



## EVALUATION OF FINE PARTICLE SIZE ETHOCEL



## POLYMER FOR USE IN CONTROLLED-RELEASE



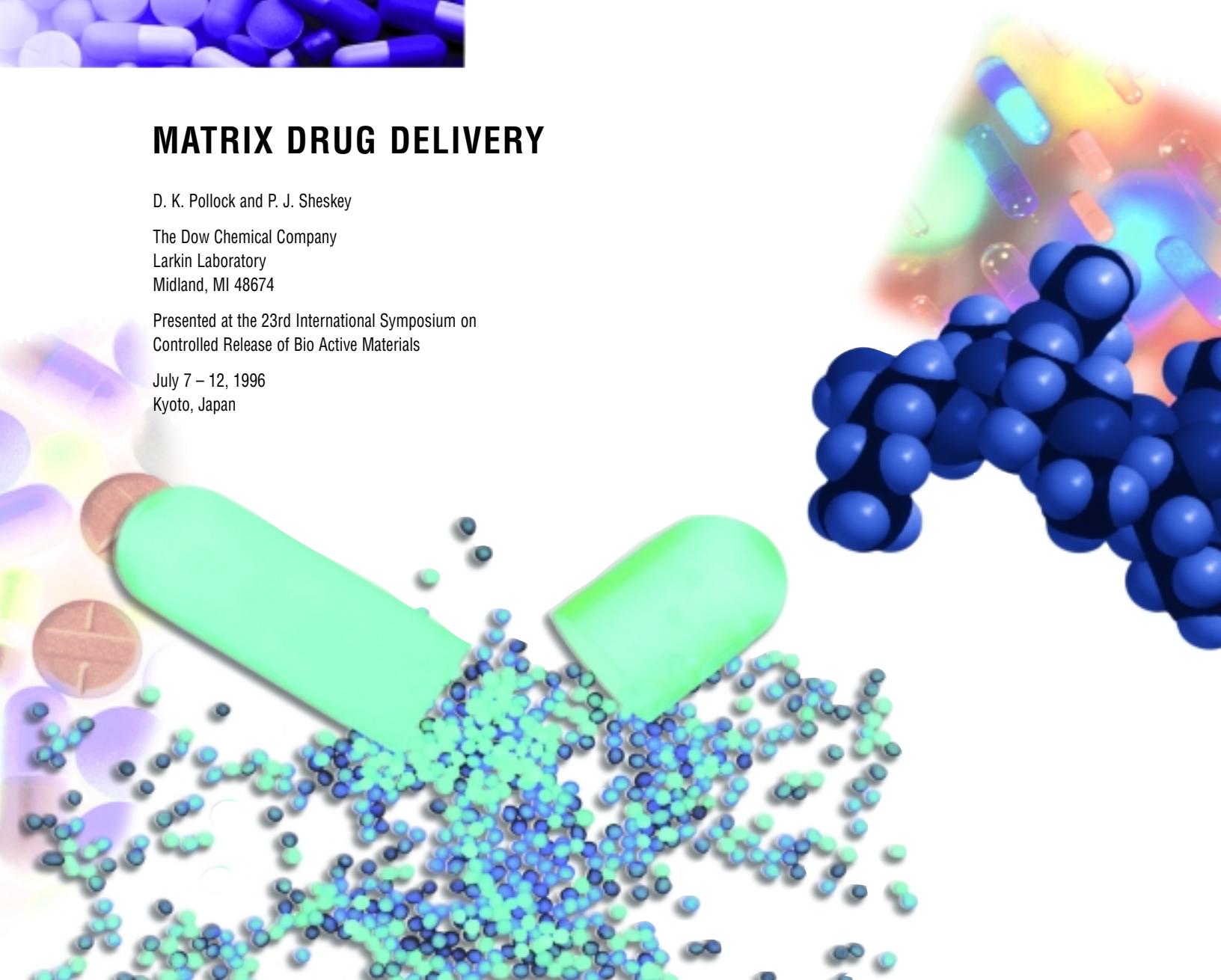
## MATRIX DRUG DELIVERY

D. K. Pollock and P. J. Sheskey

The Dow Chemical Company  
Larkin Laboratory  
Midland, MI 48674

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# Evaluation of Fine Particle Size ETHOCEL Polymer for Use in Controlled-Release Matrix Drug Delivery

## Objective

The purpose of the work was to evaluate the utility of the new ETHOCEL\* FP products in direct compression controlled release matrix formulations using a highly water soluble drug, diphenhydramine hydrochloride, as a model active. Additionally, the authors addressed such issues as viscosity grade vs. particle size and dissolution rates vs. tablet hardness for the granular and the fine particle forms of ethylcellulose.

## Background

ETHOCEL Premium ethylcellulose ethers are a family of inert hydrophobic polymers that have been used as pharmaceutical vehicles in a number of dosage forms. ETHOCEL has been used as a coating material for tablets and granules, as a tablet binder, in the preparation of microcapsules and microspheres, and as a film/matrix forming material for controlled release formulations. Until recently, ETHOCEL Premium products were available only in varying viscosity grades. The physical form of the products was granular in nature with average particle size greater than 250 microns. This was not an issue to the formulator because, in the vast majority of its uses, ETHOCEL was dissolved in an organic solvent during the preparation of the dosage form. Recent work in the literature has demonstrated the utility of ETHOCEL in its non-solvated form for direct compression of tablets. It is well established in the industry that the particle size of a dry excipient can have a dramatic effect on the characteristics of the final product. In the fall of 1995, The Dow Chemical Company introduced to the marketplace a finely milled form of its ETHOCEL Premium products. These new products are Standard 7 FP Premium, Standard 10 FP Premium and Standard 100 FP Premium.

## Methodology

### Materials

The following materials were used as received:

- Diphenhydramine hydrochloride, USP, (Wyckoff Chemical Company, Inc., South Haven, MI) aqueous solubility = 1g/mL
- ETHOCEL Standard 7 Premium & FP, NF
- ETHOCEL Standard 10 Premium & FP, NF
- ETHOCEL Standard 100 Premium & FP, NF, (The Dow Chemical Company, Midland, MI)
- Magnesium stearate, NF, (Mallinckrodt, Inc., St. Louis, MO)

### Methods

#### Tablet Formulation

The tablet formulations used throughout the study were limited to the following ethylcellulose and drug ratios: 3:1, 1:1, and 1:3 on a weight basis. Fifty-gram samples of the polymer and drug formulation were mixed in glass jars by hand using a spatula until homogeneous.

#### Tablet Preparation

Tablets were formed on an automated Carver (model C) laboratory press (Fred S. Carver Inc., Menomonee Falls, WI) equipped with 13/32 inch flat-faced, bevel-edged tooling. The pump speed was held constant at 15% of maximum

and the dwell time was held constant at 5 secs. Applied compression force varied from the minimum allowable 700 lb to a maximum of 8,000 lb in 100 lb increments. The target tablet weight was 300 mg.

#### Tablet Property Testing

Tablets were tested for thickness and hardness. Tablet thickness was measured using an Ames thickness gauge (model 27, B. C. Ames Co., Waltham, MA). Tablet hardness testing was completed using a Key hardness tester (model HT300, Key International, Englishtown, NJ).

#### Drug Dissolution

Dissolution testing of six tablet samples from each formulation was performed using a Distek dissolution system (model 2100, Distek, Monmouth Junction, NJ). The USP Apparatus 1 (basket) method was used at an agitation rate of 50 rpm. Data were acquired using a spectrophotometer (Hewlett-Packard Co., Valley Forge, PA). Dissolution profiles were generated at 37.5°C, with detection at 230 Nm for diphenhydramine hydrochloride. Tablets were introduced into 900 mL of solution that consisted of pH 7.0, 0.1 M phosphate buffer.

## Results

(Table 1) The physical characterization of ETHOCEL products used in this study.

Table 1

Polymer	Average particle size (micron)	Viscosity <sup>1</sup> (cps)	ETHOCEL content
Standard 7	310	7	48.0-49.5%
Standard 7 FP	9.7	7	48.0-49.5%
Standard 10	375	10	48.0-49.5%
Standard 10 FP	6.1	10	48.0-49.5%
Standard 100	465	100	48.0-49.5%
Standard 100 FP	41	100	48.0-49.5%

<sup>1</sup>Solution viscosity of a 5% (w/w) polymer in 80/20 toluene/alcohol at 25°C.

Figures 1-3 illustrate the comparative dissolution of diphenhydramine hydrochloride from tablets prepared with the granular and the fine powder forms of ETHOCEL Standard Premium products at two EC/drug ratios and at a constant compression force (8000 lb). The drug release rates are dramatically affected by the level of the polymer in the tablet and its initial particle size.

Figure 4 compares the three viscosity grades of the fine particle products at a constant applied pressure (8000 lb). These curves would suggest that the lower the viscosity grade of the FP polymer, the longer the release profile of the model drug.

Figure 5 clearly shows that the micronized version of ethylcellulose is more easily compressed resulting in harder tablets at any given pressure than the granular ethylcellulose.

Figures 6 and 7 illustrate that at constant hardness and particle size, the drug release profiles are not dependent on the viscosity grade of the micronized polymer. This is still consistent with Figure 4 because the tablets represented in Figure 4 were of significantly different hardness.

Figure 8 confirms the results seen in Figures 1-3 as to the utility of the micronized ethylcellulose over granular ethylcellulose even at constant table hardness.

## Conclusions

The following conclusions can be drawn based on the results found in this study, acknowledging the constraints of the materials and methods used :

1. The drug release rate is dramatically affected by the level of the polymer in the tablet and its particle size. The higher the polymer concentration and the smaller its particle size, the longer the release rate.

2. ETHOCEL FP Premium polymers are more easily compressed than granular ETHOCEL Premium polymers resulting in greater tablet hardness at equal compression forces. Likewise, FP polymers of smaller particle size are more compressible than larger ones.

3. Tablet hardness has a significant effect on drug release rates. At constant hardness there is no difference in the various ETHOCEL FP grades.

4. Even at constant hardness, ETHOCEL FP polymers offer prolonged release over that of granular material.

Figure 1:  
Drug Dissolution of ETHOCEL Standard 100 Premium Granular vs. FP

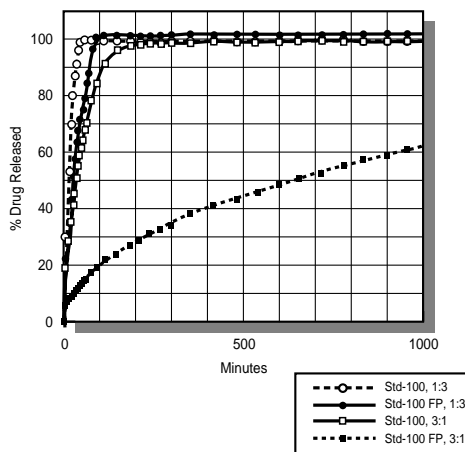


Figure 2:  
Drug Dissolution of ETHOCEL Standard 7 Premium Granular vs. FP

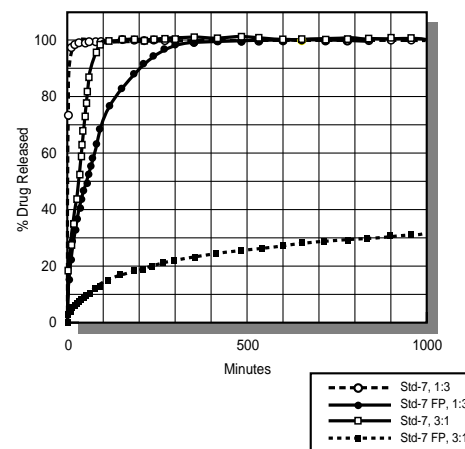


Figure 3:  
Drug Dissolution of ETHOCEL Standard 10 Premium Granular vs. FP

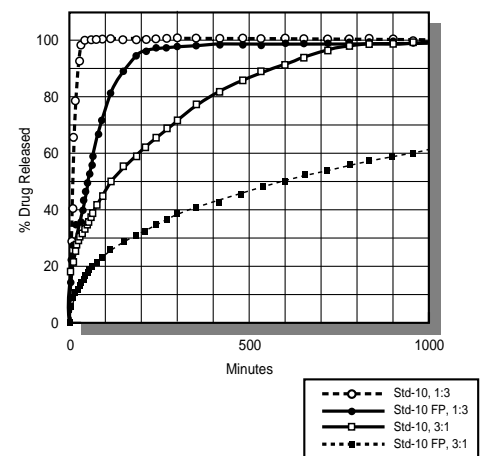
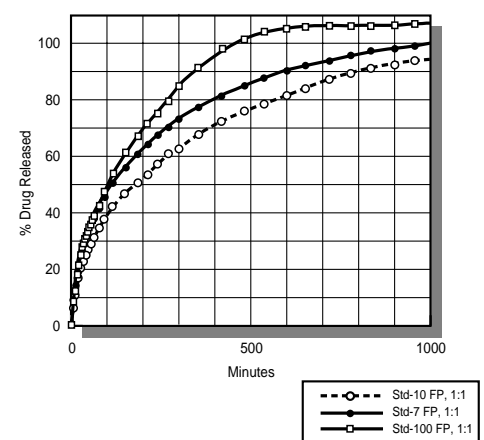


Figure 4:  
Drug Dissolution of ETHOCEL Standard FP Premium Products – Constant Applied Pressure (1:1 Polymer: Drug Ratio)



Figures 5-8 are located on the back of this brochure.

Figure 5:  
Tablet Hardness vs. Applied Pressure

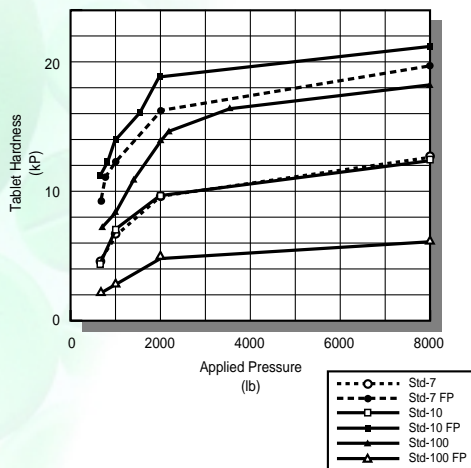


Figure 7:  
Drug Dissolution of ETHOCEL Standard FP Premium Products—Constant Particle Size and Tablet Hardness

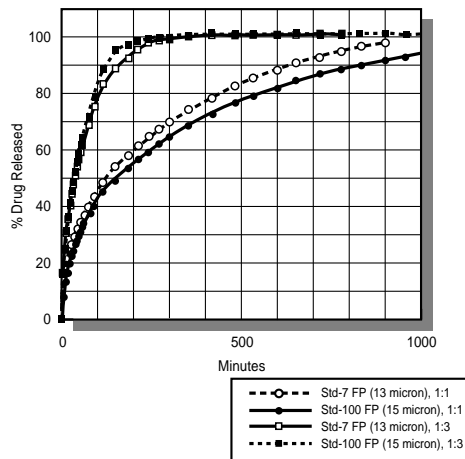


Figure 6:  
Drug Dissolution of ETHOCEL Standard FP Premium Products—Constant Tablet Hardness (1:1 Polymer: Drug Ratio)

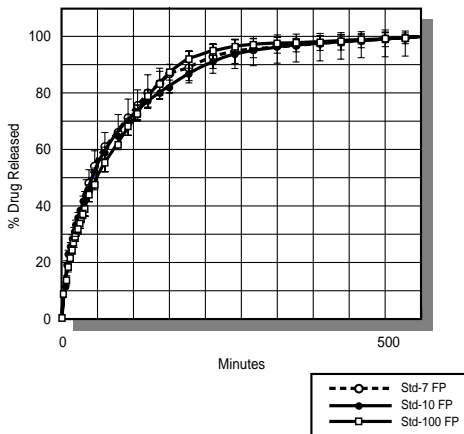
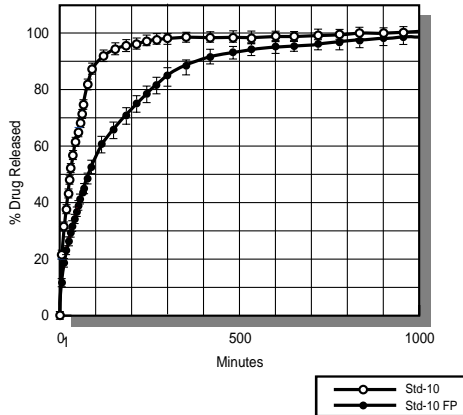


Figure 8:  
Drug Dissolution of ETHOCEL Standard 10 Premium Granular vs. FP—Constant Tablet Hardness (1:1 Polymer: Drug Ratio)



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