Real-Time Prediction of Polymer-Coated Multiparticulate Dissolution using Process Analytical Technology

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Introduction

Process Analytical Technology, or "PAT" is the term given to analytical instruments developed to measure certain attributes of product within the manufacturing process, eliminating, or substantially minimising the need for sampling for off-line analysis. This approach has several key advantages over traditional off-line analysis methods and includes process measurements in situ with instant access to data which facilitates rapid decisions during product development and manufacture. While the time between sampling and off-line results may range from minutes to days depending on the test being performed and the analytical structures in place, many PAT systems are capable of real-time measurement results enabling control decisions to be made based not just on a process recipe, but also on the true critical quality attributes (CQAs) of the material at that point in time. This allows for a more dynamic process, compensating for variabilities such as raw material variations or mechanical wear in processing components, and supports compliance with newer QA initiatives such as continuous verification. Additionally, the automated nature of PAT allows for greater data generation with minimal operator time when compared to testing samples at-line or off-line.

Many PAT instruments exist on the market today supporting measurement of several physical and chemical Quality Attributes. One critical quality attribute (CQA), however which cannot be directly measured in-line due to the long duration of the analytical test is dissolution. Many new and pipeline oral dose medicinal products are formulated to enable modified or extended release of the active ingredient to increase patient compliance and improve convenience by reducing the number of daily doses required by the patient. Multi-step Fluid Bed (Wurster) Coating processes are routinely used to produce pellets or beads with the correct release profile during formulation. Accurate and rapid measurement of dissolution performance is essential to production quality control, and to efficient process development. It can take several days or weeks before dissolution test results are available. The potential to significantly reduce product development and production cycle times is high for a real-time test that can be used to accurately predict dissolution test results of a modified release product.

While direct measurement of dissolution performance in-line may not be practical to implement, this study demonstrates the possibility of predicting dissolution drug release profiles on multiparticulates in a Wurster coating process, using an in-line measured coating thickness derived from the growth in

the material's particle size distribution. Here Colorcon Suglets® coated with Chlorpheniramine Maleate are coated with Surelease® and Opadry®EC functional coatings to obtain modified release characteristics in a Glatt GPCG2 lab-scale fluid bed system. Measurement is performed using an Innopharma Technology Eyecon$_2$™ particle analyser.

Experimental Plan

In addition to the dissolution prediction aim discussed in the introduction, combinations of other substrate sizes and coating materials were also tested as a means of exploring the Eyecon$_2$'s ability to measure coating thicknesses across a range of formulations. Table 1 shows each experiment conducted and its formulation.

Experiment	Substrate	Functional Coating	Batch Size	Inlet Air Temp	Product Temp	Spray Rate	% Solids
CPM-SR-1	CPM-coated 18/20 mesh sugar spheres	Surelease / Opadry 80:20	2 kg	70°-75°C	44°-46°C	15-20 g/m	15
CPM-SR-2	CPM-coated 18/20 mesh sugar spheres	Surelease / Opadry 80:20	2 kg	70°-75°C	44°-46°C	15-20 g/m	15
CPM-EC	CPM-coated 18/20 mesh sugar spheres	Opadry EC	1.75 kg	40°-45°C	30°-32°C	20-25 g/m	8
PRP-EC	PRP-coated 20/25 mesh sugar spheres	Opadry EC	1.75 kg	40°-45°C	30°-32°C	20-25 g/m	8
PRP-SR	PRP-coated 20/25 mesh sugar spheres	Surelease	1.75 kg	70°-75°C	44°-46°C	15-20 g/m	15

Table 1 – List of Experiments

Process settings were chosen in accordance with those recommended by Colorcon for the functional coating material in use. Coating was applied to achieve a predicted 20% weight gain in each case.

Samples were extracted from the process at time points corresponding to a predicted weight gain of 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5% and 20% based on the quantity of coating solution sprayed. Additionally, for the aqueous-based functional coat (Surelease) samples were taken at 30 minutes and 1 hour of curing, as a 1-hour cure time is recommended for this material. These samples were sent for analysis by Colorcon's analytical lab to determine dissolution and separately measure particle size distribution using a Camsizer system.

These results will be presented later with respect to in-line dissolution prediction, comparison of the Eyecon$_2$ to the off-line measurement method, and examples of other processing aspects which can be characterised and understood using in-line particle size measurement.

Materials & Equipment

Formulation

Chlorpheniramine maleate (CPM) and propranolol HCl (PRP) were layered onto sugar spheres (Suglets®, Colorcon) mesh size 18/20 (850-1000 µm) and 20/25 (710-850 µm) respectively. Drug (CPM and PRP) layered pellets (1.5 – 2 kg) were coated with Surelease aqueous ethylcellulose dispersion (E-7-19040, Colorcon) as a barrier membrane coating and Opadry Hypromellose based coating system (YS-1-19025-A, Colorcon) as a pore former at 80:20 ratios. The coating dispersion was prepared by dissolving Opadry in deionized water and then added to Surelease to obtain total solid content of 15% w/w. Opadry EC ethylcellulose organic coating system (505O190028, Colorcon) was used as an alternative fully formulated barrier membrane organic coating to evaluate the performance on CPM and PRP loaded pellets. Opadry EC coating solution was prepared in Ethanol: water (90:10). The targeted coating weight gain was 18-20% and samples were taken at every 2.5% WG.

Coating System

A GPCG-2 with a 6" Wurster was used for these experiments. The Wurster bottom spray process is commonly used in the industry to produce Controlled and Modified Release Multiparticulates for encapsulation into Oral Solid Dosage Forms. It is typically used to layer drug from a solution or suspension onto inert cores, as well as applying polymer film membranes. The co-current flow of suspended particles and atomised spray create an elegant and near perfect film on drug loaded particles that can be easily reproduced. Figure 1 is a diagram of the Wurster bowl and the component parts. Critical process parameters are: Spray Rate, Atomizing Air Pressure, Air Volume, Product Temperature, Orifice Plate Configuration and Partition Height. Understanding and control of these parameters are paramount to having a successful, robust and reproducible process.

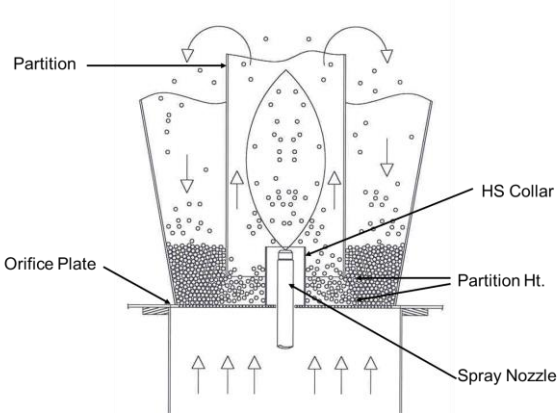

Figure 1 – Diagram of the Wurster Process

The GPCG-2 is a lab scale unit, and is commonly used for formulation and process development of these products. This system easily can be adapted by adding additional custom ports and windows to accept many PAT instruments. The product container used here had multiple SD-55 windows added to accept non-product contact PAT. The Eyecon$_2$ device was installed on the lowest positioned window, as shown in Figure 2, for optimal measurement of pellets during Wurster processing. In general, the use of particle size, as well as moisture and API content measuring devices, can be utilized to gain full process understanding at an economic scale. Process understanding gained from DoEs at this scale can be translated into a robust commercial process with integrated real time in-process product measurement and process control.

Figure 2 – Glatt GPCG2 with Wurster container and Eyecon2 installed

Analytical Instrument

The Eyecon$_2$ from Innopharma Technology was used as a means of real-time particle size measurement. The Eyecon$_2$ is a direct-imaging particle analyser which captures images of flowing or static material, and through advanced image analysis can return data on the particle size distribution and shape of the material. The Eyecon$_2$ has application in typical oral dose processes including fluid bed coating & granulation, milling and twin-screw granulation, and can be used to significantly reduce analytical time and increase process knowledge from development to commercial manufacturing.

As the Eyecon$_2$ is a non-product-contact device, interfacing was achieved by placing the Eyecon$_2$ on a window in the product container, within the down-bed. Here dense images of the multiparticulates could be captured, maximising the number of particles captured per image, and therefore minimising the time required to obtain representative measurements. Figure 3 shows the Eyecon$_2$ mounted to

Figure 3 – Eyecon2 in-place on the product container window

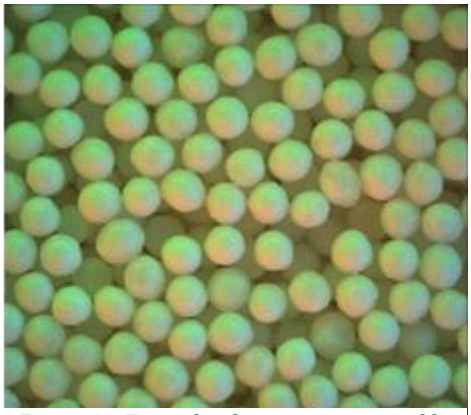

Figure 4 – Example of an image acquired by Eyecon during the trial

the product container, while Figure 4 presents an image captured by Eyecon$_2$ of the CPM-coated multiparticulates part-way through the Surelease / Opadry functional coating process.

An off-line instrument using the principle of dynamic image analysis (Camsizer) was used as an alternative method to measure particle size distribution. Drug release was measured using a UV spectrometer from 1 gram of CPM and PRP barrier membrane coated pellets in dissolution bath using USP apparatus I (baskets) at 100 rpm. USP purified water was used as a dissolution media (1000 ml) at 37.0 ± 0.5 °C.

Results & Discussion

Comparison of In-line & At-line Results

Figure 5 and Figure 9 demonstrate the data from Eyecon$_2$ tracking two of the coating processes. While data is captured on a continuous basis, only data points corresponding to every 2.5% weight gain are shown here for clearer presentation and later comparison to off-line samples taken. Dv50 is the volumetric median particle diameter, while Dv10 and Dv90 define the 10th and 90th percentiles. Together these three values provide a simple description of the particle size distribution.

A clear growth can be seen between start and end in each graph, though the overall size of the materials differs by approximately 100µm. This corresponds with the differing mesh sizes of the CPM and PRP pellets used, as noted in Table 1. It is also evident that the final two data points in Figure 5 show negligible growth. These correspond to the curing process applied to the aqueous-based Surelease, during which no further material is sprayed, thus causing no weight gain at this point. As the size DoEs not appear to change either, it can be concluded that any density, abrasion or film shrinkage effects at play during the curing step are minimal.

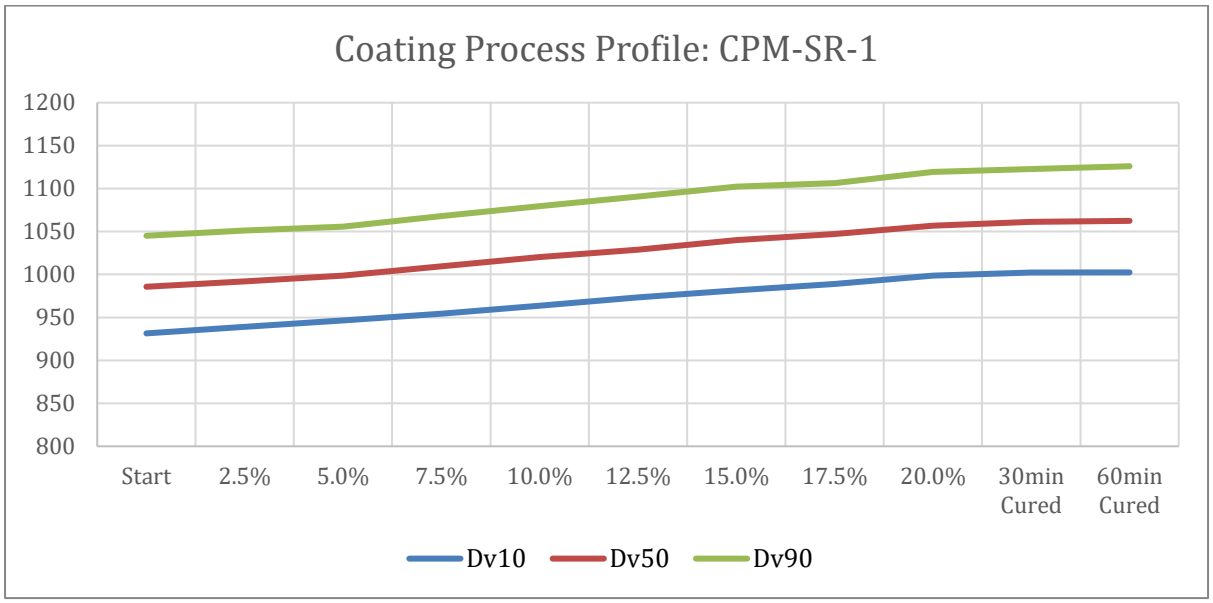

Figure 5

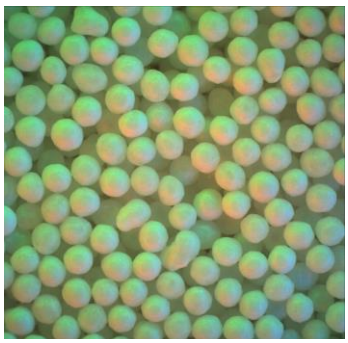

Figure 6

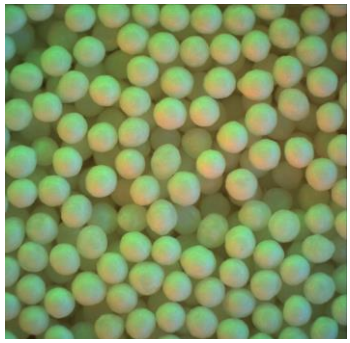

Figure 7

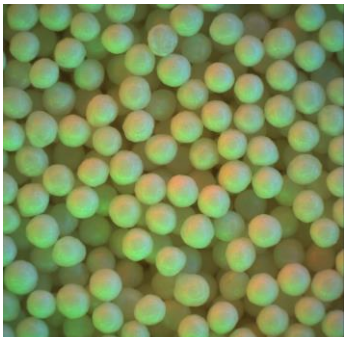

Figure 8

Eyecon images throughout coating process

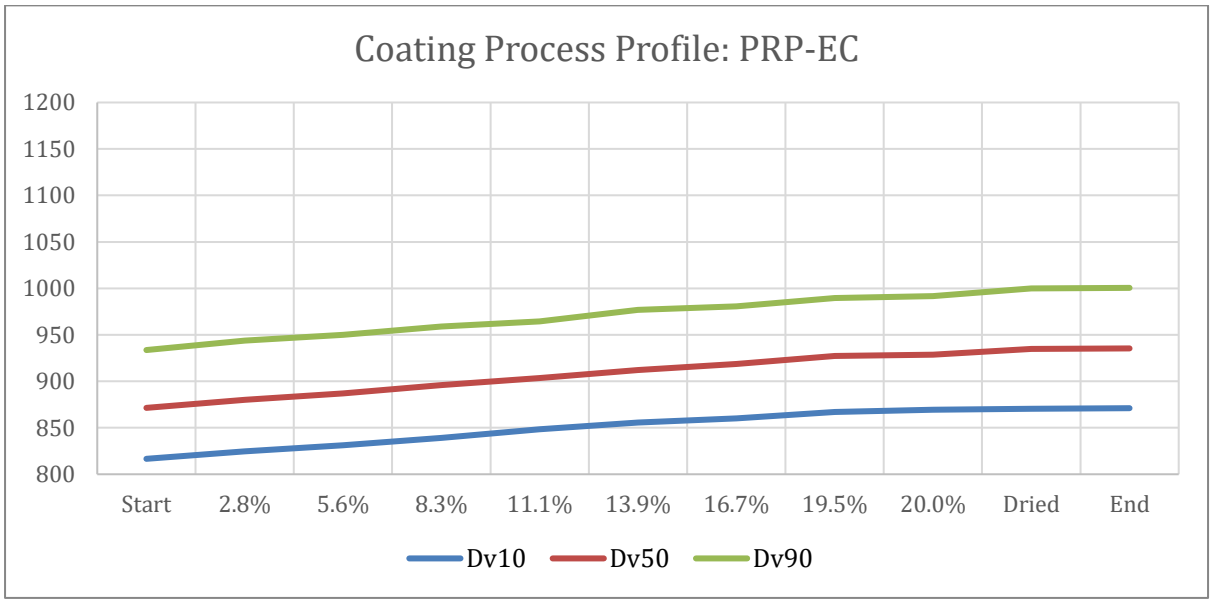

Figure 9

To allow for dissolution model building and establishment of the repeatability of the overall process and measurement techniques, two CPM with Surelease / Opadry experiments were run with identical process parameters. Figure 10 shows the Dv50s of each of these experimental runs as measured by the Eyecon.

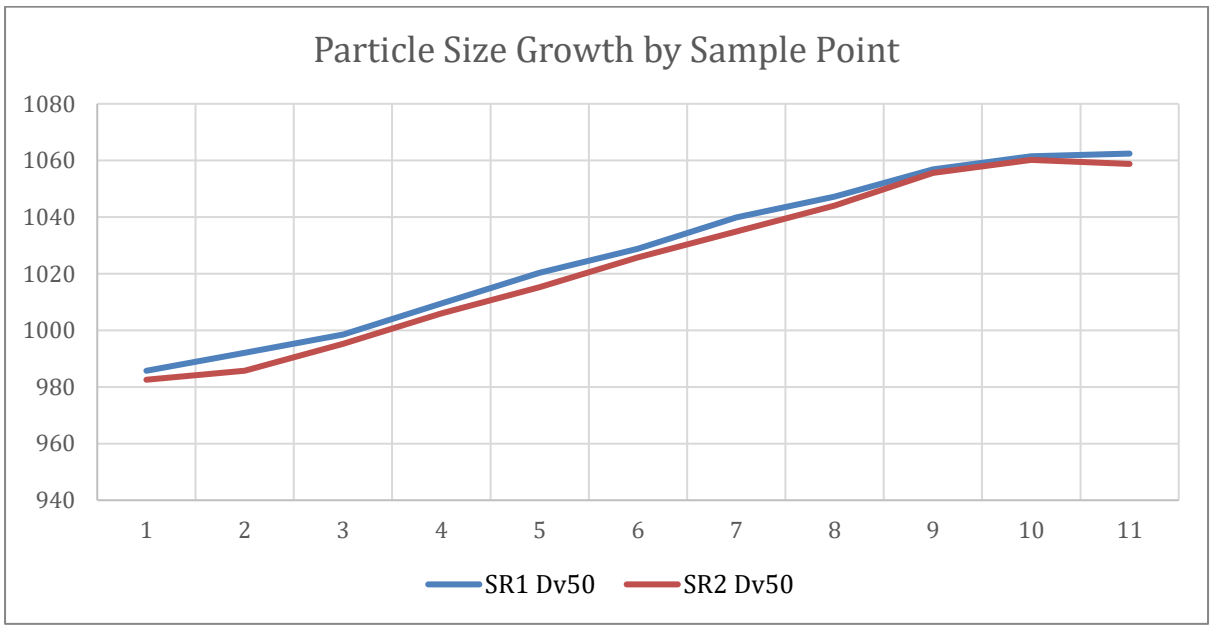

Figure 10

Minimal variance between the two processes can be seen. As the offset between the two is relatively consistent across the duration of coating, the cause of the variance can most likely be attributed to minor variability in the starting material.

Next the data measured in-line with Eycon$_2$ is compared to the off-line results derived from the Camsizer. As some variation is always present between different particle size measurement techniques (e.g. sieve, laser diffraction, back-light imaging) the primary goal is to establish a strong correlation between these two methods rather than to seek direct agreement.

Figure 11 shows the previously-presented results from Eyecon$_2$ graphed against those from the Camsizer. While a clear offset is present between the methods a similar trend can be seen.

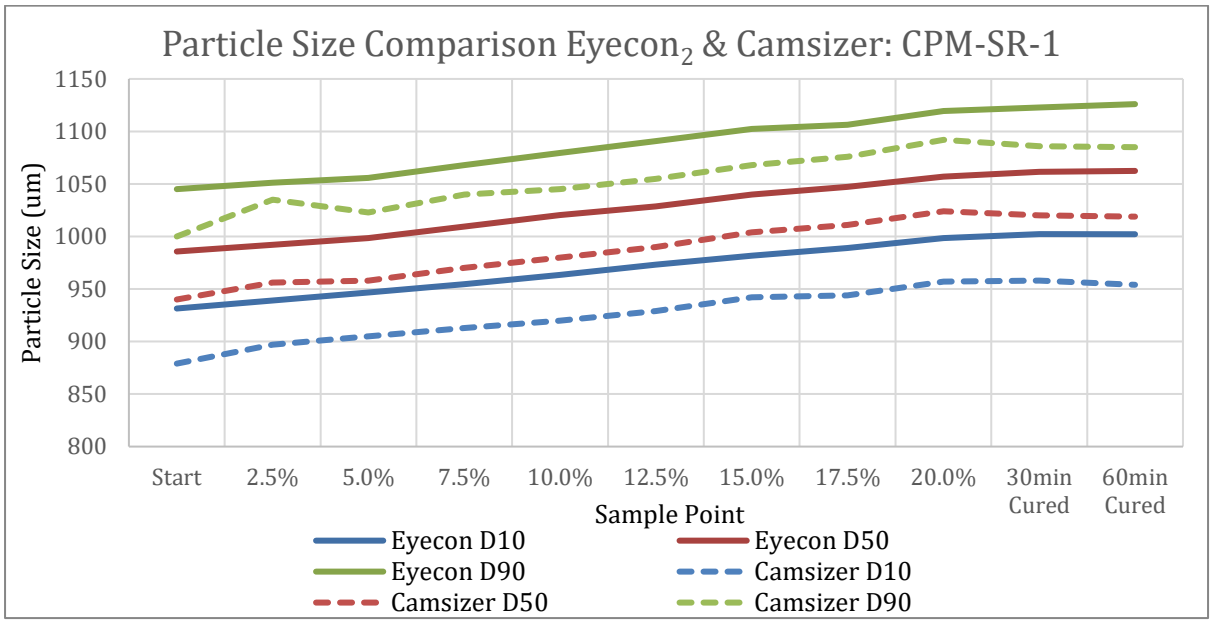

Figure 11

To further explore the quality of correlation between the two devices Figure 12 plots the Eyecon$_2$ and off-line results against each other for D10, D50 and D90 from the CPM-SR-1 experiment. It is evident from the fit lines that a high quality of correlation is present for all three values, with R^2 for the Dv10 and Dv50 greater than 0.98.

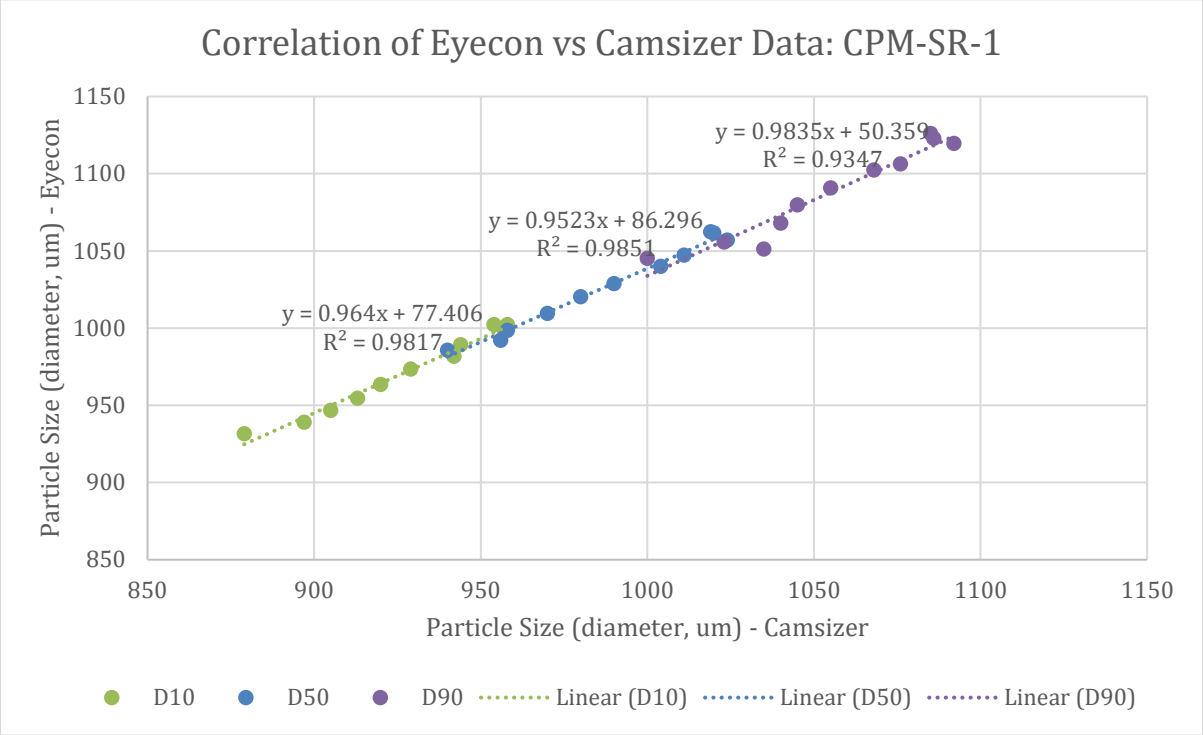

Figure 12

To ensure that this correlation holds across other experiments and material sizes Figure 13 graphs the Dv50s derived from Eyecon$_2$ against those from the Camsizer for all sample points during the DoE. The two populations visible are due to the distinct size ranges of pellets used in the CPM and PRP experiments. A strong correlation is still present with an R^2 for all points of almost 0.99. The D10 and D90 results correlate similarly, but are omitted here for clarity.

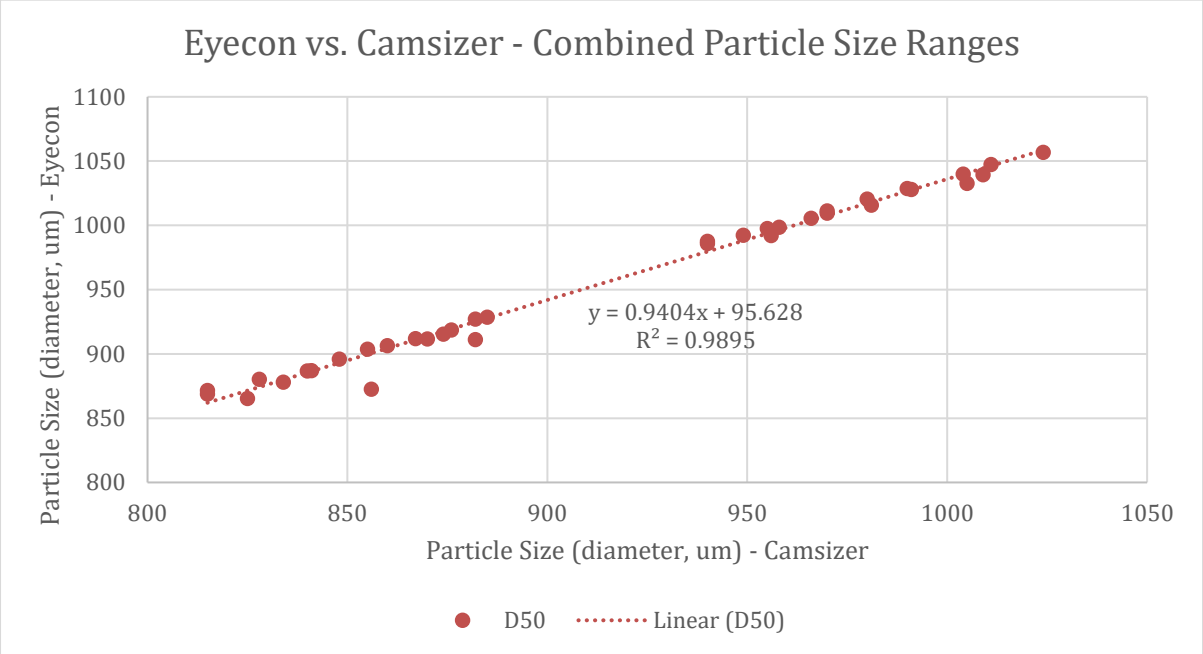

Figure 13

Calculating Film Thickness from Measured PSD

While particle size and distribution are the parameters measured by Eyecon$_2$ and many off-line methods, dissolution performance is related more to the thickness of the functional coating, or "film thickness" applied than the overall size of the pellets. As such, the film thickness must be determined from the measured size data. While the base principle is simple (diameter increase during coating / 2) there are several different ways "diameter increase" could be defined for the population. Figure 14 explores three methods: difference in the Dv50s, difference in the average of the Dv10, Dv50 and Dv90, and the difference of the average of all the volumetric percentiles made available by Eyecon$_2$. In practical terms (as shown in Figure 14) the results of all three of these methods match closely. For this reason, the Dv50 has been chosen as the value used for further analyses.

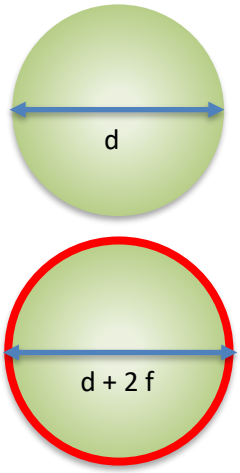

Figure 15 shows the calculated film thickness for the CPM – Opadry EC coating experiment. Here while a similar trend is evident the total film thickness is considerably lower due to differing densities of the functional coating.

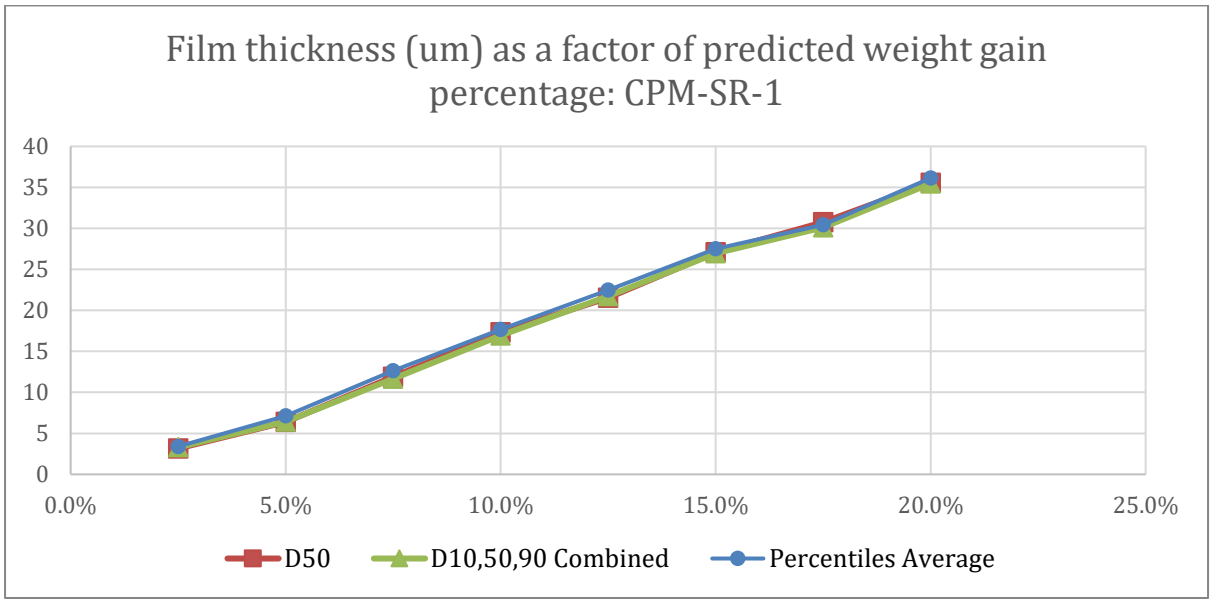

Figure 14

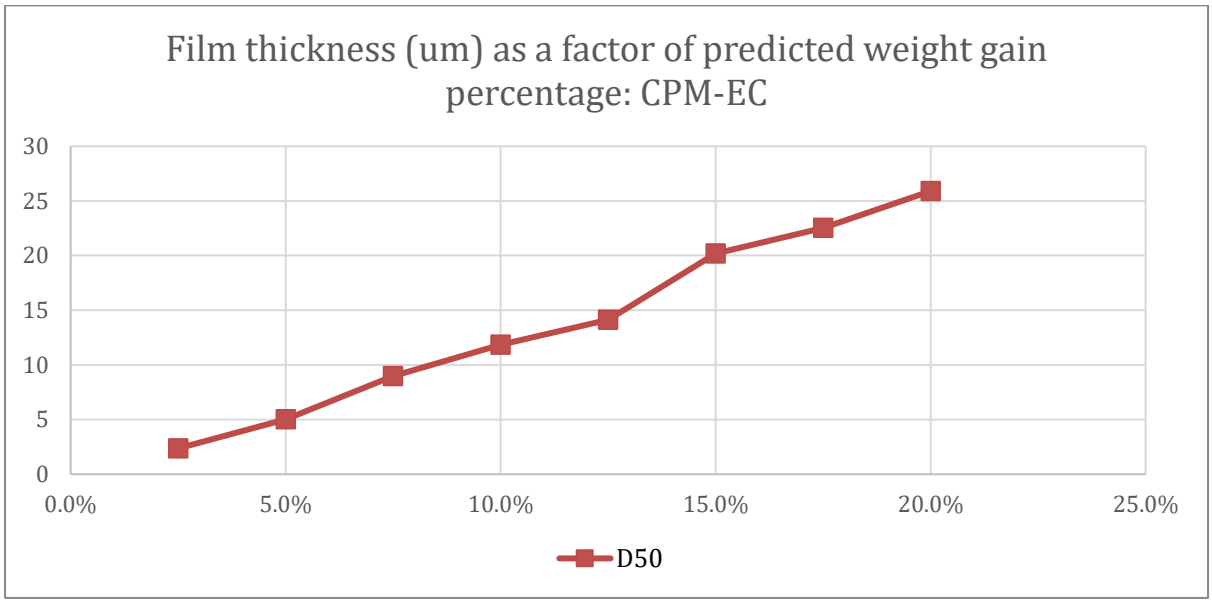
Film thickness (um) as a factor of predicted weight gain percentage: CPM-EC
30
25
20
15
10
5
0
0.0%
5.0%
10.0%
15.0%
20.0%
25.0%
D50

Figure 15

Predicting Dissolution using In-line Measurement

As a great number of factors affect dissolution beyond functional coating thickness it is necessary to build a formulation-specific model for prediction based on the in-line-measured particle size. This was done in the case of the CPM-SR experimental runs, using the data from CPM-SR-1 to build a correlated model against film thickness growth, which will then be used to predict the dissolution results for the samples taken from CPM-SR-2 While more data would ideally be used to build a more robust prediction mechanism, this approach is considered sufficient to demonstrate a proof of concept.

To build a prediction model from CPM-SR-1 the film thickness at each sampling point was first calculated as in Figure 14. This was then graphed against the dissolution result, divided into data sets for each dissolution sampling time-point (as shown for clarity in Figure 16). Figure 17 shows the result of this process, applying best-fit polynomials to each of the data sets

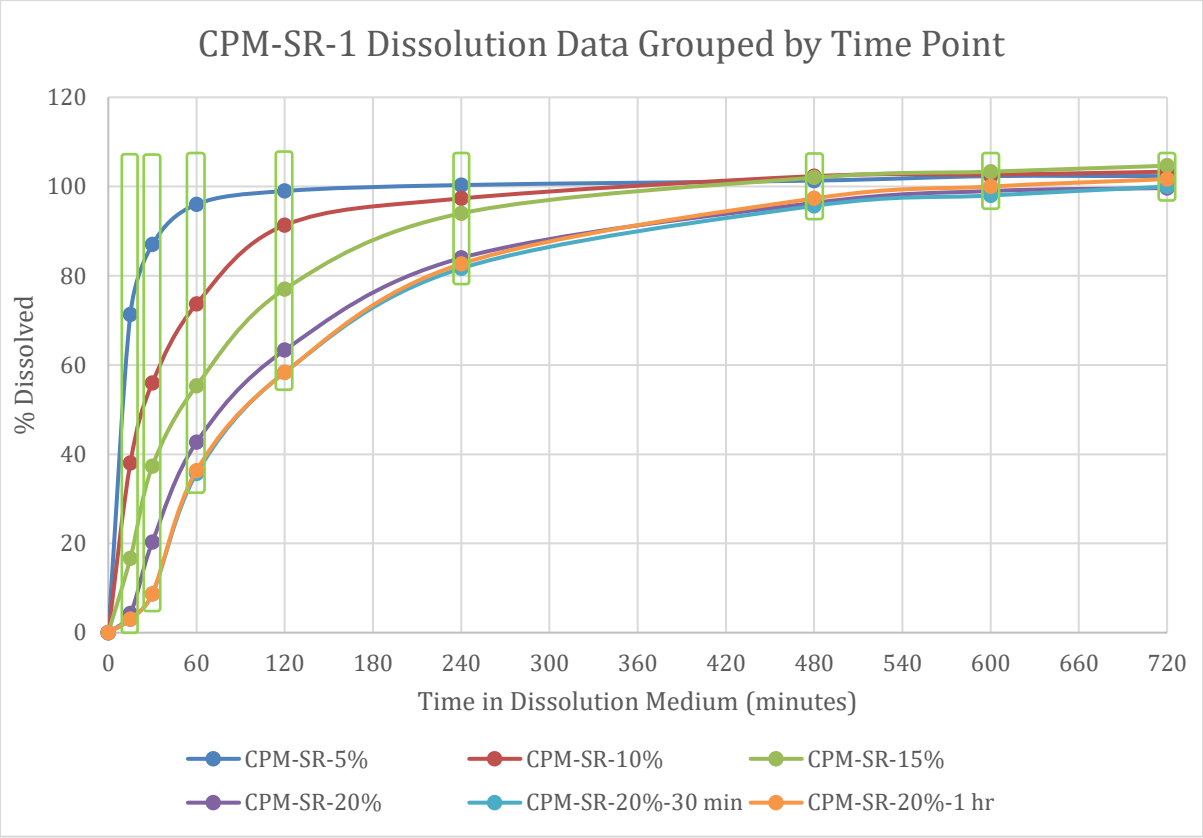

Figure 16

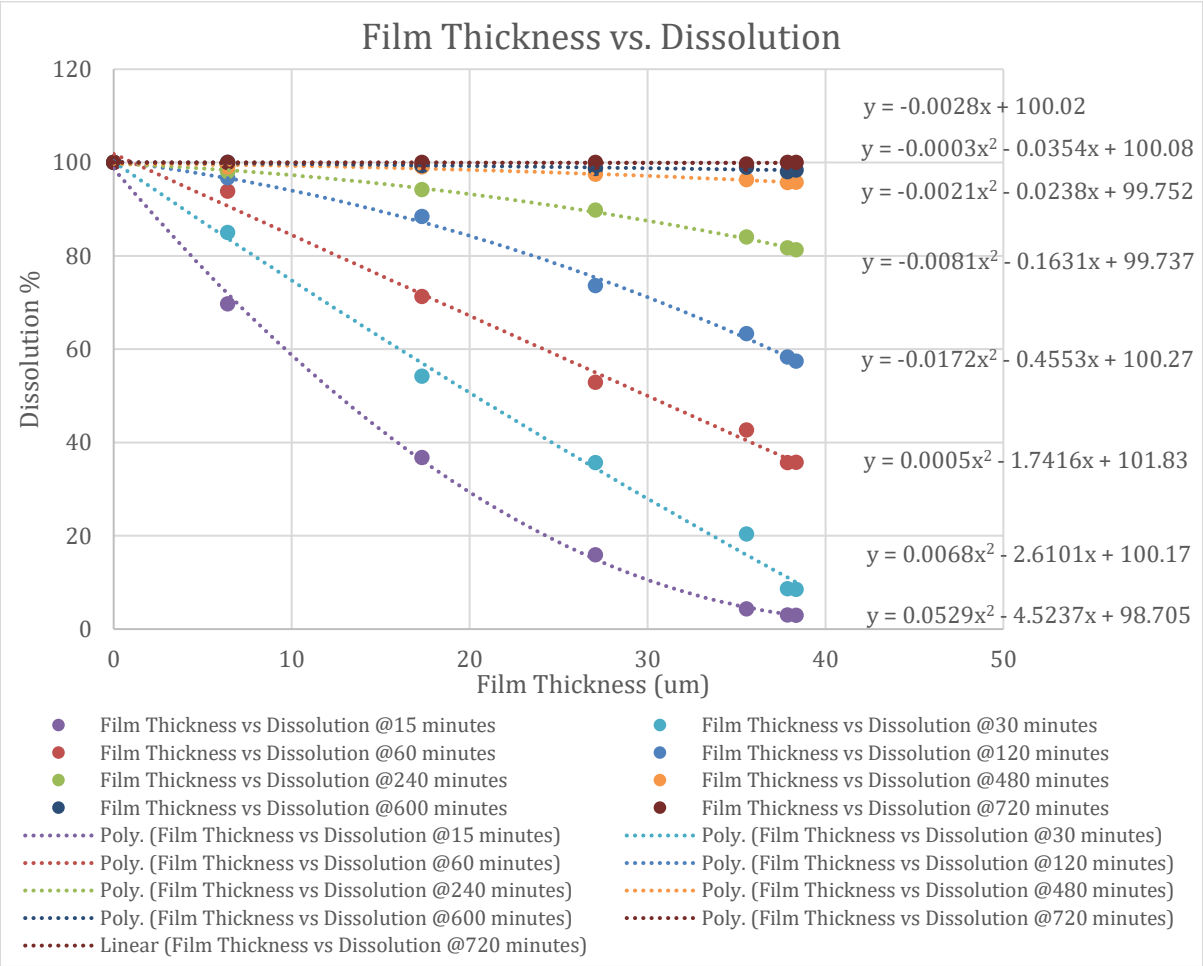

Figure 17

The equations of the best-fit polynomials shown in Figure 17 now effectively form the basis of predicting dissolution performance based on a measured film thickness. For a given thickness, an equation exists to describe the expected dissolution percentage for each time point measured in CPM-SR-1.

To apply this to CPM-SR-2 the measured film thicknesses for each sample point is substituted into the polynomial equations from Figure 17, producing the data shown in Table 2. Data from any point in the coating process could be used for this step, enabling dissolution to be predicted for any moment, but only sample points can be compared to off-line results for validation of the method so those points have been used here.

SR2		Predicted Dissolution @ (minutes)								
Sample Point	**Film Thickness**	**0**	**15**	**30**	**60**	**120**	**240**	**480**	**600**	**720**
0% WG	0.00	0%	99%	100%	100%	100%	100%	100%	100%	100%
5% WG	6.36	0%	72%	84%	91%	97%	98%	100%	100%	100%
10% WG	16.34	0%	39%	59%	73%	88%	95%	99%	99%	100%
15% WG	26.19	0%	17%	36%	57%	77%	90%	98%	99%	100%
20% WG	36.50	0%	4%	14%	39%	61%	83%	96%	98%	100%
30 min cured	38.81	0%	3%	9%	35%	57%	81%	96%	98%	100%
60 min cured	38.08	0%	3%	11%	36%	58%	82%	96%	98%	100%

Table 2 – Predicted Dissolution Results for CPM-SR-2 using In-line Particle Size Measurements

This data, when graphed, predicts the dissolution curves shown in Figure 18. Figure 19 overlays the analytical measured dissolution data, denoted (A), with the predicted (P) dissolution performance. From this graph, we can draw a conclusion as to the successfulness of the experiments.

Generally, the predicted dissolution curves overlap well with the measured results, showing the viability of the prediction method. Based on the limited size of the data set, better prediction could almost certainly be achieved by expanding the model data set from repetition of the experiment. For future experiments the results of CPM-SR-2 can also be integrated into the predictive model adding to the accuracy and robustness of the prediction algorithms.

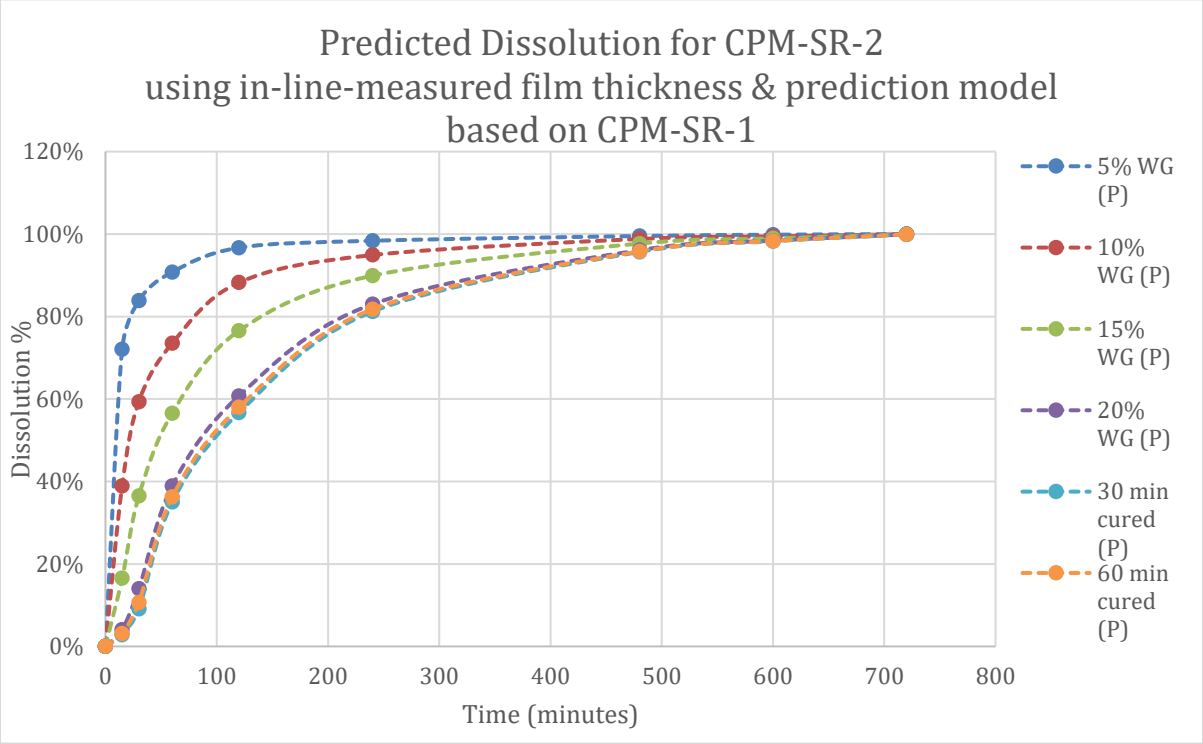

Figure 18

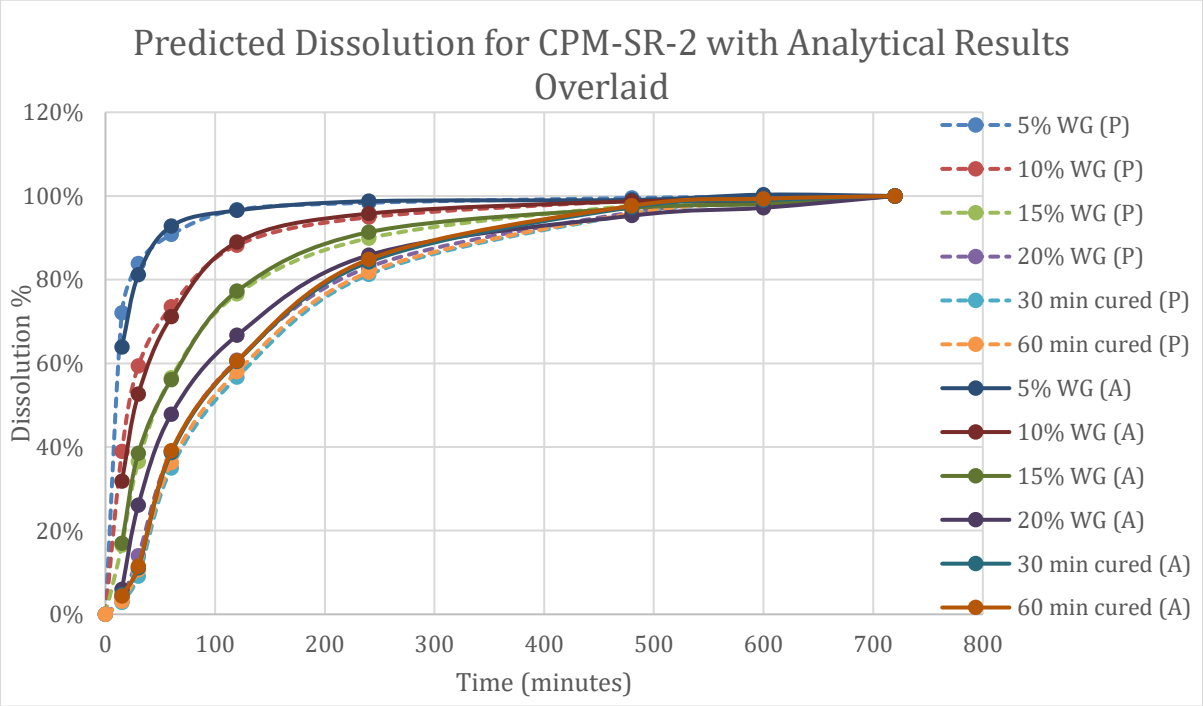

Figure 19

Conclusions

- Data from the Eyecon$_2$ demonstrated that a strong correlation exists between functional coating thickness and dissolution profile.
- It was proven that real-time dissolution prediction of a coating process using particle size data and a formulation-based model is a viable control method.
- In addition to the primary aim of dissolution prediction, several other benefits of PAT were also demonstrated:
    - Real Time Availability of In-Line PSD data with supporting images
    - Greater process understanding & material insight
    - Fast & efficient process profiling
    - Potential to use during process development, optimisation, scale up and transfer
    - Potential to use for process control or troubleshooting based on PSD trending
- Multiple sustained release profiles of different drugs could be easily achieved using Colorcon products and processing knowledge.
- The GPCG2 lab system provided an effective and flexible test-bed for experimentation with different Wurster processing parameters.

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