Pharma & Food Solutions

ETHOCEL™ Ethylcellulose

A Technical Review

A Portfolio of Versatile Solutions

to Help Address a Variety of Formulation and Processing Needs

ETHOCEL™ Premium Polymers are essentially tasteless, colorless, odorless, non-caloric and very inert physiologically. Dow Pharma &Food Solutions, a business unit of The Dow Chemical Company, offers nine different ETHOCEL™ Polymers for pharmaceutical applications. These include a variety of molecular weights, which translate into a range of viscosities.

Comparison of ETHOCEL™ Grades

ETHOCEL™ Standard Grade	4 Premium	7 Premium	7 FP Premium	10 Premium	10 FP Premium	20 Premium	45 premium	100 Premium	100 FP Premium
Viscosity (mPa.s)	3 - 5.5	6 - 8	6 - 8	9 - 11	9 - 11	6 - 8	6 - 8	90 - 110	90 - 110
Ethoxyl Content (% wt)	48 - 49.5	48 - 49.5	48 - 49.5	48 - 49.5	48 - 49.5	4 - 49.5	48 - 49.5	48 - 49.5	48 - 49.5
Loss on Drying (% wt)	2 Max	2 Max	2 Max	2 Max	2 Max	2 Max	2 Max	2 Max	2 Max
Particle Size (microns)	N / A	N / A	140 Max, 5 - 15 Mean	N / A	100 Max, 3 - 15 Mean	N / A	N / A	N / A	150 Max, 30 - 60 Mean
Solvent Solubility	Ethanol, Acetone, Isopropanol, Methanol, and Combinations of All								

By selecting among these variables, it is possible for ETHOCEL™ to be used in a variety of pharmaceutical functions including: barrier coatings for modified / controlled release, granulation and direct compression aides, and extrudate for hot melt extrusion processes.

Barrier Coating for Modified/Controlled Release

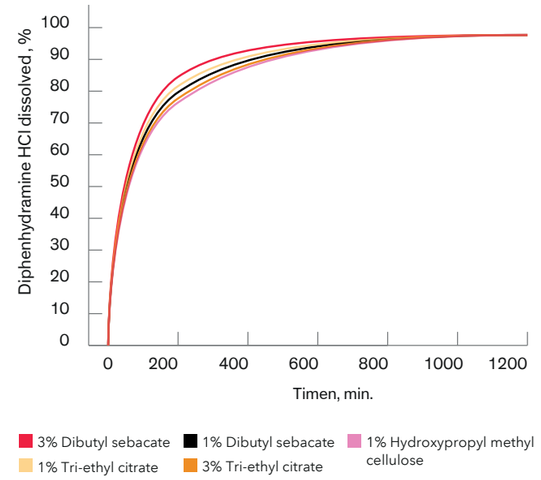
ETHOCEL™ Polymers have a long history in film and bead coating for controlled release applications. ETHOCEL™ forms a strong film with good adhesion. These polymers can offer a versatile diffusion barrier whose properties can be modified by film thickness (weight gain), level of water soluble pore-forming additives (such as METHOCEL™), plasticizer choice, solvent(s) used, or the viscosity (molecular weight) of ETHOCEL™.

This investigation explored different dissolution rates of multiparticulate beads which have been coated with ETHOCEL™ to form barrier membranes. Variables that significantly impact properties of coatings made with ETHOCEL™ include the molecular weight, solvent system, additives, and the amount of ETHOCEL™ applied.

In all experiments, barrier coatings were applied to non-pareils (30 – 35 mesh) which had been coated with Diphenhydramine HCl using a mini-fluid bed coater. Tri-ethyl citrate (TEC) and dibutyl sebacate (DBS) were the plasticizers used while hydroxypropyl methyl cellulose (HPMC) was used as the pore-former. ETHOCEL™ Std. 4, 7, 10, 20, 45, and 100 Premium were used to determine the influence of molecular weight on drug release rate. Lastly, a comparison of 7% weight gain vs. 13% weight gain was used to determine the influence of film thickness.

In Figure 1, ETHOCEL™ Std. 10 Premium was combined with either 1 or 3% TEC or DBS to measure the effect of plasticizer choice or combined with 1% HPMC to measure how water soluble pore-former additives influence drug release rates. As illustrated by Figure 1, all dissolution profiles were similar for plasticizer choice or pore-former additive. Pore-formers are commonly used in barrier coatings of multiparticulates since pure films made with ETHOCEL™ demonstrate drug dissolution rates too slow for pharmaceutical needs. In this experiment only a 1% addition of HPMC was used, a larger percentage of the total formulation could significantly increase drug dissolution rate.

Figure 1: Influence of Plasticizer Choice or Pore-Former [1]



Dissolution results are for Diphenhydramine HCl coated on non-pareil seeds followed by 13% weight gain coating of ETHOCEL™ Std. 10 Premium with either TEC, DBS, or HPMC.

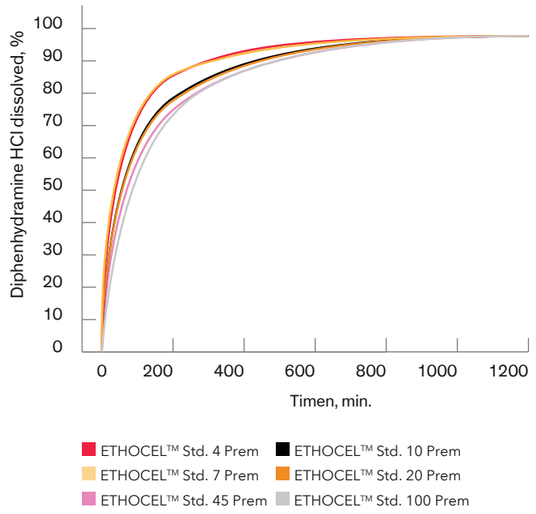
[1]The properties shown are typical but not to be construed as specifications, data is based on results from internal studies

In Figure 2, ETHOCEL™ Std. 4, 7, 10, 45, and 100 Premium were used to coat the Diphenhydramine HCl coated non-pareils to a 13% weight gain. Dissolution rates decreased as a function of increasing viscosity grade. Viscosity grades are determined by the molecular weight of the ethylcellulose polymer chain.
A higher molecular weight film is going to form a greater number of entanglements resulting in a film with fewer defects and reduced free volume causing drug transport to decrease through the polymer layer. Another way to decrease drug release rates is by increasing film thickness (weight gain).

Figure 3 demonstrates ETHOCEL™ Std. 10 Premium at 13% weight gain has a slower drug release rate than ETHOCEL™ Std. 10 Premium at 7% weight gain. For slowing drug release rate, it is generally more efficient to increase weight gain of ETHOCEL™ than to increase viscosity grade use in a coating solution.

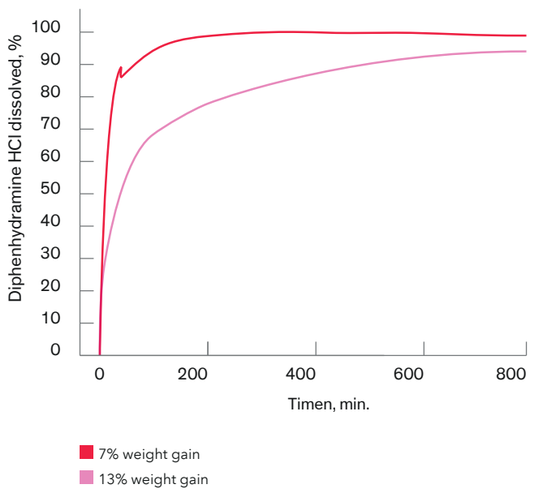
Barrier coatings made with ETHOCEL™ from organic solutions are also stable over time. Stability is a critical component to the pharmaceutical industry since final product performance must remain consistent even at longer shelf storage times. Figure 4 shows 0, 1, 3, and 6 month stability profiles of non-pareils with Diphenhydramine HCL coated with ETHOCEL™ Std. 10 Premium and DBS. Samples were either left in ambient conditions or placed in accelerated storage conditions (40°C & 75% relative humidity). In both accelerated and ambient conditions, the performance of barrier membranes made with ETHOCEL™ remained stable.

Figure 2: Influence of Molecular Weight on Dissolution Rates [1]



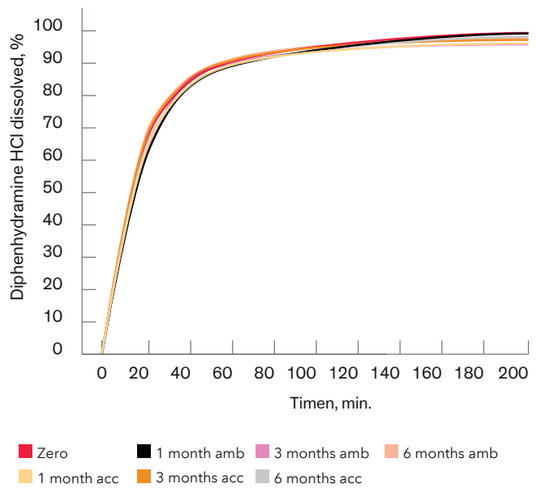
Dissolution results are for Diphenhydramine HCl coated on non-pareil seeds followed by 13% weight gain coating of ETHOCEL™ Std 4, 7, 10, 20, 45, or 100 Premium with DBS.

Figure 3: Influence of Film Thickness on Dissolution Rates [1]



Dissolution results are for Diphenhydramine HCl coated on non-pareil seeds followed by either 7% or 13% weight gain coating of ETHOCEL™ Std. 10 Premium with DBS.

Figure 4: Influence of Storage Conditions [1]



Dissolution results are for Diphenhydramine HCl coated on non-pareil seeds followed by 7% weight gain coating of ETHOCEL™ Std 10 Premium with DBS. Samples were taken at 0, 1, 3, and 6 months at ambient (amb) and accelerated (acc) conditions.

[1]The properties shown are typical but not to be construed as specifications, data is based on results from internal studies

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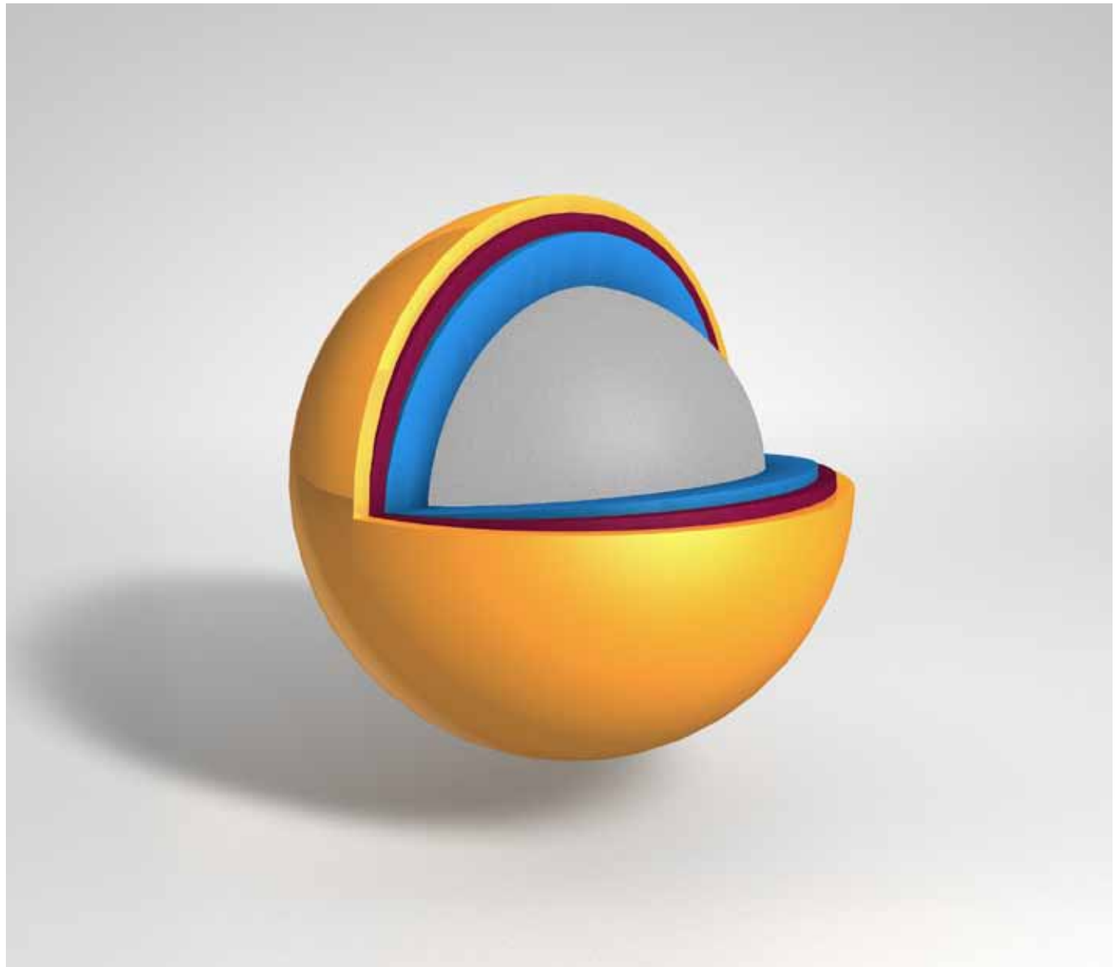
The following conclusions were drawn:

- **Plasticizer selection between TEC and DBS at these levels did not make a big difference; however, the use of plasticizer is critical to apply a flexible, relaxed barrier coating to give consistent performance results**
- **Increasing the viscosity grade (molecular weight) of ETHOCEL™ used at the same weight gain will give decreased drug release rate**
- **ETHOCEL™ barrier coatings from organic solutions will give stable performance results in accelerated and ambient storage conditions**



Direct Compression
For Matrix Tablets

This investigation involved the use of ETHOCEL™ in a dry system by directly compressing unmilled and milled ETHOCEL ™ Polymer into tablets. These tablets form a matrix from which the drug can be released over time. Typically using ETHOCEL™ involves hydrating the ethylcellulose polymer in an organic solvent and applying the solution to a substrate. However, this investigation is a completely different method of controlled drug release using ethylcellulose polymers because it does not use the polymer in the hydrated state.

Drug dissolution and tablet physical testing were completed on milled and unmilled ETHOCEL™ Std 7 Premium samples. ETHOCEL™ Std. 7 Prem. (unmilled – 313 µm), ETHOCEL™ Std. 7 Prem. (milled - 12.8 µm), and ETHOCEL™ Std. 7 Prem. (milled - 4.8 µm) will be used as sample identifier, where 313, 12.8 and 4.8 µm refer to the median particle size.

The tablet formulation used throughout the study was limited to the following ETHOCEL™ and drug ratio (Diphenhydramine HCL): 25% ETHOCEL™: 75% drug, 50% ETHOCEL™: 50% drug, and 75% ETHOCEL™ : 25% drug. 300 mg tablets were formed using a Carver (model C) laboratory press equipped with 13/32 in flat-faced-bevel-edged tolling using a compression force of 8,000 lb and a dwell time of 5 sec.

Table 1 shows the effects of milling and increased ethylcellulose content on tablet crushing strength. Tablet crushing strength values for tablets using a 25% level ETHOCEL™ Std. 7 Prem (unmilled – 313 µm) ranged from 7 to 13 kN. ETHOCEL™ Std. 7 Prem. (unmilled – 313 µm) and EC Std 7. Prem. (milled – 12.8 µm) had similar crushing strength values even with the large difference in their median particle sizes. Tablets using ETHOCEL™ Std 7. Prem (unmilled 4.8 µm) had the highest value at 13 kN. Tablets manufactured with 75% ETHOCEL™ Std. 7 Prem. (unmilled – 313 µm) had crushing strength values of 18 to 22 kN. Increasing polymer weight content had a significant impact on the strength of the tablets.

Table 1: Results of Tablet Physical Testing

Sample ETHOCEL™ Std. 7 Prem.: Drug Ratio	**Tablet Crushing Strength (kN, sd)**
ETHOCEL™ Std 7 Prem. (unmilled)	
25%: 75%	7.8, 0.94
75% : 25%	22.0, 0.59
ETHOCEL™ Std 7 Prem. (milled – 12.8 µm)	
25%: 75%	7.6, 1.59
75% : 25%	22.2, 1.36
ETHOCEL™ Std 7 Prem. (milled – 4.8 µm)	
25%: 75%	13.3, 1.53
75% : 25%	17.9, 1.32

Figures 5 – 8 show drug release from tablets containing unmilled and milled ETHOCEL™ Std. 7 Premium at concentrations of 25% (Figure 6), 50% (Figure 5), and 75% (Figure 7).
It was observed that as polymer particle size decreased, drug release decreased (Figure 5 – 7); furthermore, as polymer concentration increased drug release decreased (Figure 8).

A secondary study utilizing the same methods was completed with milled and unmilled ETHOCEL™ Std. 100 Premium. This study demonstrated the same trends in respect to polymer concentration and particle size. However, when comparing ETHOCEL™ Std 7 Prem. to ETHOCEL™ Std. 100 Prem. polymer viscosity had little effect on drug release times.

The following conclusions were drawn:

- Polymer particle size had a significant effect on drug release times. The finely ground (milled) ETHOCEL™ samples extended the release of the model drug compound several times longer than the unmilled ETHOCEL™ samples
- Polymer viscosity grade (molecular weight) had a minor effect on drug release because the ethylcellulose was not in a hydrated state during drug dissolution
- Tablet crushing strengths were higher in tablets containing finely ground ETHOCEL™ than those containing unmilled ETHOCEL™.

Figure 5: Drug Dissolution from Tablets Containing ETHOCEL™ (1)
Std. 7 Prem. at 50% and Diphenydramine HCl at 50%

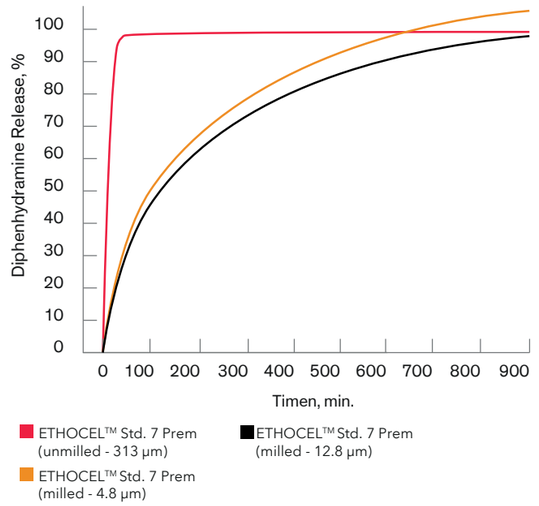


Figure 6: Drug Dissolution from Tablets Containing ETHOCEL™ (1)
Std. 7 Prem. at 25% and Diphenydramine HCl at 75%

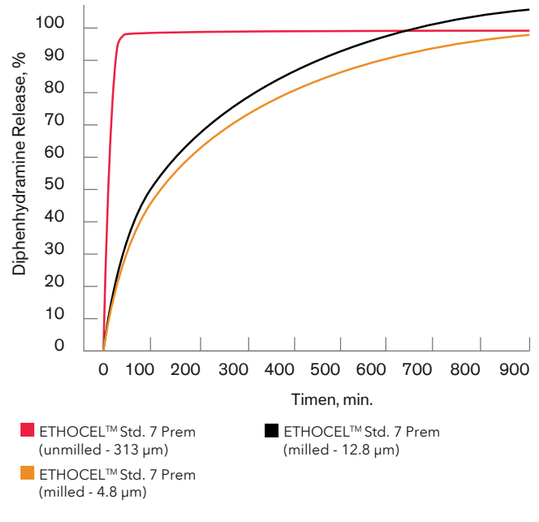


Figure 7: Drug Dissolution from Tablets Containing ETHOCEL™ (1)
Std. 7 Prem. at 75% and Diphenydramine HCl at 25%

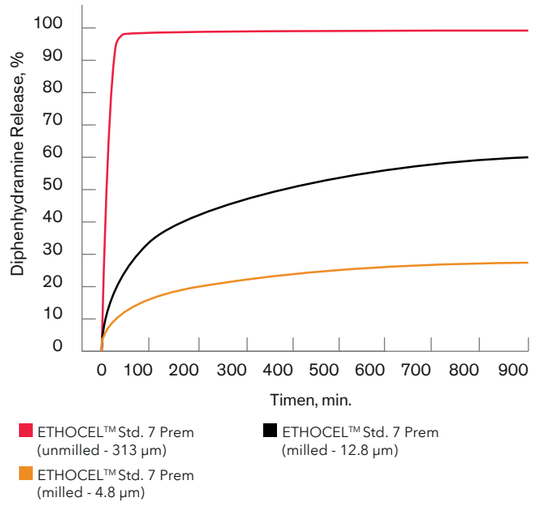
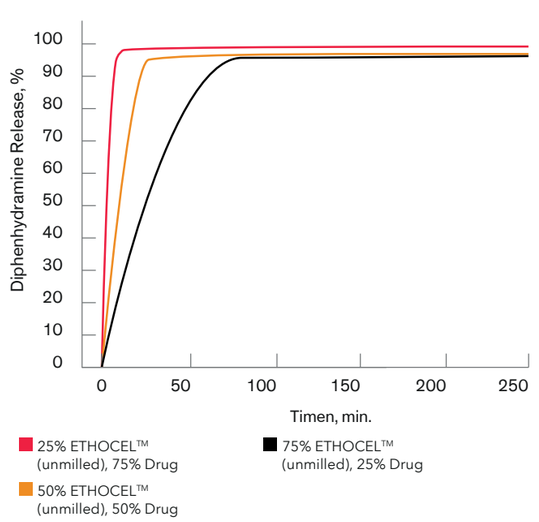


Figure 8: Drug Dissolution from Tablets Containing ETHOCEL™ (1)
Std. 7 Prem. and Diphenydramine HCl



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Hot Melt Extrusion

ETHOCEL™ possesses excellent thermoplasticity and softens between 135 °C to 160 °C making it a versatile and powerful tool in pharma hot melt extrusion (HME). Pharmaceutical companies can obtain specific release profiles while shaping their formulations into a wide variety of final dosage forms including tablets, multiparticulates and core-sheath systems. Another driver for hot melt extrusion is improved bioavailability of poorly soluble drugs (PSD). The desired result from HME of a PSD is the formation of a solid solution, wherein the drug remains in its amorphous form within the polymer matrix.

ETHOCEL™ possesses distinctive polymer attributes to add in keeping poorly soluble drugs in the amorphous state, but these same attributes cause very slow drug dissolution. The objective of this study was to explore additives that improved drug dissolution rates.

ETHOCEL™ Std. 10 Prem. was combined with ketoprofen (USP classified “Very Slightly Soluble” 0.14 mg/ml) and water soluble additives of either POLYOX WSR N-10 (PEO), POLYOX™ WSR 301, or METHOCEL™ E5 Prem. LV (HPMC) to form extrudate for drug dissolution. Some extrudate was further milled to aid in dissolution properties.

Table 2 gives the experimental formulations and process conditions for hot melt extrusion from a conical twin screw.

Table 2: Experimental Formulations and Process Conditions

Sample ID	Polymer	%	Water Soluble Additive	Dissolution Promoter (%)	Ketoprofen (%)	Process Temp (°C)
45 - 1	EC Std. 10	35	HPMC E5	45	20	150
45 - 10	EC Std. 10	35	PEO N-10	45	20	150
45 - 11	EC Std. 10	35	PEO 301	45	20	150
45 - 13	EC Std. 10	35	MC A15	45	20	150

All samples formed excellent extrudate with amorphous ketoprofen distributed throughout (Table 3).
All samples except for EC Std. 10 Prem containing METHOCELTM A15 demonstrated improved dissolution rates (Figure 9; table 3).
Further milling of the extrudate resulted in increased ketoprofen solubility (Figure 10)

Table 3: Ketoprofen Extrudate Quality and Dissolution

Sample ID	Melt Quality	Extrudate Ketoprofen Morphology (X-RAY)	Dissolution Promoter (%)	Ketoprofen (%)
45 - 1	Uniform Melt	Amorphous	Amorphous	50.6
45 - 10	Uniform Melt	Amorphous	Amorphous	63.8
45 - 11	Uniform Melt	Amorphous	Amorphous	66.8
45 - 13	Uniform Melt	Amorphous	Amorphous	37.4

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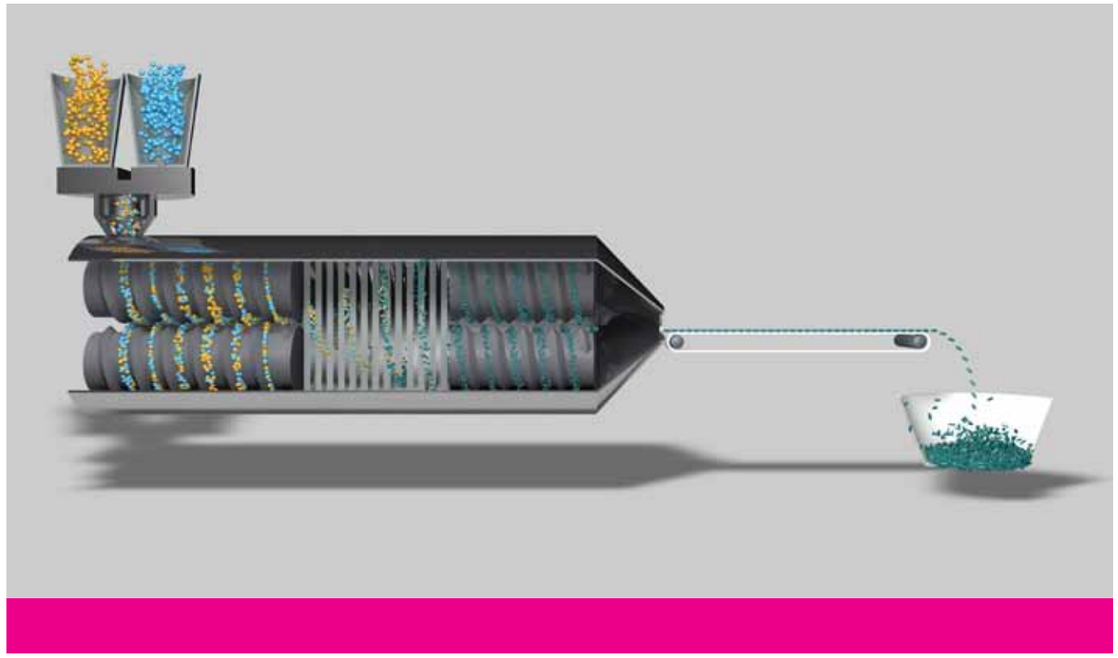


Figure 9 also demonstrates the complete dissolution profile over a 24 hr period. The dissolution of ETHOCEL™ Std. 10 with additives HPMC or PEO are clearly faster than with METHOCEL™.

The Following Conclusions were Drawn:

- **A broad assortment of water soluble additives can be added to ETHOCEL™ formulations to improve drug dissolution through HME**
- **Amorphous solid solutions of poorly soluble drugs were obtained for all formulations studied through the HME process.**
- **POLYOX™ and METHOCEL™ were the most effective dissolution promoters**
- **Milling of extrudate further enhanced dissolution rates.**

Figure 9 – Ketoprofen Dissolution Results for Extruded Tablets of Ethylcellulose Based Formulations Incorporating PEO or HPMC [1]

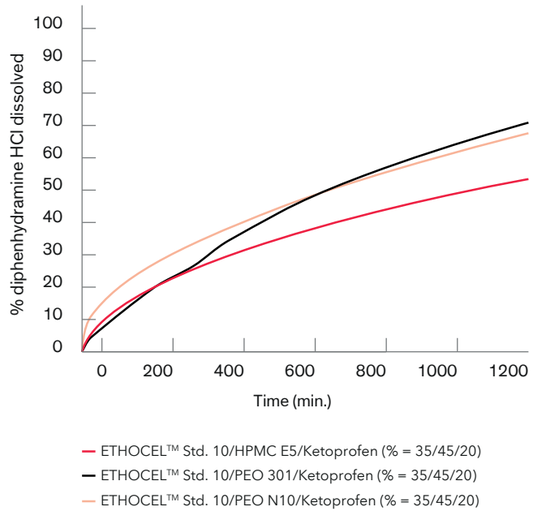
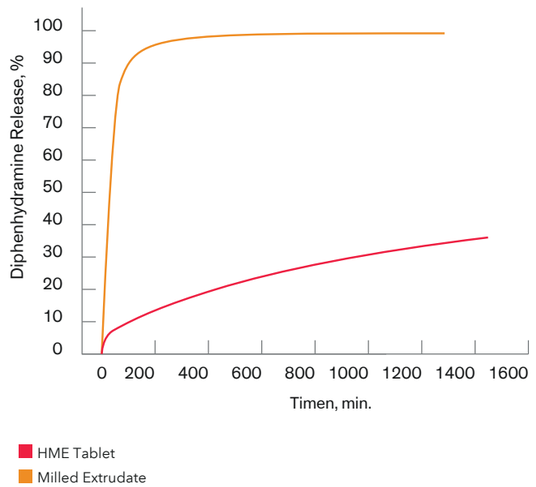


Figure 10 - Dissolution Profiles of Milled Extrudate in Capsules Compared to HME Tablets for ETHOCEL™ STD 10/ MC A15/Ketoprofen (25/55/20) [1]



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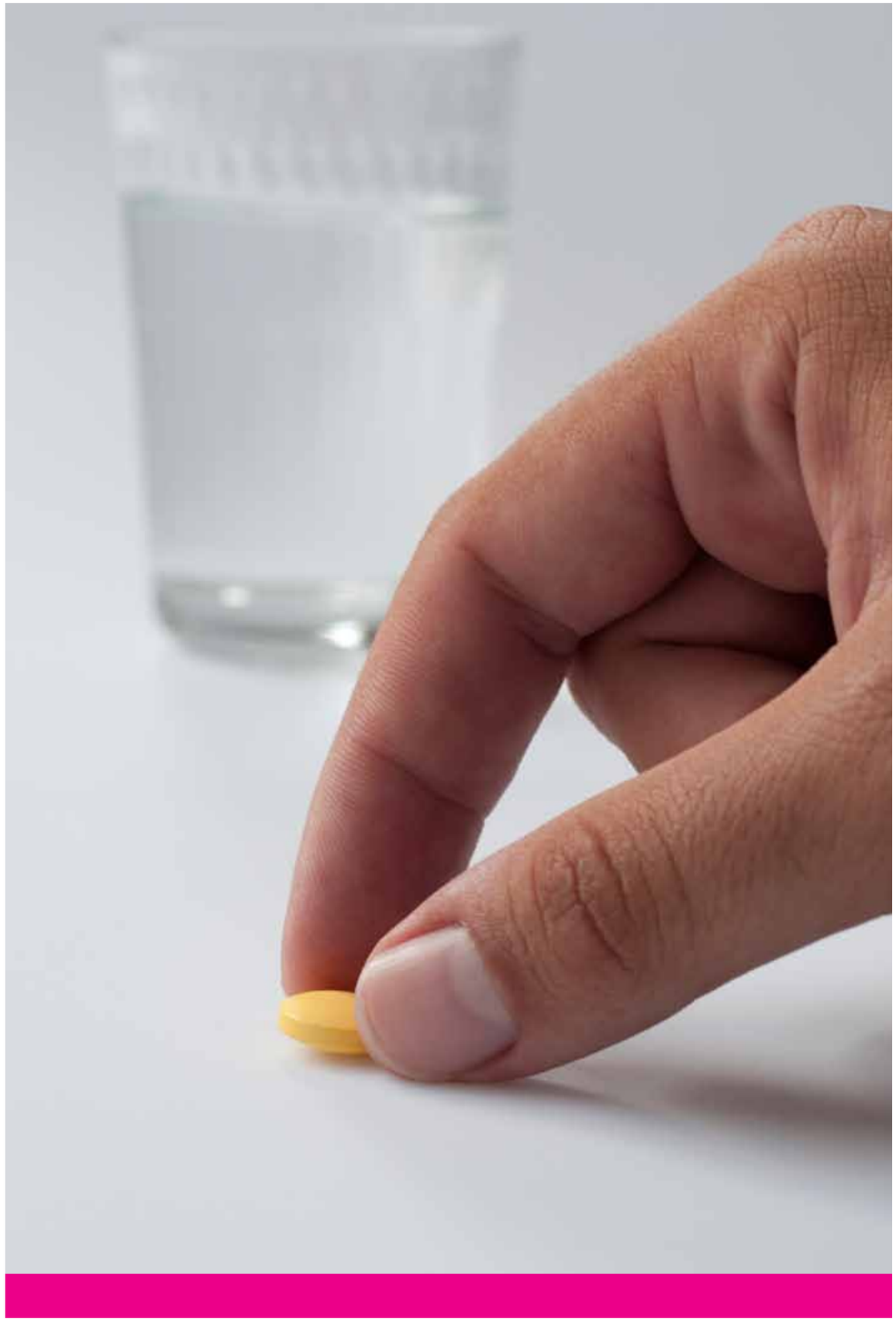

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