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The Impact of Hydroxypropyl Methylcellulose and Methylcellulose Molecular Weight and Degree of Substitution on Crystallization Inhibition of Felodipine in Aqueous Media

Yonglai Yang, Vivian Bi, Thomas Dürig

Ashland Specialty Ingredients, Wilmington, DE 19808 USA

Introduction

Hydroxypropyl methylcellulose (HPMC) is an excellent crystallization inhibitor and has been widely used in drug solubilization. There are different grades of HPMC with various degrees of substitution and molecular weight (MW). In this study, felodipine (FEL) was used as a model compound and the impact of HPMC molecular weight and degree of substitution on its crystallization inhibition effect was investigated.

Methods

Materials

Felodipine was purchased from RIA International LLC (East Hanover, NJ). The structure and selected properties of felodipine are shown in Figure 1.

Benecel™ E3, E15, E50, E4M, F50 and K4M HPMC, as well as A15 and A4M methylcellulose (MC) were manufactured by Ashland Inc. (Wilmington, DE). The molecular weight and degree of methoxyl and hydroxypropyl substitutions of different grades of HPMC and MC are listed in Table 1.

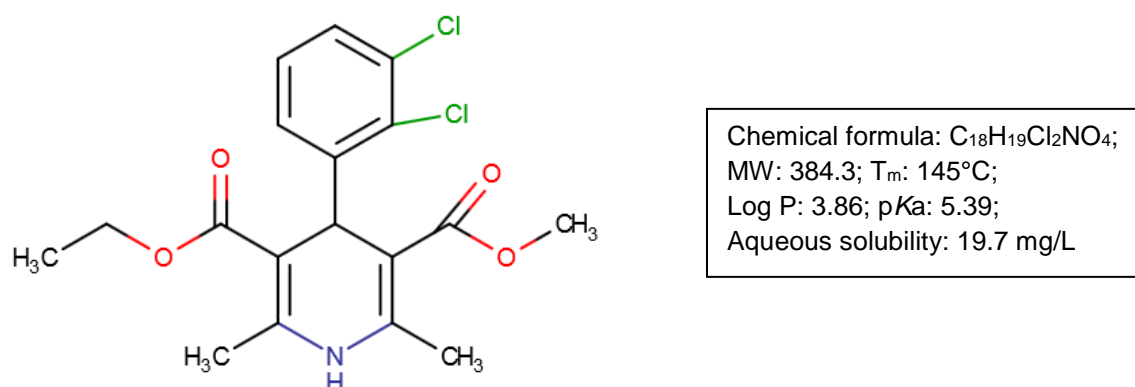


Figure 1. Structure and selected properties of felodipine
 (<http://www.drugbank.ca/drugs/DB01023>)

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 25–29, 2015, Orlando, FL

Table 1. MW and degree of methoxyl and hydroxypropyl substitutions of different grades of HPMC and MC

Grade	Molecular Weight	% OCH ₃	% POOH
E3	20,000	28–30	7–12
E15	50,000	28–30	7–12
E50	90,000	28–30	7–12
E4M	400,000	28–30	7–12
F50	90,000	19–30	3–12
A15	50,000	27.5–31.5	-
A4M	400,000	27.5–31.5	-
K4M	400,000	20–24	7–12

Experimental Procedure

- 1) Prepare a stock solution of felodipine in methanol (10 mg/mL);
- 2) Add 250 μ L of stock solution into 10 mL of 0.075 wt% HPMC or MC solution in pH 6.5 fasted-state simulated intestinal fluid (FaSSIF), keeping the sample solution at 37°C while stirring at 200 rpm;
- 3) Monitor the concentration of felodipine in solution for 90 min by an *in situ* UV-Vis probe using a μ ON μ DISS Profiler™. Triplicate experiments were performed for each sample; the averaged concentrations along with the standard deviations at each time point were plotted.

Results and Discussion

Molecular Weight Effect

Benecel E3, E15, E50 and E4M HPMC were used to investigate the molecular weight effect. The concentration profiles of felodipine in these different HPMC solutions are shown in Figure 2. It can be seen that the crystallization inhibition effect improved with the increase of HPMC molecular weight up to E50; further increase to a higher MW (E4M) did not show further improvement in crystallization inhibition. The relationship between MW and the effectiveness of crystallization inhibition was plotted as relative C_{plateau} (the plateau concentration of the selected solution containing HPMC over the solution without HPMC, *i.e.*, drug only) versus MW, as shown in Figure 3. $\text{Rel } C_{\text{plateau}}$ is indicative of the degree of precipitation inhibition after the concentration reached the plateau. The data showed that MW changes in the lower middle MW range resulted in large changes in $\text{Rel } C_{\text{plateau}}$. However, after reaching a threshold level in MW, further MW increase resulted in only negligible change in $\text{Rel } C_{\text{plateau}}$.

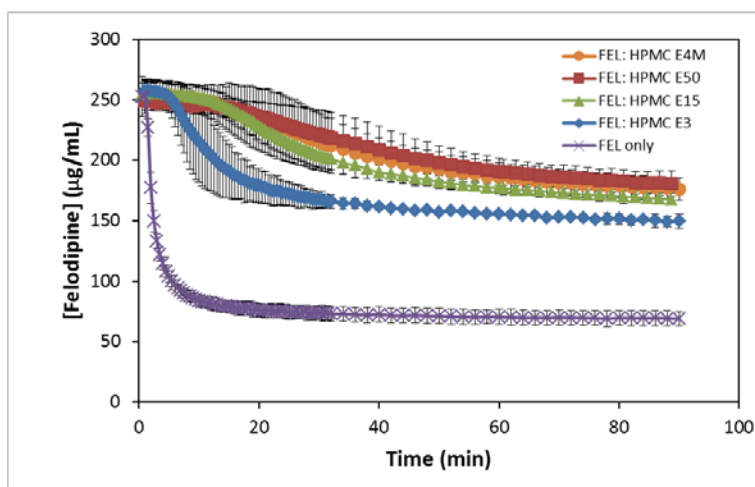


Figure 2. Felodipine precipitation profiles in the presence of HPMC with different MW

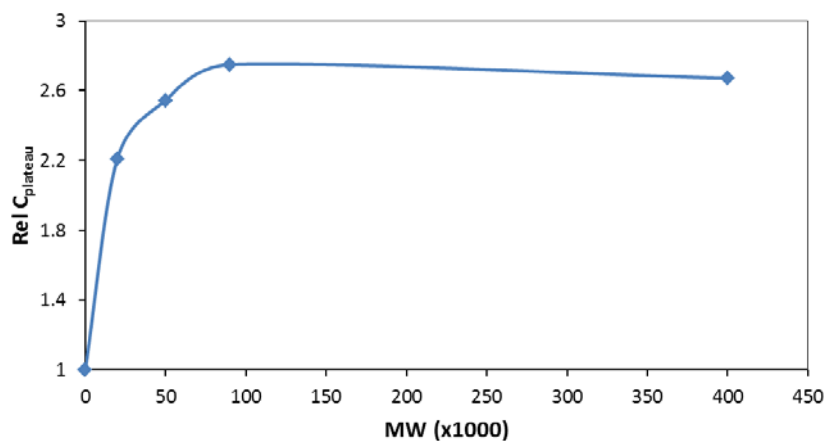


Figure 3. MW effect demonstrated using relative C_{plateau} (compared to drug only) versus MW (in Daltons)

Substitution Effect

Plots of Benecel E50 vs. F50 HPMC, E15 HPMC vs. A15 MC, and E4M, K4M HPMC vs. A4M MC were used to investigate the effect of degree of substitution on precipitation inhibition. The concentration profiles of felodipine in the presence of HPMC or MC with different substitution groups are shown in Figures 4 to 6. The results showed that crystallization inhibition was affected by the degree of methoxyl and hydroxypropyl substitutions of HPMC or MC.

E50 vs. F50 HPMC (Figure 4)

Effectiveness of crystallization inhibition: E50 > F50. Type E and type F have a similar degree of methoxyl substitution (hydrophobic group), which led to similar interactions with the poorly water-soluble drug. Type E has a higher extent of hydrophilic substitution that increases its affinity with aqueous media, combined with hydrophobic substitution, therefore the E50 grade exhibited better performance compared with the F50 grade.

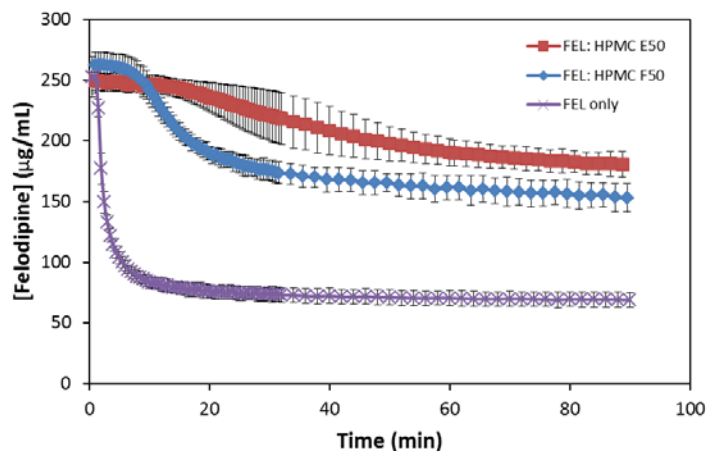


Figure 4. Felodipine precipitation profiles in the presence of HPMC (E50 vs. F50)

E15 HPMC vs. A15 MC (Figure 5)

Effectiveness of crystallization inhibition: E15 > A15. Compared to type E with a combination of hydrophobic and hydrophilic substitutions, type A is only substituted with hydrophobic methoxyl groups at a relatively higher level. The results showed that the E15 grade had a proven ability to inhibit the precipitation of felodipine in the examined condition, which demonstrated the importance of a polymer that combines both hydrophobicity and hydrophilicity in order to effectively stabilize the drug molecules.

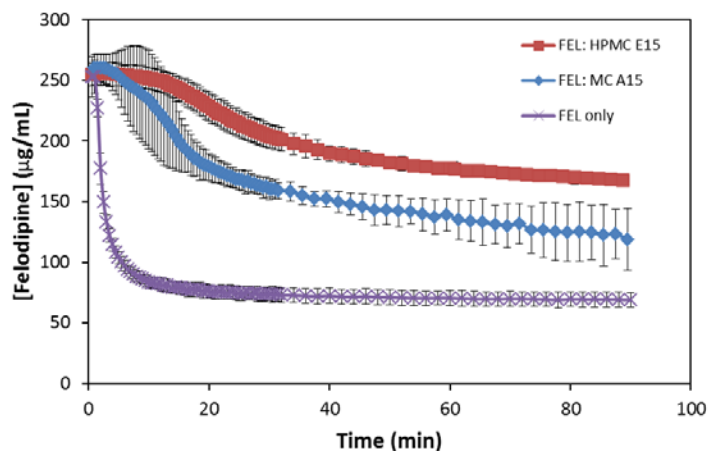


Figure 5. Felodipine precipitation profiles in the presence of HPMC or MC (HPMC E15 vs. MC A15)

E4M, K4M HPMC vs. A4M MC (Figure 6)

Effectiveness of crystallization inhibition: E4M > A4M > K4M. Types E and K have similar levels of hydrophilic groups, but type E has a higher level of hydrophobic groups, which contributed to the improvement in crystallization inhibition. Compared with type K, type A possesses a much higher hydrophobic substitution, but does not have substituted hydrophilic groups. The results showed that the A4M grade was better than the K4M grade in inhibiting crystallization of felodipine. It is concluded that the level of hydrophobic substitution in HPMC was the predominant factor impacting crystallization inhibition for drugs like felodipine with relatively high log P values (an indication of the hydrophobicity of the drug).

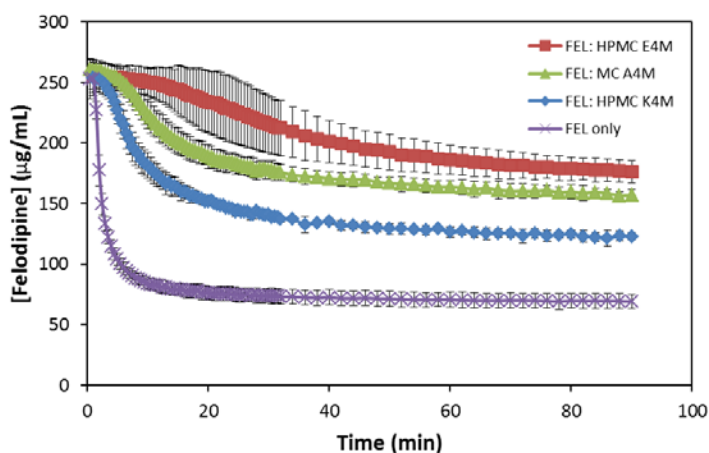


Figure 6. Felodipine precipitation profiles in the presence of HPMC or MC (E4M, K4M HPMC vs. A4M MC)

Conclusions

Increasing HPMC molecular weight could enhance its crystallization inhibition effect on felodipine up to a threshold level of MW, while further MW increases will result in only minor changes. The differences in hydrophobicity and hydrophilicity due to substitutions on HPMC were major compositional factors affecting polymer performance in crystallization inhibition. The results demonstrated that the extent of hydrophobic substitution played a dominant role in stabilizing the drug with a relatively high log P. Because of its combination of hydrophobic and hydrophilic substitutions, E type HPMC was the most effective crystallization inhibitor for felodipine.