Effect of Polymer (Ethylcellulose), Plasticizer (Dibutyl Sebacate) and Curing Time on the Dissolution Rate of Multi-Layer Sustained Release Pellets

C. Hollis\(^1\), C. Conde\(^2\), and H. Cocolas\(^1\)

\(^1\)Catalent Pharma Solutions, Winchester, KY 40391, U.S.A;
\(^2\)Conde IndusServices Corp, San Lorenzo, PR 00754, Puerto Rico
Christin.Hollis@catalent.com

ABSTRACT SUMMARY
The objective of this study is to re-center the in vitro drug release from multi-layer sustained release pellets to be within the specification by altering the amount of applied plasticizer and rate-controlling polymer within the SUPAC guideline. The effects of seal coating and curing time on the drug release were also studied. Adjustments, within SUPAC guideline Level I change, to the formulation were made in order to achieve a dissolution rate at the center of the specifications.

INTRODUCTION
The multiparticulate drug system is manufactured by adhering drug to the surface of sugar spheres by a fluidized bed coating process [1]. The initial rate-controlling polymer is applied to the drug-layered pellets for controlling drug release. Subsequently, a seal coating is applied as a protective outer layer. The illustration of the system is depicted in Figure 1.

![Figure 1. Illustration of the multiparticulate system, which consists of: (A) sugar sphere, (B) drug layer, (C) rate-controlling layer, (D) seal coat.](image)

The drug release of the system is monitored at 1, 2, 4, and 8 hour time points. Based on the historical drug release data, there was a downward shift in the 4-hour time point. Although the dissolution results were still within specifications, 65-90%, the recent average values had shifted to 69% from being historically centered at 73%. Based on the FDA Guidance for Industry Level I SUPAC-MR Modified Release Oral Solid Dosage Forms, a change of less than or equal to 5% w/w of the total release controlling excipients in the original approved formulation is permissible [2]. Thus, an effort was made to evaluate the roles of controlled-release components (e.g. polymer and plasticizer) and manufacturing process (e.g. curing time) to the percent of drug release. The objective of this study was to re-center the drug release by adjusting the formulation within the Level I SUPAC guideline.

EXPERIMENTAL METHODS
To evaluate the effect of the polymer (ethylcellulose), plasticizer (dibutyl sebacate), seal coat (Opadry®), and curing time, a number of samples, detailed in Table 1, were collected from 5 batches. The first four batches were manufactured with the plasticizer at target and varied (e.g. +10%, -10%), with Batch 2 set as a duplicate. In all of the four batches, 100% of the polymer was applied. However, in-process samples were withdrawn after 90, 95, 97, and 100% of the polymer had been applied. Additional samples were obtained subsequent to the application of seal coating and the curing period. For Batch 5, only 95% of polymer was applied.

Table 1. Details of the manufactured batches and sampling periods

<table>
<thead>
<tr>
<th>Batch #</th>
<th>Plasticizer</th>
<th>% Polymer</th>
<th>Seal (Y/N)</th>
<th>Curing Time (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Target</td>
<td>90</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Target</td>
<td>95</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>+10 %</td>
<td>97</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>-10%</td>
<td>100</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Target</td>
<td>90</td>
<td>N</td>
<td>0</td>
</tr>
</tbody>
</table>

The sustained release, multi-layer pellets were manufactured in the Glatt® GPCG-15 equipped with a 12” Wurster insert at a batch size of 16.9 kg. The polymer dispersion was applied at an initial rate of 50 g/min and increased to 100 g/min at steady state condition. The seal coating solution was applied subsequent to the polymer dispersion at the steady state rate. The inlet temperature was adjusted between 40 to 60°C in order to achieve a target product temperature of 38°C. Atomization air pressure was maintained at 1 bar, and air volume was targeted at 475±100 cfm.

Dissolution was performed under sink condition in USP I (basket) at 100 rpm in vessels containing...
500 mL of 0.1N hydrochloric acid (37°C). At specific time points, 10 mL samples were withdrawn, filtered, and analyzed by HPLC. 10 mL of fresh, 37°C, 0.1N HCl was added to each vessel to keep the total volume at 500 mL.

RESULTS AND DISCUSSION

Upon evaluation, it was noted that the plasticizer addition only affected the dissolution rate only after the pellets had been cured. Figure 2 presents the dissolution profiles of 4 batches after the 2-hour curing process, where an increase in the overall dissolution was observed as the amount of plasticizer increased. The decrease in the plasticizer (by 10%) did not seem to significantly affect the dissolution rate. Additionally, prior to the curing process, the variation in the amount of plasticizer did not significantly affect the dissolution rate.

![Figure 2. Dissolution rate as a function of % plasticizer, with target amount of rate-controlling polymer and seal-coat applied, after 2 hour curing time.](image)

As expected, when the percent of rate-controlling polymer applied increased, the rate of water diffusion through the polymeric layer was limited. This resulted in a decrease in the dissolution rate. This trend was observed in all of the five batches; an example is presented in Figure 3.

![Figure 3. Dissolution rate of pellets from Batch #2, with various amount of rate-controlling polymer applied.](image)

The effect of curing time on the dissolution rate was only seen in the first 2 hours. The cured pellets exhibited a decrease in % drug dissolved at 1 and 2 hour time points. At 4 and 8 hours, the effect of the curing was not as significant (Figure 4). It is believed that the pellet membrane had been equilibrated by the water molecules and the process condition. Thus, the impact of curing time was no longer significant.

![Figure 4. The effect of curing time on dissolution rate (Batch #2).](image)

Based on statistical analysis (Minitab® 16), the experiments revealed that the individual effect of %polymer was significant (p=0.002), while that of %plasticizer was not (p=0.131). The interaction effect of %polymer*%plasticizer was quite significant (p=0.034). The collected results predicted that a reduction of polymer as much as 4% could potentially increase the percent dissolved at the 4-hour time point close to the center point. Additionally, by keeping the absolute amount of plasticizer constant, there will be an increase in the ratio between plasticizer to polymer, which could further increase the %release closer to the middle of the specification.

CONCLUSION

The study evaluated the role of sustained release components (i.e. polymer, plasticizer) and manufacturing process (i.e. curing time) on the rate of drug release from a multi-layer sustained release pellets. Adjustments, within SUPAC guideline Level I of permissible change, to the formulation were made in order to achieve a dissolution rate at the center of the specifications.

REFERENCES