

UNIQUE TOGETHER

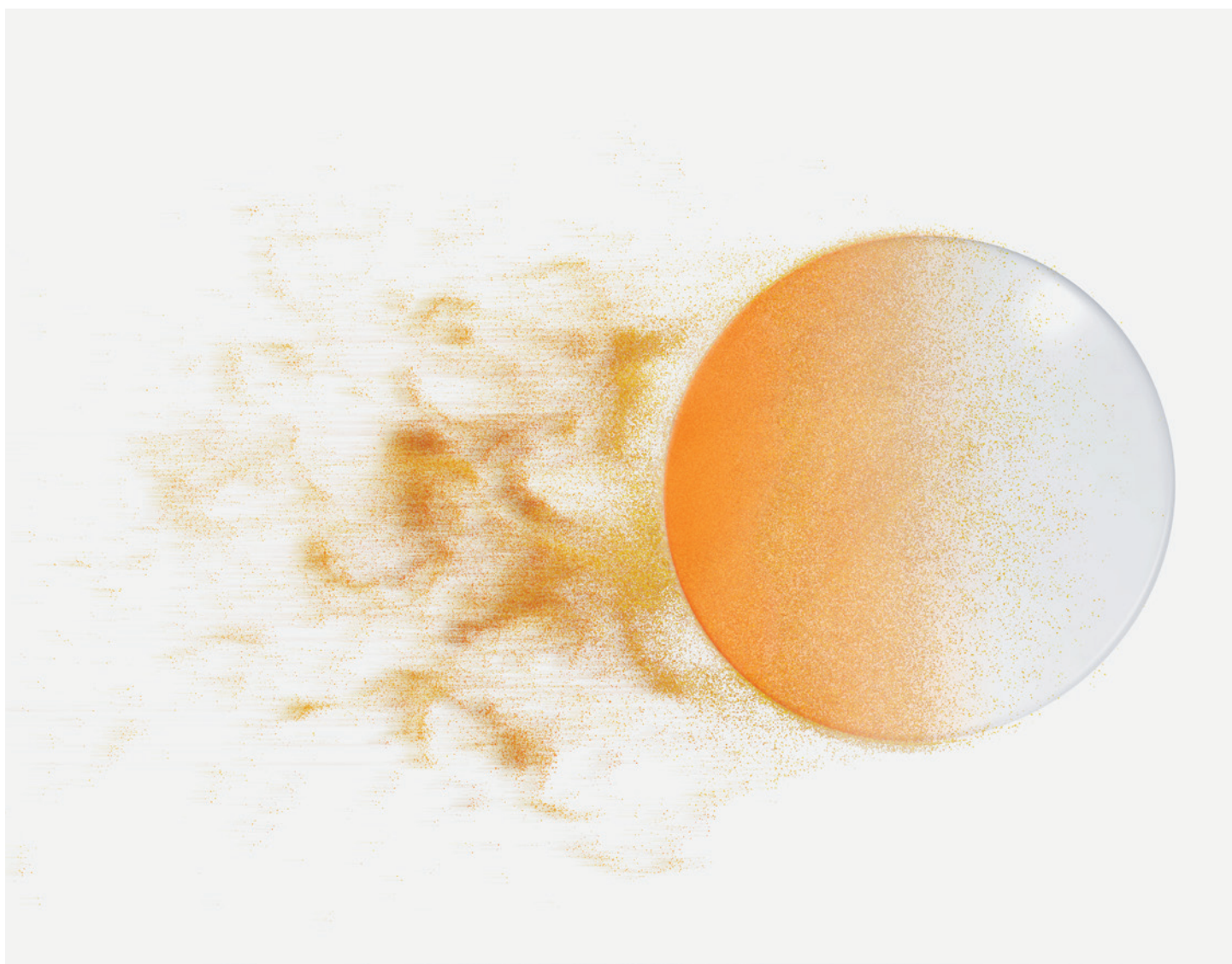


CONTROLLED RELEASE ALLIANCE

Dow Pharma Solutions

ETHOCEL™ High Productivity (HP) Polymers

Safe. Fast. Efficient.



Improving Productivity Through Innovation

ETHOCEL™ Polymers is the oldest trademarked brand available from The Dow Chemical Company and continues to be an exciting source of innovation. The constant pursuit of production excellence has differentiated ETHOCEL™ from the competition by producing ethylcellulose that adheres to exceptionally narrow viscosity limits, contains fewer insoluble fibers and is more reproducibly ethoxylated than other ethylcellulose producers. With this latest innovation, ETHOCEL™ has been optimized for use in dry powder layering processes using rotor granulation technology.

Rotor granulation technology enables coating of multiparticulates, powders and even mini-tablets without the need for solvents or aqueous-based polymer dispersions. The dry powder process uses just enough moisture to allow the polymer to adhere to the substrate, but the polymer is added as a dry powder.

The new tailored ETHOCEL™ HP offering is ideally suited for the dry powder coating process. Trials show that using ETHOCEL™ HP (High Productivity) in a rotor coater allows for improved efficiency and shorter coating times, while completely eliminating the need for environmentally-harmful solvents. This new technology can be a powerful solution for customers looking to improve sustainability metrics or avoid installation of costly solvent handling systems without experiencing the long coating time and potential stability issues of aqueous-based dispersions.

Customers looking for innovative solutions to their controlled release and taste masking challenges will find that using ETHOCEL™ HP in a dry powder coating process gives them the confidence of working with a familiar and well understood ETHOCEL™ polymer while avoiding concerns with tackiness and stability often found with other barrier membrane solutions.

Commercial availability of the ETHOCEL™ HP product is the culmination of an extensive collaboration between equipment manufacturer Freund-Vector Corporation, developers of the innovative GRANUREX® rotor processing equipment and Controlled Release Alliance partner Colorcon, with their industry leading SUGLETS® sugar spheres product for drug layering. Formulation development support and distribution of ETHOCEL™ HP will be managed by the Controlled Release Alliance and led by Colorcon.

Why Go With This Solvent-Less System?

ETHOCEL™ HP can help you:

- Realize 70% improvements in processing time versus current MUPS coating technologies
- Consistently achieve 98 - 99% coating efficiency
- Improve sustainability through elimination of solvents
- Avoid additional costs related to solvent use – including disposal, capital and infrastructure modifications
- Improve operational safety



Figure 1. VFC-LAB 3 FLO-COATER® with GXR-35 Rotor Insert.



Figure 2. GRANUREX® GXR-35 Rotor.

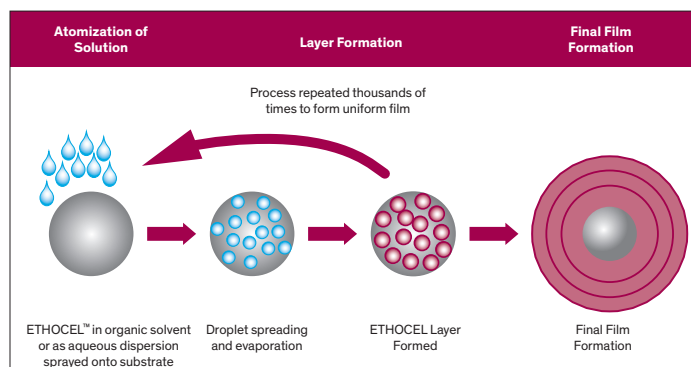


Figure 3. The spray coating process.

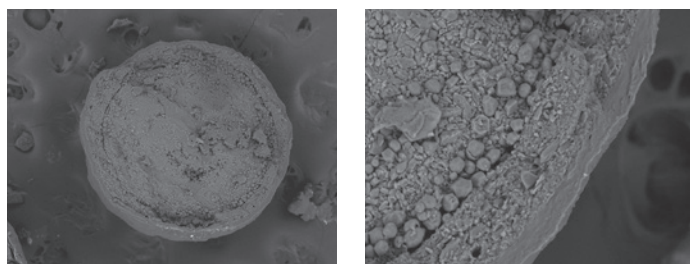


Figure 4. Cross sectional image (left) and magnified view (right) of ETHOCEL™ barrier membrane formed from solvent solution.

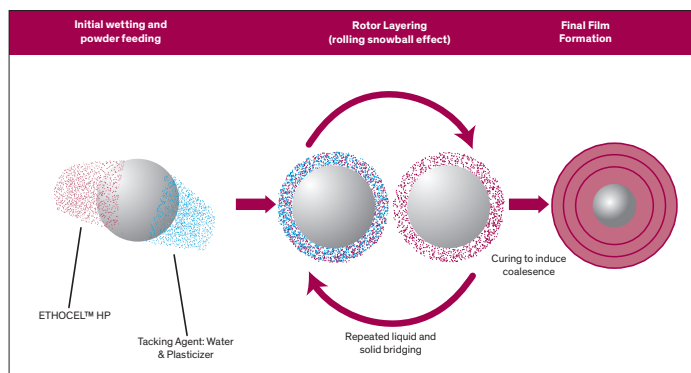


Figure 5. The dry powder layer process.

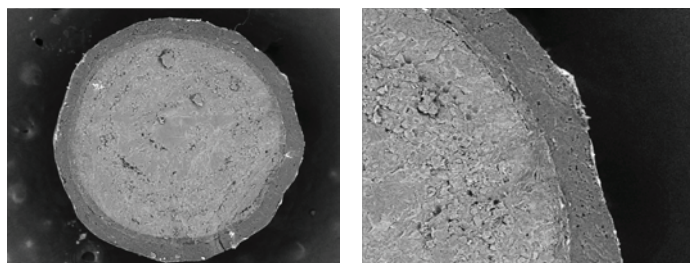


Figure 6. Cross sectional image (left) and magnified view (right) of ETHOCEL™ HP barrier membrane formed from dry powder rotary coating process.

How The Spray Coating Process Works

Typical spray coating systems of ethylcellulose rely on dissolution of the polymer in a solvent to apply the coating onto the substrate. The film formation process occurs by atomizing the solution into small droplets that coalesce on the surface of the substrate allowing the carrier medium to evaporate, leaving an ethylcellulose film on the surface of the substrate. This process is repeated thousands of times during the coating process, resulting in many layers of ethylcellulose that coalesce into a solid, homogenous film. This process is well understood and allows for great film-formation resulting in stable, reproducible coatings. A similar process can also be used with aqueous dispersions of ethylcellulose, but with the additional requirement of a curing step to relax the ethylcellulose particles into a coherent film.

How The Dry Powder Layering Process Works

The dry powder layering process applies the ethylcellulose from a dry state onto a substrate by wetting the substrate with a tacking agent comprised of plasticizer and water. Immediately after wetting, the dry polymer powder is applied to the surface of the substrate with the wetting agent acting as a bridge between the dry powder particles and the surface of the substrate. The presence of the plasticizer lowers the glass transition temperature (T_g) of the polymer to allow the particles to soften and fuse in a subsequent curing step. The wetting agent and dry powder are continually sprayed on to the substrates, building additional polymer layers very quickly. After sufficient coating, the dry powder coated substrates are cured through a heating step which can often be performed in the unit while the substrates continue to spin in the rotor. The dry powder process greatly improves efficiency as the wetting liquid and powder are directly placed into the substrate bed. The process equipment is extremely versatile, allowing API-layering, polymer coating and film curing to occur within the same piece of equipment.

How Does ETHOCEL™ HP Work In This Process?

ETHOCEL™ HP was specifically designed for enhanced performance in a dry powder coating process. The mean particle size and particle size distribution have been optimized for controlled release performance.

These case studies demonstrate product attribute effects and improvements over standard manufacturing technologies in enhanced productivity, decreased coating times, and better environmental impacts by removing solvent use.

Since ethylcellulose is applied from the dry state, a curing step is required to ensure proper film formation and stability. Curing can be done in-situ in the equipment (referred to as “dynamic curing”) or in tray ovens (“static curing”).

Table 1 shows the extremely narrow particle size distribution of ETHOCEL™ HP which allows for optimal particle packing when applied as dry particles. Broad particle size distributions have the potential to interfere with efficient particle arrangement and can result in voids or film defects.

Particle size specification	ETHOCEL™ Std	ETHOCEL™ FP	ETHOCEL™ HP
D10	N/A	N/A	< 3
Mean	N/A	3-15	< 8
D90	N/A	N/A	< 15
Maximum	N/A	100	N/A

Improving Particle Size For Improved Film Formation

Acetaminophen drug release was determined for 20% weight gains of ETHOCEL™ milled to various mean particle size and particle size distributions (Figure 7). 25% dibutyl sebacate plasticizer was used with respect to ethylcellulose weight and was dissolved in water and added with the wetting liquid. No pore formers were used and all samples were statically cured for 2 hours at 60°C. As mean particle size was reduced and particle size distributions were tightened, film formation was improved resulting in more controlled release of the active ingredient. Larger mean particle sizes resulted in highly porous films even after curing, whereas micronized ETHOCEL™ resulted in a fully formed film and slowest drug release.

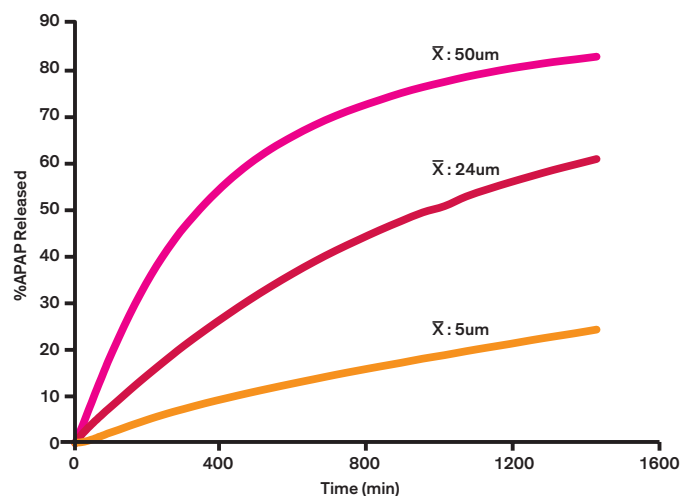
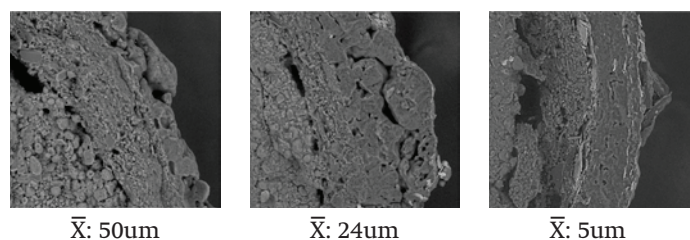


Figure 7. Influence of particle size on film formation and drug release.



Sample	D10 (μm)	Mean (μm)	D90 (μm)
ETHOCEL™ HP	1	5	9
Medium Size	4	24	55
Large Size	8	50	108

Fast Coating Times and Weight Gain Influence

Figure 8 illustrates how the dry powder delivery of ETHOCEL™ HP Polymers significantly reduce process times for a full scale 250kg batch as compared to aqueous ethylcellulose and organic ETHOCEL™. The data presented includes a 2 hour cure step required for applications of aqueous dispersions of ethylcellulose and a 30 minute cure step required for ETHOCEL™ HP. For example, at 20% weight gain, a full scale 250kg batch with ETHOCEL™ HP can be completed in under 2 hours whereas organic ETHOCEL™ requires 12 hours and aqueous ethylcellulose 8 hours.

Metoprolol Tartrate drug release was determined for ETHOCEL™ HP barrier coatings ranging from 15 - 30% weight gain. 40% plasticizer (75:25 oleic acid:DBS) was used with respect to ETHOCEL™ HP weight and dissolved in water. No pore formers were used and samples were dynamically cured for 1 hour at an inlet air temperature of 80°C. Figure 9 shows how drug release was predictably controlled by incremental weight gain.

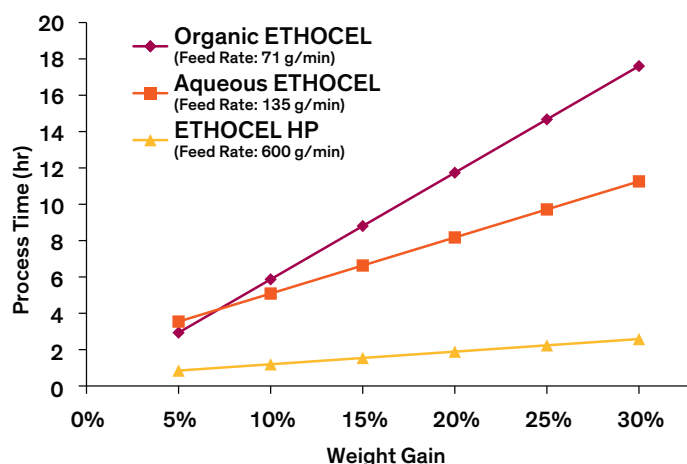


Figure 8. Equivalent performance coating times including curing.

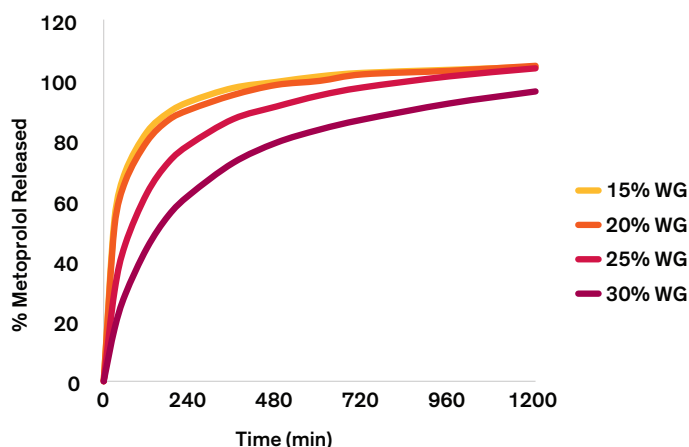


Figure 9. Influence of ETHOCEL HP weight gain on Metoprolol Tartrate drug release.

Equivalent Performance to Solution Coating

Metoprolol tartrate drug release was determined for 20% weight gain of ETHOCEL™ HP. 40% dibutyl sebacate plasticizer was used with respect to ETHOCEL™ HP weight and dissolved in water. No pore formers were used and samples were statically cured for 2 hours at 60°C. Metoprolol tartrate drug release was also determined for 10% weight gain of ETHOCEL™ Std 10 Premium which was dissolved in 90% isopropanol and 10% water. 10% dibutyl sebacate plasticizer was used with respect to ETHOCEL™ Std 10 Premium weight and dissolved in the same solution. No pore formers were used and samples were not cured.

The ETHOCEL™ HP applied at 20% weight gain has equivalent performance to organic ETHOCEL™ applied at 10% weight gain without any lag in drug release in the first 60 minutes (Figure 10). Although a higher amount of ETHOCEL™ HP was needed in this example, total coating time only took 221 minutes including the 2 hour cure step whereas organic ETHOCEL™ took 293 minutes. More time saving could have been achieved by switching to dynamic curing.

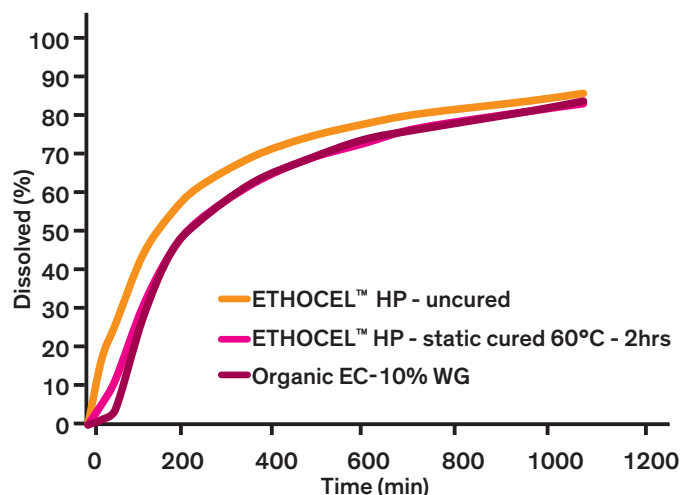


Figure 10. Metoprolol tartrate drug release for ETHOCEL™ HP rotary coatings and organic ETHOCEL™ spray coatings.

Curing Influence

Due to the dry powder nature of the rotary coating process, a cure step is required to achieve full film coalescence. Film coalescence is obtained through appropriate selection of plasticizers during the powder application step and adequate product temperature during a dynamic curing step. Dynamic curing is a time saving process which allows the film curing step to take place in the rotor processor in a true one step, one pot process. Heated forced air, also known as drying air, is introduced at the end of the coating process to remove residual moisture and begin the curing process while the beads continue to rotate. The result is polished, opalescent beads with a smooth, continuous ethylcellulose film coating. Evidence of full film formation can be obtained visually and is confirmed by reproducible drug release upon accelerated stability testing.

Experiments have demonstrated that several well-known plasticizers can be effectively used with ETHOCEL™ HP Polymers. Figure 11 shows the glass transition temperature (T_g) of ETHOCEL™ HP films with several common plasticizers and their combinations. Plasticizer combinations, especially those with oleic acid, were particularly effective at lowering the T_g of ETHOCEL™ HP.

Selection of an appropriate plasticizer package may be formulation dependent, but for the best results the product temperature should reach 10°C above the T_g of the ETHOCEL™ HP / plasticizer combination. An example of product temperature profiles obtained with a 2 kg R&D Scale rotor granulator set to 60°C and 80°C drying air can be seen in Figure 12.

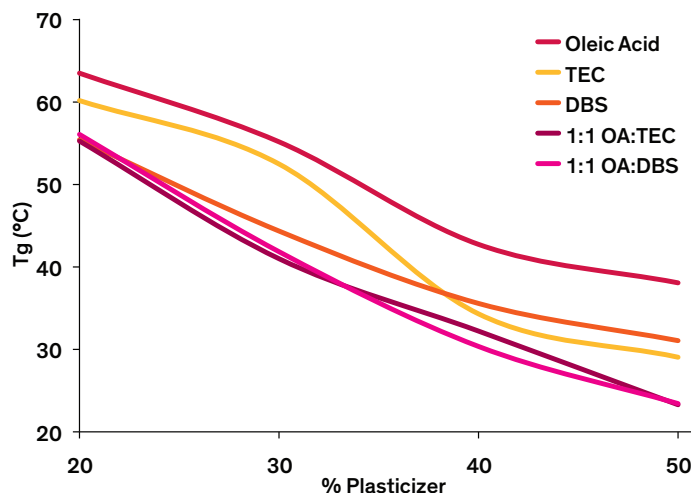


Figure 11. Glass transition temperatures of ETHOCEL films with plasticizers at various concentrations.

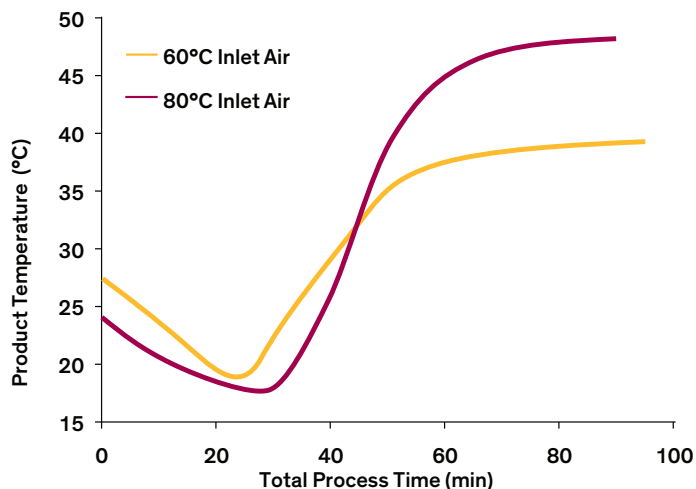


Figure 12. Product temperature profile of multiparticulate beads during ETHOCEL HP coating and dynamic curing at two different drying temperatures.

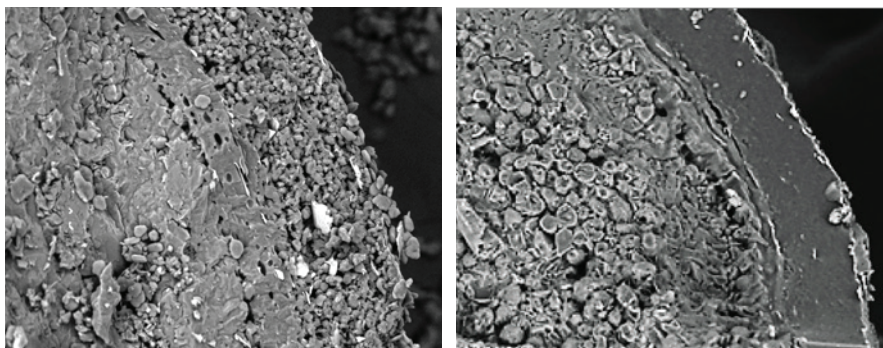


Figure 13. Cross-sectional images of uncured (left) and cured (right) samples coated with ETHOCEL HP.

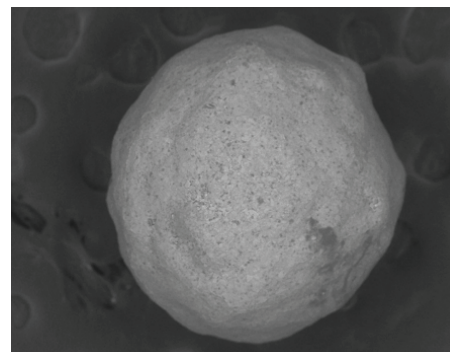


Figure 14. Surface morphology of ETHOCEL HP coated multiparticulate after dynamic curing.

Stability

Consistency in drug release performance over extended storage times is an important consideration for formulation performance and serves to demonstrate that adequate curing of the ETHOCEL™ HP Polymers film has occurred. In the examples below, two different plasticizers were used in conjunction with two different sets of curing temperatures, with both resulting in stable drug release profiles under accelerated stability conditions (40°C/75% RH).

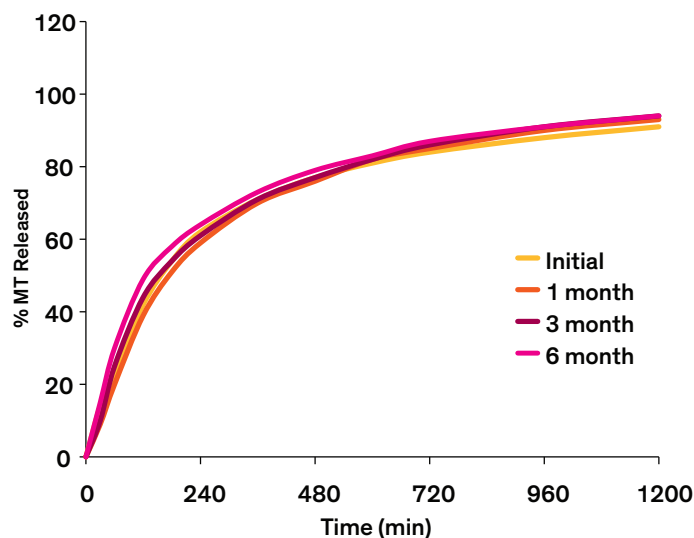


Figure 15. Drug release stability of ETHOCEL HP coated Metoprolol tartrate multipaticulates prepared with 40% DBS plasticizer and dynamically cured at 40°C product temperature.

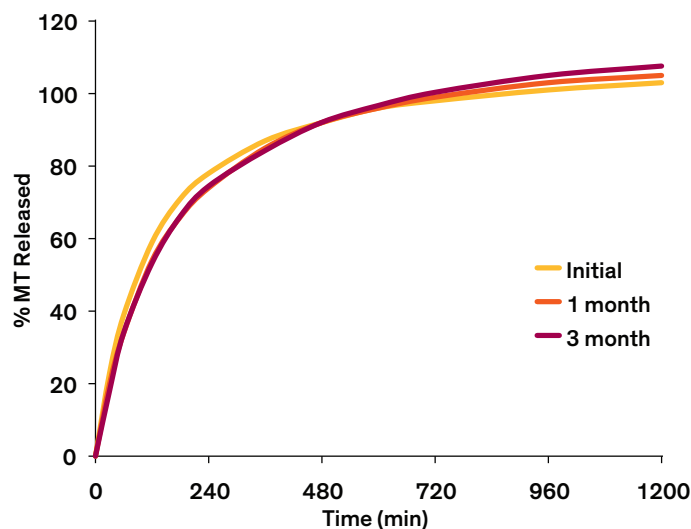


Figure 16. Drug release stability of ETHOCEL HP coated Metoprolol tartrate multipaticulates prepared with 20% DBS plasticizer and 20% oleic acid and dynamically cured at 50°C product temperature.

ETHOCEL™ High Productivity is an innovative new product which helps customers increase productivity while still maintaining the advantages of Dow manufactured ETHOCEL™ such as tight viscosity, narrow ethoxyl distribution, and reduced fiber content. Using ETHOCEL™ HP could result in 40-70% reduction in process time versus solvent and aqueous spray coating systems. In addition to the controlled release market, ETHOCEL™ HP and the rotor technology can also be extended to taste masking to help eliminate the bitter taste of actives upon swallowing. Proven to be most effective as a solvent-less coating, this new technology enables customers to achieve processes which are sustainable, environmentally friendly, and safe for their employees.



Controlled Release Alliance

Dow-Colorcon Alliance: UNIQUE TOGETHER

Dow Pharma & Food Solutions and Colorcon, together in the Controlled Release Alliance, bring joint resources in polymer and formulation expertise to accelerate your pharmaceutical product development efforts and reach markets throughout the world. Colorcon has exclusive, global sales and distribution rights for Dow products used in controlled release applications, including ETHOCEL™ Polymers.

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