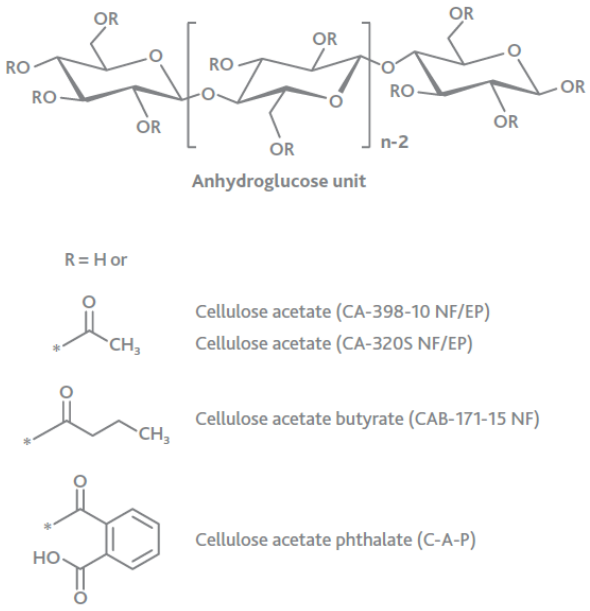
Company: Eastman
February 17, 2026

Cellulose acetates are cellulose esters that play a pivotal role in advanced drug delivery systems, particularly in osmotic-controlled release formulations. This white paper explores the physicochemical properties of cellulose esters, their application in osmotic pump systems, and the innovative controlled porosity osmotic pump (CPOP) technology that enables zero-order drug release independent of pH.

The evolution of drug delivery systems has significantly improved therapeutic outcomes by enabling controlled and sustained release of active pharmaceutical ingredients (APIs). Among these innovations, osmotic drug delivery systems (ODDS) stand out for their ability to provide zero-order release kinetics, largely independent of gastrointestinal pH, motility, and other physiological variables (Swanson D., et al., 1987; Grundy et al., 1996). A major advancement in this field is the CPOP, which was developed as an extension of elementary osmotic pumps. Unlike traditional osmotic systems that require a predrilled orifice, CPOP employs a semipermeable membrane embedded with leachable, pore-forming agents.

Cellulose, a natural polysaccharide composed of β-D-glucose subunits, can be chemically modified to form esters or ethers. Cellulose acetate and acetate butyrate chemistry belongs to the cellulose esters class of polymers that form semipermeable films and are used in coating pharmaceutical tablets to obtain controlled release profiles. Cellulose acetate phthalate is an enteric polymer that dissolves above pH 6.0.

Figure 1. Cellulose esters in drug delivery



Eastman provides three different grades of cellulose esters that possess suitable semipermeable film forming properties, making them ideal for osmotic drug delivery systems:

- Cellulose acetate CA 320S NF: relatively high permeability
- Cellulose acetate CA 398-10 NF: low permeability
- Cellulose acetate butyrate (CAB 171-15 NF/EP): relatively least permeability

Cellulose esters have been used in multiple commercially available osmotic drug delivery systems, including Procardia XL, Adalat, Topamax, Concerta, Invega, etc., due to the precise controlled release possible while formulating with these polymers.

Controlled porosity osmotic pump (CPOP) technology

CPOP systems represent a significant advancement in oral drug delivery. They eliminate the need for mechanical drilling by incorporating water-soluble additives into the semipermeable membrane. Upon contact with gastrointestinal fluids, these additives dissolve to form micropores that facilitate drug release.

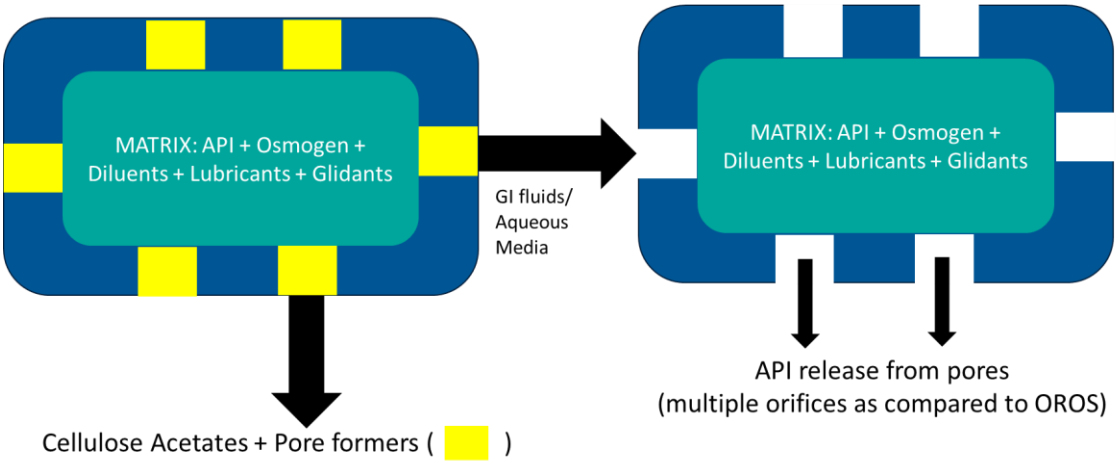
Advantages of CPOP vs. conventional osmotic systems with drilled orifice:

- **Eliminates laser-drilled orifice**
  Drug release occurs through a semipermeable membrane with controlled porosity, removing the need for mechanical drilling and complexities.
- **Simplifies manufacturing and reduces costs**
  No specialized equipment is required, making production more economical.
- **Consistent and controlled drug release**
  Maintains zero-order release kinetics unaffected by gastrointestinal pH or motility
- **Improved bioavailability and therapeutic efficacy**
  Ensures steady plasma drug concentrations over extended periods
- **Suitable for all biopharmaceutical classification system (BCS) classes of APIs**
  Solubilizing agents within the core may be added to facilitate drug release from a CPOP system incorporating BCS Class II and IV (water-insoluble) APIs. For highly water-soluble APIs, there is no need to incorporate additional solubilizers.
- **Enhanced patient compliance**
  Reduces dosing frequency, making treatment more convenient

Mechanism of action

The CPOP works through a series of well-orchestrated steps to ensure controlled drug release. Upon oral administration, the tablet encounters gastrointestinal fluids, allowing water to permeate through the cellulose ester-based semipermeable membrane. As water enters, it dissolves the embedded pore-forming agents within the membrane, leading to the formation of micropores and transforming the membrane into a porous structure (See Figure 2). This process continues as water further infiltrates the tablet core, dissolving both the osmogen and the drug, thereby generating internal osmotic pressure. The resulting pressure drives the dissolved drug solution out through the newly formed micropores. **The rate of drug release is precisely controlled by several factors, including the thickness of the membrane, the concentration of pore-forming agents, the solubility of the drug, and the osmotic pressure gradient**. Ultimately, this system achieves zero-order kinetics independent of pH and/or gastrointestinal motility, enhancing therapeutic efficacy and patient compliance.

Figure 2. Mechanism of CPOP



Eastman case study

The study was conducted using metoprolol succinate as the model API. The me metoprolol succinate ER tablet requires a precisely tuned controlled-release profile because it is prescribed for patients with cardiovascular (CVS) issues such as angina, heart failure, and hypertension. The high water solubility of metoprolol succinate poses a formidable challenge for controlled-release formulation, making it an ideal choice to demonstrate the power of CPOP coatings. Metoprolol succinate was blended with diluents by geometric mixing, followed by blending with an osmogene, and finally blended with glidant and lubricant to yield free-flowing powder. The powder was then compressed using 10-mm SC punches to a tablet weight of approximately 330 mg with thickness of approximately 4.4 mm.

The resultant tablets were then coated with cellulose acetate CA 398-10 NF polymer coating solution, the composition of which is detailed in Table 1.

Table 1. Coating solution composition

Ingredient	Concentration
Acetone	83.5%
Isopropyl alcohol (IPA)	9.3%
CA 398-10 NF/EP	6.0%
Polyethylene glycol (PEG) 400	20% relative to CA398-10 NF/EP content
Porogen	As detailed in Table 2

Table 2. List of porogens (pore-forming agents) used and their concentrations tested

Porogen	Concentration (% CA 398-10 NF conc)
Polyvinyl pyrrolidine (PVP)	10, 20, 40
Cellulose acetate phthalate (C-A-P)	10, 20, 30, 40
Tween 80	10, 20, 40
Triethyl citrate (TEC)	10, 20, 40
Hydroxypropyl cellulose (HPC)	10, 20, 40

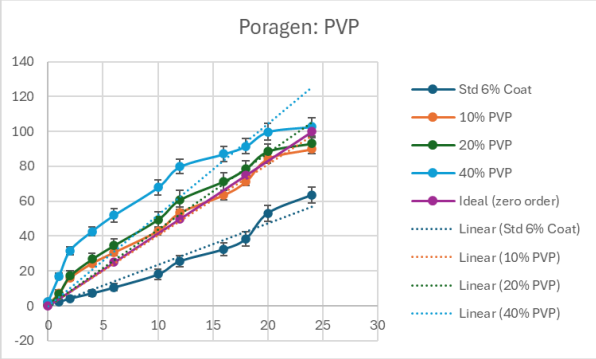
Solutions were prepared by first dissolving CA 398-10 NF/EP in the acetone/IPA mixture. This was followed by the addition of PEG 400 and the appropriate porogen, with additional mixing as needed to dissolve or suspend the porogen (depending on porogen solubility in the solvent system). Tablets were coated with no orifice being drilled and tested for dissolution and adherence to a true zero-order release profile. See Table 3 for the profile that was targeted.

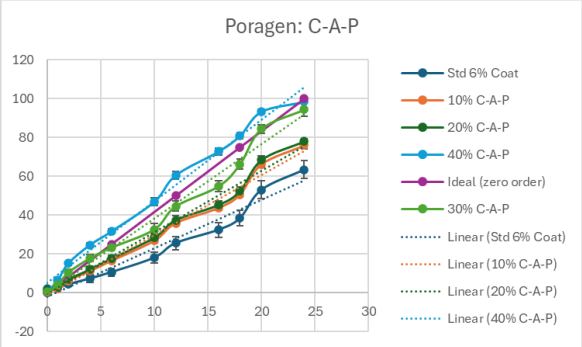
Table 3. Zero-order profile targeted for developed tablets

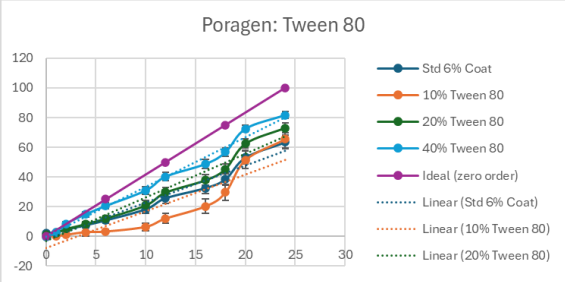
Parameter	Condition
Media	Phosphate buffer pH 6.8, 500 ml
Apparatus	USP apparatus 2
RPM	50
Test points (hr)	1, 2, 3, 4, 6, 10, 12, 18,20, 24
Measurement wavelength	222 nm
Target profile	
6 hr	25%
12 hr	50%
18 hr	75%
24 hr	100%

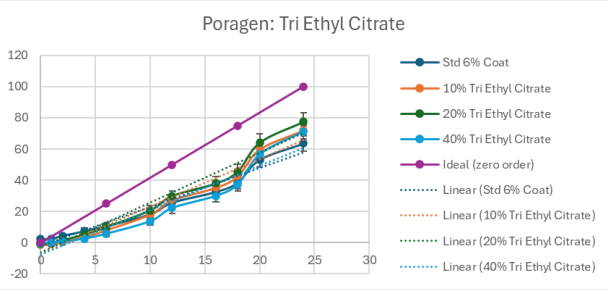
The dissolution profiles obtained for different porgens and at different percentage inclusion are illustrated in the Figure 3 graphs, along with a purple line in each graph representing an ideal zero-order release desired with cellulose acetate coatings and useful for APIs like metoprolol for maintaining constant plasma levels of the API.

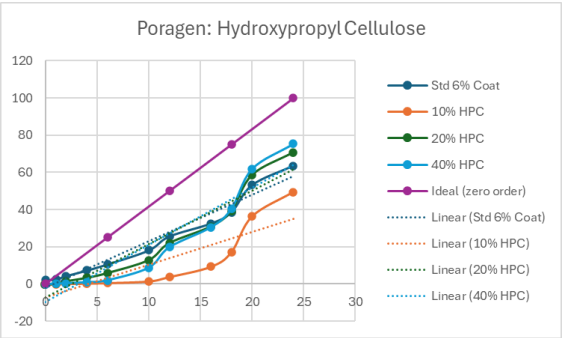
Figure 3. Dissolution profiles for porogen evaluation











As seen in Figure 3, only PVP and C-A-P polymers helped to show good correlation to ideal zero-order release desired to ensure more than 85% drug release at last time point.

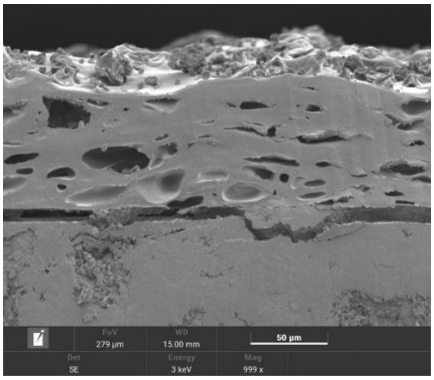
Tablets with a standard 6% coat of CA 398-10NF and 1.2% plasticizer without porogens did not demonstrate a strong sustained release profile. Including porogens increased the release rate for PVP and C-A-P polymers significantly, thereby achieving desired zero-order dissolution profile. Some of these profiles were also compliant to metoprolol ER tablet dissolution profile as desired to meet USP compliance (1 hour, not more than 20% release; 4 hours, 20%–40% release; 8 hours, 40–60% release; and 20 hours, not less than 80% release).

For other porogens, namely TEC and HPC, release profile did not improve significantly compared to one without porogens. However, for polysorbate 80, there was a little, modest rise in release profile as the percentage of porogens increased from 10% to 40%.

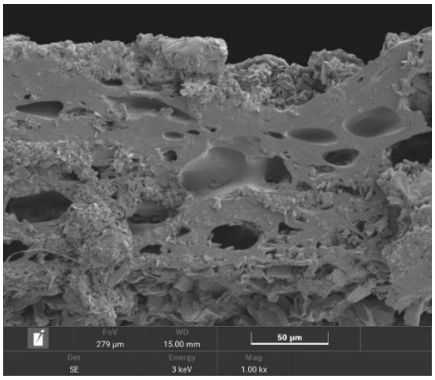
See Figure 4 for cross-sectional images of 10% PVP in CA 398-10 NF-based coated tablets before and after dissolution. It is visible that pores have opened to facilitate complete drug release in a sustained manner over 24 hours.

Figure 4. SEM images of tablet coating before(A) and after (B) dissolution for coating having 10% PVP as porogens

(A) Before dissolution



(B) After dissolution



Conclusions and recommendations

With the exception of triethyl citrate, all selected porogens exhibited increasing release rate with increasing porogen concentration. This suggests incorporation of a water-soluble moiety in a CA 398-10 coating solution can be used to modulate drug release driven by osmotic pressure in lieu of drilling a hole to facilitate drug release. The 10% PVP concentration provided the best metoprolol release profile without exceeding the target release rate, while 30% C-A-P is a strong secondary option. Both the 20% PVP and 40% C-A-P are close to but modestly exceed the target release rate. These formulations could be viable, depending on the therapeutic index of the selected API. The coating process was evaluated further, and it was observed that reproducible release rates can be achieved, suggesting the process can be validated.

You may connect with the Signet and Eastman teams to learn more about CPOP coating and process parameter optimization. To get in touch, please complete the contact form on our website: Contact us | Pharmaceutical Ingredients | Eastman.

References

1. D R Swanson, B L Barclay, P S Wong, and F Theeuwes; "Nifedipine gastrointestinal therapeutic system," *Am J Med*. 1987 Dec 21;83(6B):3-9. doi: 10.1016/0002-9343(87)90629-2.
2. J S Grundy and R T Foster; "The nifedipine gastrointestinal therapeutic system (GITS): Evaluation of pharmaceutical, pharmacokinetic and pharmacological properties," *Clin Pharmacokinet*. 1996 Jan;30(1):28-51.doi: 10.2165/00003088-199630010-00003.