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Analysis of the Transformation of Caffeine in Poly Acrylic Acid
Daniel P. Brooks

ABSTRACT

Understanding the inhibitory affects of polymer excipients on the hydration of active pharmaceutical ingredients (API) during wet granulation may significantly influence the current procedure of industrial tablet production by reducing unwanted transformations. The anhydrate to hydrate transformation of API crystals often influences the bioavailability of a drug due to differences in solubility compared to the anhydrous crystals. This unwanted transformation may be inhibited through the use of a specific polymer as an excipient. The hydrate transformation of caffeine was analyzed in a high shear aqueous slurry. Small amounts of polymer excipients were added to the slurries to determine the effects on the transformation. The caffeine transformation was monitored using in-line Raman spectroscopy via an immersion probe at regular intervals. A calibration was used to construct the kinetic transformation profiles by quantifying the relative amounts of hydrate and anhydrate caffeine as determined by the ratio of specific peak intensities in the Raman spectra. The results showed that poly acrylic acid (PAA) was effective at inhibiting the transformation at concentrations as low as 0.01 mg/mL and showed complete inhibition for at least 400 min at a PAA concentration of 2.0 mg/mL. The results from other polymers including hydroxypropyl methyl cellulose (HPMC), poly vinyl pyrrolidone (PVP) and poly ethylene oxide showed little to no inhibition at concentrations of 2.0 mg/mL. In addition, seeding experiments were performed to determine if nucleation or crystal growth inhibition was the source of overall inhibition. Analysis of kinetic profiles showed PAA inhibited both the nucleation of hydrate and the growth of caffeine hydrate crystals.

INTRODUCTION

A common method for the production of drug tablets is wet granulation. This process starts by mixing the active pharmaceutical ingredient (API) with other compounds called excipients. This mixture is sprayed with water to form granules and then blended to ensure even distribution of the API. After several other production steps, the granules are eventually pressed into tablets.

It is not uncommon for an unwanted transformation to take place during this process. The API is often an anhydrous crystal (no water molecules are incorporated into the crystal structure) that has specific properties, which determine the bioavailability. If the API becomes hydrate, many of the physical properties of the crystal may change. Solubility is a physical property that is often altered by this transformation. If the hydrated crystal is less soluble than the anhydrous crystal, the bioavailability and effectiveness of the API is altered.

The anhydrate to hydrate transformation occurs by a solvent mediated transformation (SMT). This process includes three steps. The first is the anhydrate crystals dissolving in water. The second is the nucleation of a hydrate crystal, which can only occur if the concentration of dissolved material is above a threshold amount and the molecules are able to rearrange themselves properly. After a crystal nucleus has formed, the final step is crystal growth. The growth is accomplished by the addition of molecules to the nucleus while maintaining the new
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arrangement. If the anhydrate to hydrate transformation is to be prevented, the solvent mediated transformation must be stopped at any one of these steps.

One previously determined way to stop this transformation is by introducing polymers as excipients during tablet production. Current research\(^2\) shows that certain polymers inhibit the hydration of certain API anhydrates; however, the inhibition is dependent on specific API-polymer interactions. This research was aimed at exploring the key variables that affect the hydrate transformation of APIs. More specifically, what influence does the amount and types of polymer cross-linking have on hydrate inhibition of caffeine.

EXPERIMENTAL

Preliminary Slurry Experiments

Slurry experiments were performed with a variety of polymers to determine if select polymers could inhibit the hydrate transformation of caffeine (see Figure 1). A control of 2.5g of caffeine and 50mL of water were mixed to form a slurry. This control slurry transformed in 10 - 12 minutes. The endpoint of transformation was determined visually. The caffeine is initially anhydrous and the slurry is very fluid. After transformation occurs, the slurry becomes very thick and paste-like. The following polymer solutions were tested at a concentration of 2mg/mL:

- Plasdone K-12 (PVP)
- Methocel E5 (HPMC)
- Polyox WSR N10 (poly (ethylene oxide))
- Polyvinyl Alcohol (PVA)
- Poly Acrylic Acid (PAA)

Figure 1. Molecular structure of caffeine and polyacrylic acid.

Raman Spectroscopy of Caffeine in Slurry

Preliminary results indicated that PAA and PVA both showed caffeine transformation inhibition, therefore more detailed experiments were performed. Instead of visually determining the endpoint of transformation, the kinetics of transformation were monitored using Raman spectroscopy. An immersion probe was inserted into the mixing slurry and spectra were collected every 30 seconds. Quantification of spectra was performed using bivariate calibration that analyzed the height ratio of the peaks at 1660 cm\(^{-1}\) and 1700 cm\(^{-1}\) (see Figure 2).

The four grades of Carbopol

Carbopol 907 is a straight polymer chain of the four. The other three products are being dissolved. The solubility of caffeine is 50mg/mL for the anhydrous is 49mg/mL.

Anhydrous Crystal

Carbopol 907

Carbopol 907

Carbopol 907

Carbopol 907

Table 1. Ph

Crystal Growth of Hydrate

The solubility of caffeine is 50mg/mL for the anhydrous is 49mg/mL.

anhydrous caffeine in 50mL.
The four grades of Carbopol used in this experiment were 907, 934, 971 and 974 (see Table 1). Carbopol 907 is a straight poly acrylic acid chain with no cross-linking and the lowest viscosity of the four. The other three polymers have a high degree of cross-linking.

Figure 2. Raman spectra of both crystal structure of caffeine.

<table>
<thead>
<tr>
<th>PAA Grade</th>
<th>Viscosity</th>
<th>MW between cross-links</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbopol 907</td>
<td>&lt; 4000</td>
<td>No cross-links</td>
</tr>
<tr>
<td>Carbopol 971</td>
<td>4000 – 11,000</td>
<td>100,000</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>29,000 – 39,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Carbopol 974</td>
<td>29,000 – 39,000</td>
<td>30,000</td>
</tr>
</tbody>
</table>

Table 1. Physical properties of PAA

Crystal Growth of Hydrated Caffeine in Supersaturated Solution

The solubility of caffeine is different depending on whether the anhydrous or hydrated crystals are being dissolved. The solubility of the hydrate is 21mg/mL in water at 25°C, and the solubility for the anhydrous is 49mg/mL. The initial experiment conducted involved dissolving 2g of anhydrous caffeine in 50mL (40mg/mL) of heated solution. The solutions analyzed were
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Carbopol 907, 934, PVA and water (control). The concentrations for each of the polymers were 0.002mg/mL, 0.02mg/mL, and 0.2mg/mL for a total of ten samples in the experiment. The samples were set out overnight to cool and to allow for crystallization of caffeine hydrate to occur.

UV-Vis Spectroscopy of Caffeine in Solution

To determine if the solubility of caffeine is affected by the presence of PAA, an eight point UV-Vis calibration curve for caffeine was built by using precisely measured standard solutions ranging in concentration from 0.001545mg/mL to 0.01545mg/mL. Such dilute concentrations of caffeine were needed to maintain absorbance values between 0.1 and 1, which ensures a minimum amount of error.

This experiment was setup differently than the previously conducted crystal growth experiment in a few ways. First, the sample size was much larger (18 samples). Second, the initial concentration of the caffeine in solution was lowered to 25mg/mL (just above the solubility of the hydrate). Third, by using previously hydrated caffeine in some of the samples, the transformation process was bypassed and only the solubility of hydrate in various solutions was considered. The purpose of this experiment had two points: To determine if the solubility of caffeine is different in the polymer solutions (as compared to water) and to determine if the concentration of caffeine in solution differs depending on the amount of crystal grown.

RESULTS AND DISCUSSION

Slurry Experiments

The slurries containing 2mg/mL PVP, HPMC and Polyox all transformed within a 10 – 13 minute range (water controls transformed at 7-9 min). Both the 2mg/mL PVA and PAA slurries were allowed to run for over 48 hours without transforming.

These results were consistent with the previous research1. Experiments confirmed that the slurry apparatus and laboratory technique were appropriate to both replicate previous experiments and continue with new research.

Raman Spectroscopy of Caffeine in Slurry

Several trials of each of the polymers were run at three concentrations: 0.01mg/mL, 0.1mg/mL, and 0.2mg/mL. Transformation data is summarized in Table 2. Typical transformation profiles of caffeine in the presence of PAA at concentrations of 0.01mg/mL and 0.1mg/mL are shown in Figure 3. At 0.01mg/mL, the slurry experiments ran on the same time range as using pure water, so diluting to lower concentrations was not applicable. At 0.1mg/mL, the slurry experiments took significantly longer to transform indicating that the transformation process was being inhibited. Experiments performed at higher concentrations (>1mg/mL) resulted in complete lack of transformation. General comparisons of transformation data is shown in Figure 4.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Conc. (mg/mL)</th>
<th>St</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbopol 907</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Carbopol 907</td>
<td>0.1037</td>
<td></td>
</tr>
<tr>
<td>Carbopol 907</td>
<td>0.2074</td>
<td></td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>0.1073</td>
<td></td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>0.2146</td>
<td></td>
</tr>
<tr>
<td>PVA</td>
<td>0.01018</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Slurry results with slurry ran before transformation.
each of the polymers were run in the experiment. The
formation of caffeine hydrate to

of PAA, an eight point UV-
filtered standard solutions
which dilute concentrations of
1, which ensures a
crystal growth experiment in
second, the initial concentration
(solubility of the hydrate).
the transformation process
was considered. The purpose
caffeine is different in the
centration of caffeine in

slurry experiments took
process was being inhibited.
complete lack of
in Figure 4.

Table 2. Slurry results with varying concentration of polymers. Start time is the time the
slurry ran before transformation began. Trans time is the duration of time passed during
transformation.
Figure 3. Examples of transformation profiles of Carbopol 934 at varying concentrations.
Figure 4. Time comparisons between various polymers at consistent concentrations.
Seeding experiments were performed to determine which stages of SMT the inhibitory polymers were affecting. The seeding was accomplished by inserting a small crystal of caffeine hydrate into the slurry. The presence of a seed made a significant difference in the transformation profile of Carbopol 934 at 1.0mg/mL (see Figure 5). Without seeds, no transformation is observed. However with seeds, a very slow transformation is observed. These results indicate that the PAA inhibits both nucleation and crystal growth of caffeine hydrate.

Crystal Growth of Hydrated Caffeine in Supersaturated Solution

The appearance of the crystals in the most dilute Carbopol solutions (0.002mg/mL) was identical to those grown in the water, which was very thick and paste like. However, in the most concentrated Carbopol solutions, the crystals were long, thin spikes radiating from a single nucleation point. The crystal growth for the PVA solutions was not observed in the most concentrated, and in both dilutions the crystals were very bulky. Upon observing the results if this experiment, a point was made that inspired a series of new experiments to be done. If all of the samples started with the same amount of caffeine in solution and some of the samples appeared to grow more crystals, how did the concentration of caffeine in solution after crystal growth compare? In addition, it was observed that the amount of crystals was not consistent for each of the different solutions. This indicated that the concentration of the polymer affected the results.

UV-Vis Spectroscopy of Caffeine Hydrate

Upon completion of the calciation and saturated crystal growth experiments, the solutions of PVA were represented in order to compare the results. In addition, six solutions were created, with caffeine hydrate as the starting material.

Figure 5. Transformation profile showing affect of seeding at high concentration.

Figure 6. Eight point calibration curve for UV-Vis spectroscopy.

Since the initial concentration of caffeine hydrate was significantly lower than the supersaturation observed, the solutions for each experiment were run at an appropriate concentration.
Upon completion of the calibration curve (see Figure 6), a new set of samples for a super saturated crystal growth experiment was made. This time, all four grades of the Carbopol and the PVA were represented in concentrations of 0.1mg/mL and 1.0mg/mL along with water as a standard. In addition, six samples were made (all 4 Carbopol, PVA and water) at 1.0mg/mL using caffeine hydrate as the starting material.

Since the initial concentration of caffeine was lower, the degree of crystal growth was significantly lower than the first experiment. However, consistency within the results was observed. The solutions for each sample were extracted and diluted by a factor of 2000 to achieve an appropriate concentration to apply the calibration curve. Then each sample was analyzed by
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the UV-Vis spectrometer by random selection for a minimum of three trials. With the exception of the 1.0mg/mL PVA sample (undetermined error) and water (extensive crystal growth), the concentration of caffeine in solution for all other samples ranged between 20 and 25mg/mL (see Figure 7 & Table 3). This is consistent with previously reported results. The error and variability that did occur is most probably associated with the significant amount of dilution involved with the preparation of each sample.

![Conc. of Caffeine in Polymer Solution](image)

Figure 7. Concentration of dissolved caffeine in solution after crystal growth.

<table>
<thead>
<tr>
<th>Poly Type</th>
<th>Carb 907</th>
<th>Carb 907</th>
<th>Carb 934</th>
<th>Carb 934</th>
<th>Carb 971</th>
<th>Carb 971</th>
<th>Carb 974</th>
<th>Carb 974</th>
<th>PVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc (mg/mL)</td>
<td>1.0</td>
<td>0.1</td>
<td>1.0</td>
<td>0.1</td>
<td>1.0</td>
<td>0.1</td>
<td>1.0</td>
<td>0.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3. Polymer identification and concentration for figure 7 (above).

**REFERENCES**

2. Simonelli, A.P.; M. polyvinylpyrrolidone. *Inten.*
3. Wilkstrom H, Rant. influencing anhydrate-to-hydrate transformations of *CRYST*.

**CONCLUSION**

The consistent results discussed in this experiments and have established that the concentration of both samples is low and the ability to inhibit hydration is significant. It has been shown that UV-Vis spectrophotometry is a valuable tool for this.

Research will continue by investigating the influence of temperature and pH dependent transformations on hydration and inhibits the hydration of caffeine.

Daniel is a senior and will be doing research with Dr. Gift in Secondary Education – Mathematics.
CONCLUSION

The consistent results discussed within this report have confirmed previously conducted experiments and have established a foundation for future investigation. It has been determined that the concentration of both poly acrylic acid and poly vinyl alcohol is directly proportional to the ability to inhibit hydration of caffeine in both slurry and supersaturated solution. It has also been shown that UV-Vis spectroscopy can be used to determine the concentration of caffeine in solution.

Research will continue by means of image capture microscopy, more in-depth slurry experiments, and pH dependent transformation experiments in an attempt to understand why poly acrylic acid inhibits the hydration of caffeine when other polymers of similar size and structure do not.

REFERENCES


