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## Summary

We explored viscometry as a means to detect deviations in the content uniformity of controlling excipients for a controlled-release formulation. A method which may be broadly applicable to CR and ER tablets was developed. We show that viscometry has a higher precision and sensitivity than dissolution and compliments results from dissolution.

## Introduction

Content uniformity of a drug substance is a key quality property for all tableted drug products. It is essential that tablets deliver the label dose for both efficacy and safety reasons. For controlled- and extended-release formulations the concerns are magnified, because many such products contain a higher dose of drug than what is present in an IR formulation.

While it is required that CU evaluation of a drug substance be performed as a quality release test, the content uniformity of critical controlling excipients in CR or ER tablets is not, yet clearly delivery system performance impacts the safety and efficacy of the drug product. Drug release rate does speak directly to performance, but because it is subject to variable affects such as hydrodynamic inconsistency, broad tolerances in release performance are still considered acceptable.

Moreover, dissolution cannot serve as a direct measure of controlling excipients. Some direct measure of the controlling excipients, typically hydrophilic polymers, would be invaluable in testing for their uniformity within CR tablets. While a direct, general and routinely accessible assay for such excipients is not practical, the property of viscosity that hydrophilic polymers exhibit acts as a viable surrogate for this purpose.

We believe that viscometry would be useful for quality control, formulation and process development/scale-up of CR products. Though viscosity is a bulk property of any formula and is affected by all components of a formulation to some degree, viscosity is most sensitive to variations in the controlling polymers. We demonstrate that viscometry is a very sensitive tool for measuring the controlling excipients in ER and CR tablets.

## Experimental Method

**Sample Preparation:** Blend samples were handled as powders and parsed using a riffler. Compressed tablets were dissolved directly. Samples were first dispersed in ethanol. Unless otherwise noted, final dissolution of the dispersion was completed with the addition of 0.2M phosphate buffer at pH 8.0. The sample is stirred for one hour at RT. (It is critical that the sample not suffer losses from evaporation.) The mixture is chilled at 3-5°C for a minimum of 1h and then centrifuged for 30min at 1000rpm. The resulting clarified samples are tested directly in a viscometer.

**Viscosity Measurement:** Viscosity was read using a Cannon-Fenske routine viscometer, size 400, (Cannon Instrument Company), which was mounted in a water bath for temperature control and stability. A 7ml sample is accurately charged into the viscometer and the temperature allowed to stabilize for 5min. The efflux time was measured using a digital stop watch and kinematic viscosity (in centistokes) was calculated per directions supplied with the viscometer. It is possible to retest the same sample multiple times to confirm that the sample temperature has stabilized. Viscosity measurements are extremely sensitive to temperature.

## Results and Discussion

### Reproducibility and Effect of Centrifugation:

A blend sample solution containing the formulation controlling excipients Methocel K4M to Methocel 100LV in a ratio specific to the formula was prepared and split into two equal parts. In this case 0.4M phosphate buffer pH 8.0 was used. One part of the solution was centrifuged for 30min at 1000rpm to remove undissolved particulates prior to measuring viscosity. The viscosity of the un-centrifuged solution was measured repeatedly, (as shown in Table 1). In this case, repeat measurement was accomplished by refreshing the viscometer each time with new solution. Each read represents a new viscometer load.

**Table 1.** – Reproducibility and Effects of Centrifugation on Viscosity of CR Formulation Blend Solutions

Solution	Un-centrifuged Sample	Centrifuged Sample
1	451	416
2	446	421
3	445	423
4	449	428
Viscosity AVG	448	422
SD	2.75	4.98
%RSD	0.61%	1.18%

Measurement reproducibility is high. The variation in readings for the un-centrifuged samples represent a difference of 5sec for the extreme times for readings that take over 300sec; this means that the method introduces very little user error. This consistency in method performance was also observed between different operators (data not shown).

Removing the particulate from the sample lowered the measured viscosity of the solution and in this case increased the SD. However, because of the potential that particulates might clog the narrow bore of the viscometer, it was decided to routinely remove the larger particulates by gentle centrifugation.

### Sample to Sample Variation:

Three independent blend samples were prepared as described and their viscosity was measured after centrifuging for 30 minutes at 1000rpm to assess sample to sample variation. The method demonstrates low sample to sample variation, (as shown in Table 2).

**Table 2.** – Sample to Sample Variation

Solution	Time	Seconds	Viscosity
1	6:28	388	464
2	6:35	395	472
3	6:33	393	470
		Average	469
		St Dev	4.31
		RSD	0.92%

### Excipient Variation in a Tablet Blend:

A stock blend without the rate controlling excipient HPMC K4M was prepared. From this stock, five separate blends were prepared with the HPMC K4M adjusted to 0, +/-5%, and +/-1% from the original formula concentration. The viscosity of each sample was measured in duplicate. In this formulation, HPMC K4M represented approximately 10% of the final formulation by weight whereas the drug load was approximately 50%.

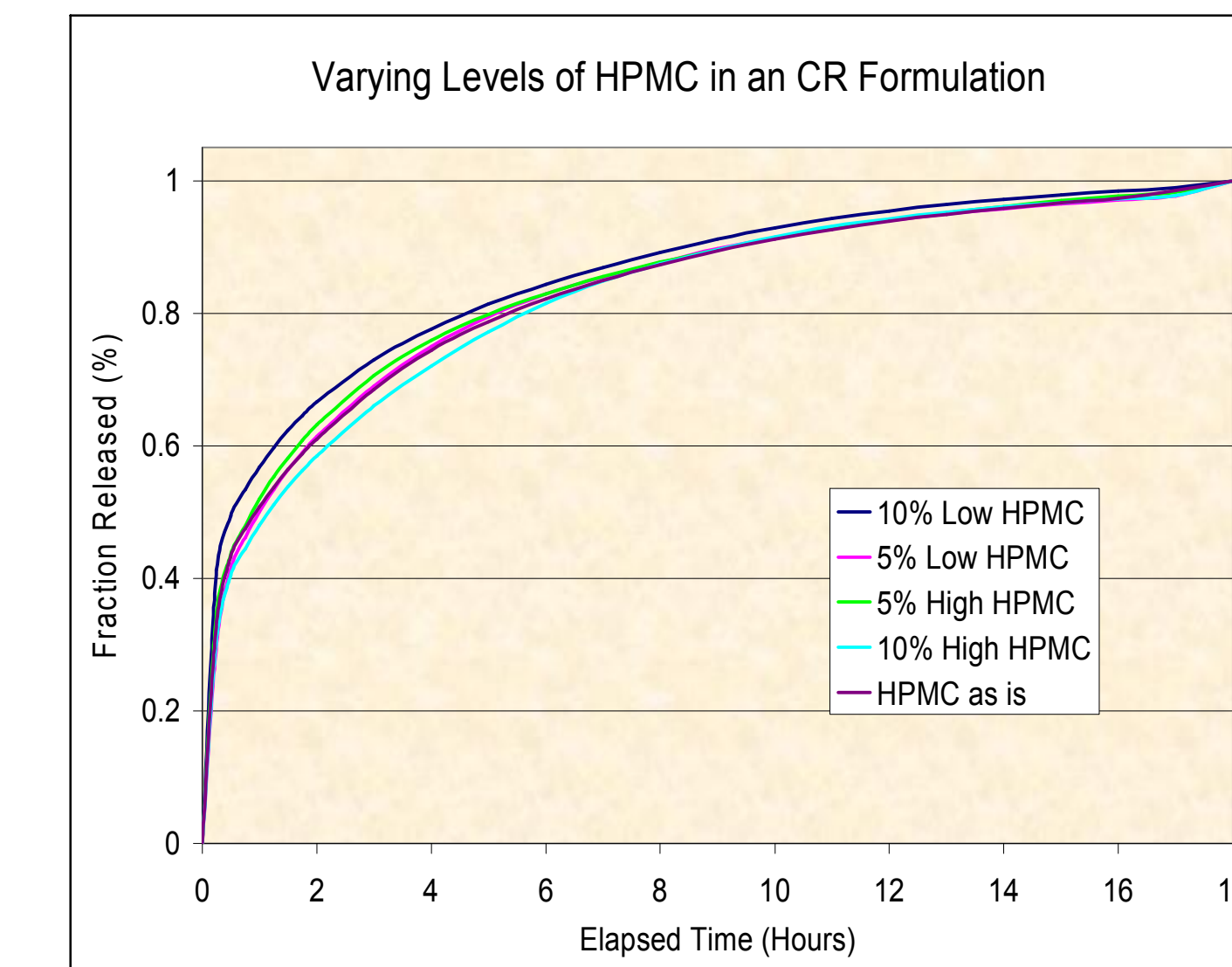
**Table 3.** – Impact on Viscosity Due to Varying Levels of Rate-Controlling Excipient.

Sample	Viscosity	Avg. Viscosity	% Difference
-10%	293	293	-15.6%
	293		
-5%	307	309	-11.0%
	311		
0%	346	347	NA
	348		
+5%	393	394	13.5%
	394		
+10%	442	442	27.4%
	442		

Lowering or raising the HPMC K4M by 5% results in greater than 10% difference in kinematic viscosity measurement. Lowering the HPMC K4M by 10% resulted in greater than 15% difference in viscosity measurements, while raising the HPMC K4M by 10% from the original formula yielded a 27% relative difference, (as shown in Table 3)

Tablets made from the blends described above were examined in a USP Type II dissolution apparatus with six tablets tested for each formula variation.

**Graph 1.** – Impact on Dissolution Profile Due to Varying Levels of HPMC K4M



The means and individual data all fall within the margin of error typical for dissolution for the range of HPMC used.

## Conclusion

We have shown that viscometry is an extremely sensitive and capable method of measuring differences in the content of controlling excipients in CR products. Though viscometry is not capable of providing specific content values for these excipients, it provides a more sensitive measure of the content uniformity of those excipients than dissolution alone.

## References

1. Dow Methocel Cellulose Ethers Technical Handbook; Dow Chemical Company; 1997.

