My Dosage Design Tool Predicts, Process Analytical Technology Confirms Film Thickness of Fully Formulated Aqueous and Organic Ethylcellulose Coating

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AAPS
Poster Reprint 2017

Purpose

Ethylcellulose is a widely used polymer in the formulation of modified release drug delivery systems; applications are either using organic solvent or fully formulated aqueous dispersions. Complete film formation of functional polymers on drug loaded substrates is critical in fluid bed coating application. Process analytical technology (PAT) is the term given to analytical instruments developed to measure key attributes affecting the quality / functionality of the product within the manufacturing process, eliminating, or substantially minimizing sampling need for off-line analysis. A proprietary theoretical modeling tool developed by Colorcon, My Dosage Design™ (MDD), helps formulators to develop multiparticulate (MP) dosage forms by calculating optimal particle size, surface area, film thickness, the volume of the final dosage and capsule size required to fill. Film thickness of the barrier membrane coating was predicted using MDD and compared with experimental film thickness data from PAT analyzer (Eyecon$_2$™, Innopharma). The purpose of this study was to evaluate the performance of both aqueous and solvent based ethylcellulose coating systems by predicting film thickness using MDD and validating with in-line particle size measurement via Eyecon$_2$.

Methods

Chlorpheniramine maleate (CPM) was layered onto sugar spheres (Suglets®, Colorcon) mesh size 18/20 (850-1000 µm). CPM layered spheres (1.5 – 2.0 kg) were then coated (CPM-SR-1) with Surelease® aqueous ethylcellulose dispersion (E-7-19040, Colorcon) as a barrier membrane coating, with hypromellose-based film coating system (Opadry®, Colorcon) as a pore-former at 80:20 ratio. The coating was prepared by dispersing Opadry in deionized water, then adding to Surelease, obtaining total solids content of 15% w/w. A second batch of CPM layered spheres were coated (CPM-SR-2) to confirm reproducibility. An ethylcellulose organic coating system (Opadry EC, Colorcon) was used as an alternative fully formulated barrier membrane to evaluate the coating process performance on CPM loaded spheres (CPM-EC). Opadry EC coating solution was prepared in a 90:10 ethanol: water hydroalcoholic mixture at 8% solids (w/w). A Glatt fluid bed GPCG-2 with 6" Wurster column was used for these experiments. The process parameters from these batches are shown in Table 1. Target weight gain (WG) for the barrier membrane coating was 18-20% w/w, with samples collected at 2.5% WG intervals. Additionally, Surelease: Opadry coated samples were cured for 30 minutes and 1 hour at 60°C to ensure full film coalescence.

Particle size analysis of the coated multiparticulates was carried out using three distinct methodologies: in-line, off-line, and calculated. Eyecon$_2$ (Innopharma Technology) is a PAT tool used as a means of real-time particle size measurement as shown in Figure 1. Particle size was measured by off line measurement at different WG using a Camsizer Dynamic Image Analyzer (Horiba Inc., USA). In this study, the MDD tool (Figure 2) was used to calculate and predict the film thickness of barrier membrane at different weight gain and compared with Eyecon$_2$ and Camsizer data.

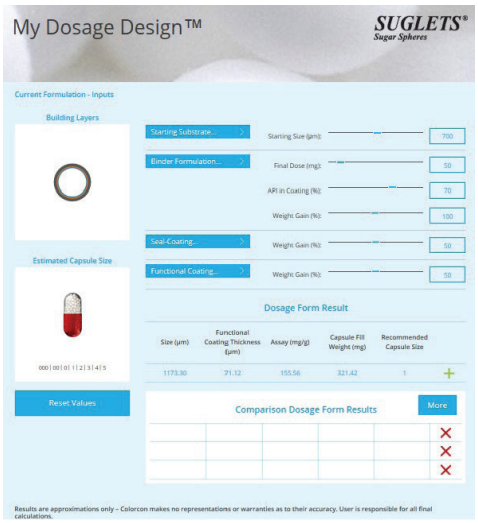
Drug release was measured from a 1.0 g sample of CPM barrier membrane coated multiparticulates in USP apparatus I (baskets) at 100 rpm, using USP purified water as the dissolution media (1000 ml) at 37.0 ± 0.5 °C.

Table 1: Multiparticulate Coating & Process Parameters

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

Figure 1: Fluid Bed Wurster Process Equipped with Eyecon$_2$

Figure 2: MyDosage Design™ Tool (accessible through Colorcon)

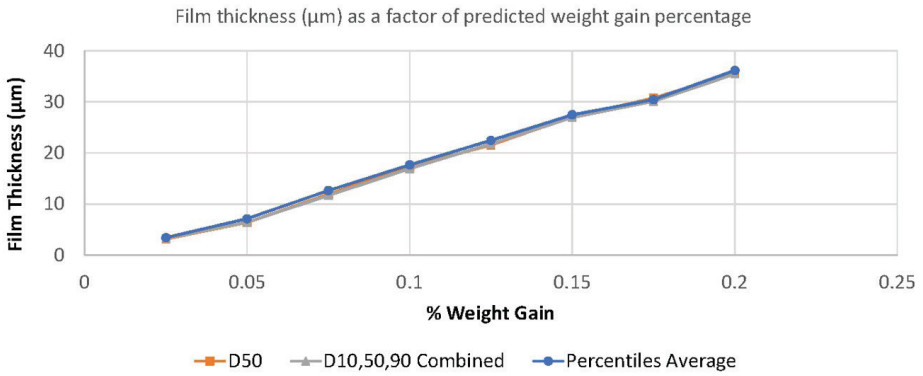


Results and Discussion

Calculating Film Thickness from Measured Particle Size Growth

While particle size growth is measured by Eyecon$_2$ (in-line), Camsizer (off-line) and predicted by MDD, dissolution performance is related more to the thickness of the functional coating than the overall size of the spheres. As such, the film thickness must be determined from the measured particle size diameter growth data. Figure 3 explores three methods: difference in the D_{50}, difference in the average of the D_{10}, D_{50} and D_{90}, and the difference of the average of all the volumetric percentiles made available by Eyecon$_2$. Figure 3 shows the results of all three of these methods match closely. The D_{50} has been chosen as the value used for further analyses (Figure 4).

Figure 3: Film Thickness Measurement by 3 Different Methods for CPM-SR-1



Predicting Dissolution Using Film Thickness Measurement

As a number of factors affect dissolution beyond functional coating thickness, it is necessary to build a model for prediction based on the particle size growth and film thickness measured by in-line/off-line measurement (Table 2) and predicted by the MDD tool (Figure 5). 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 is then used to predict the dissolution results for the samples taken from CPM-SR-1. Whilst more data would ideally be used to build a more robust prediction mechanism, this approach is considered sufficient to demonstrate proof of concept.

Figure 4: Film Thickness Measurement for CPM-EC as a Function of Predicted WG %

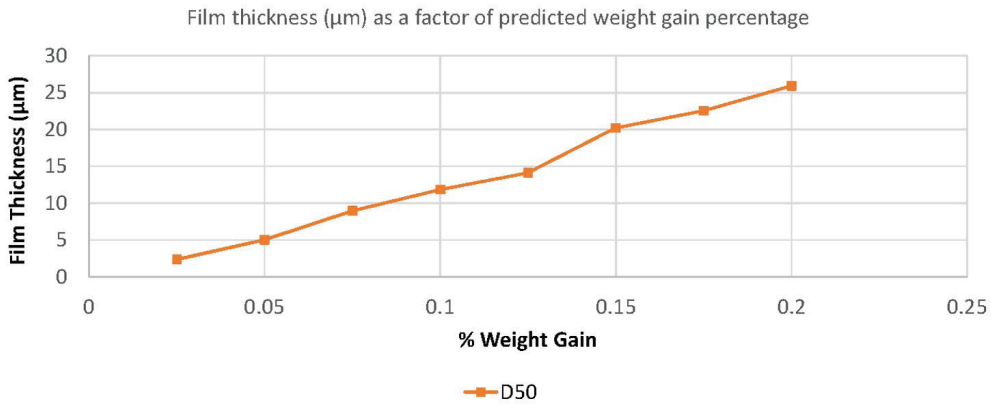


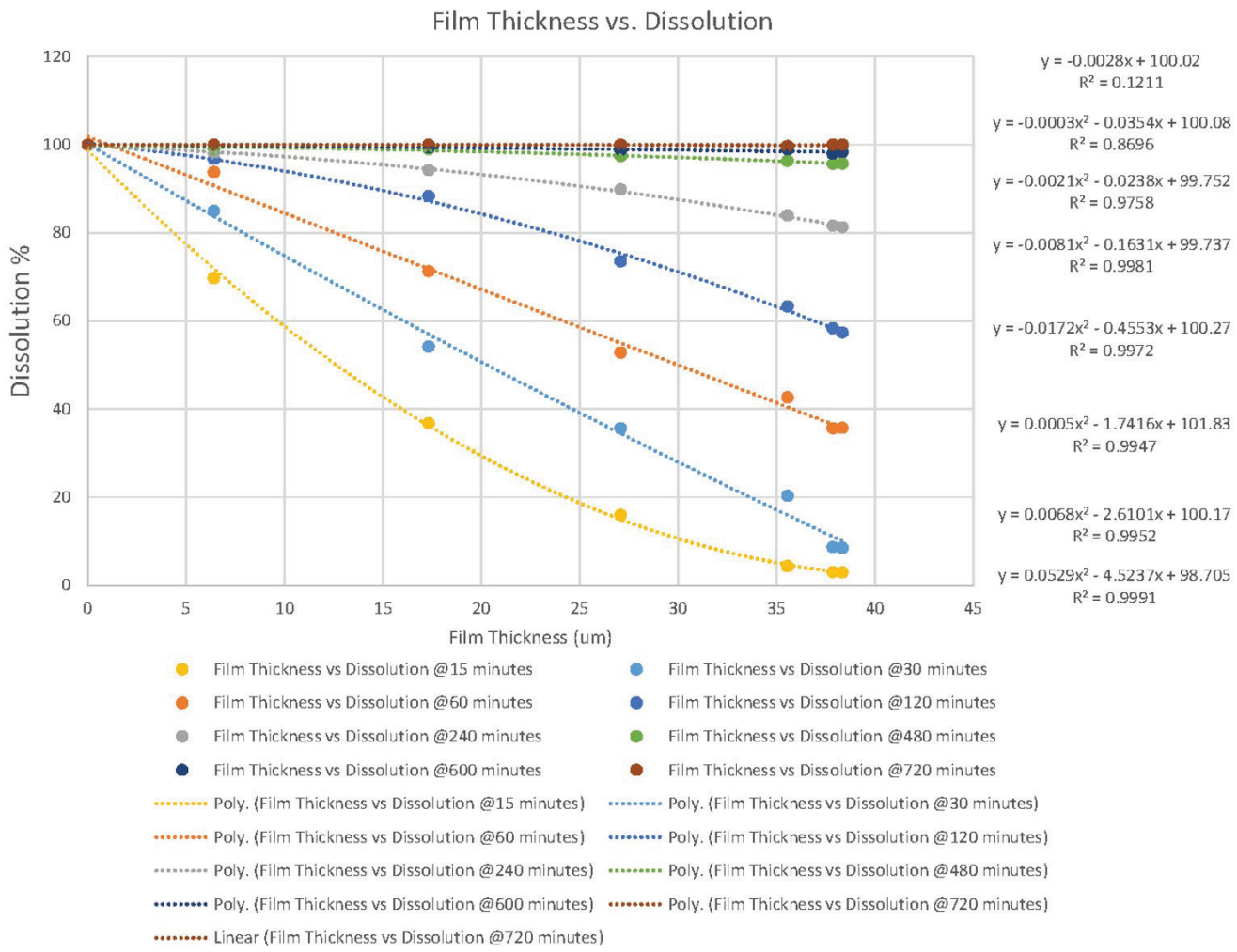
Figure 5: Film Thickness Measurement of CPM-SR-1 using MDD tool

Table 2: Film Thickness Comparison between Camsizer, Eyecon2 and My Dosage Design Tool of CPM-SR-1

Weight Gain	Eyecon$_2$ Film Thickness (µm)	Camsizer Film Thickness (µm)	MDD Tool Film Calculated Thickness (µm)
CPM-SR 5%	6.4	9	11.6
CPM-SR-1 10%	17.3	20	22.7
CPM-SR-1 15%	27.8	32	33.4
CPM-SR-1 20%	40.5	42	43.6

To build a predictive model from CPM-SR-1 the film thickness at each sample point was first calculated as in Figure 3. This was then plotted against the dissolution results and divided into data sets for each dissolution sampling time-point. Figure 6 shows the result of this process.

Figure 6: Film Thickness Vs % Dissolution at Different Time Points for CPM-SR-1



The equations of the best-fit polynomials shown in Figure 6 effectively form the basis of predicting dissolution performance, based on an experimentally determined film thickness. For each given thickness, an equation exists to describe the expected dissolution percentage for each time point measured in CPM-SR-1.

For CPM-SR-2 the measured film thicknesses for each sample point is substituted into the polynomial equations, producing the data shown in Table 3. Data from any point in the coating process could be used for this step, enabling dissolution to be predicted for any time point, but only sample points can be compared to off-line results for validation of the method, so those points are used here.

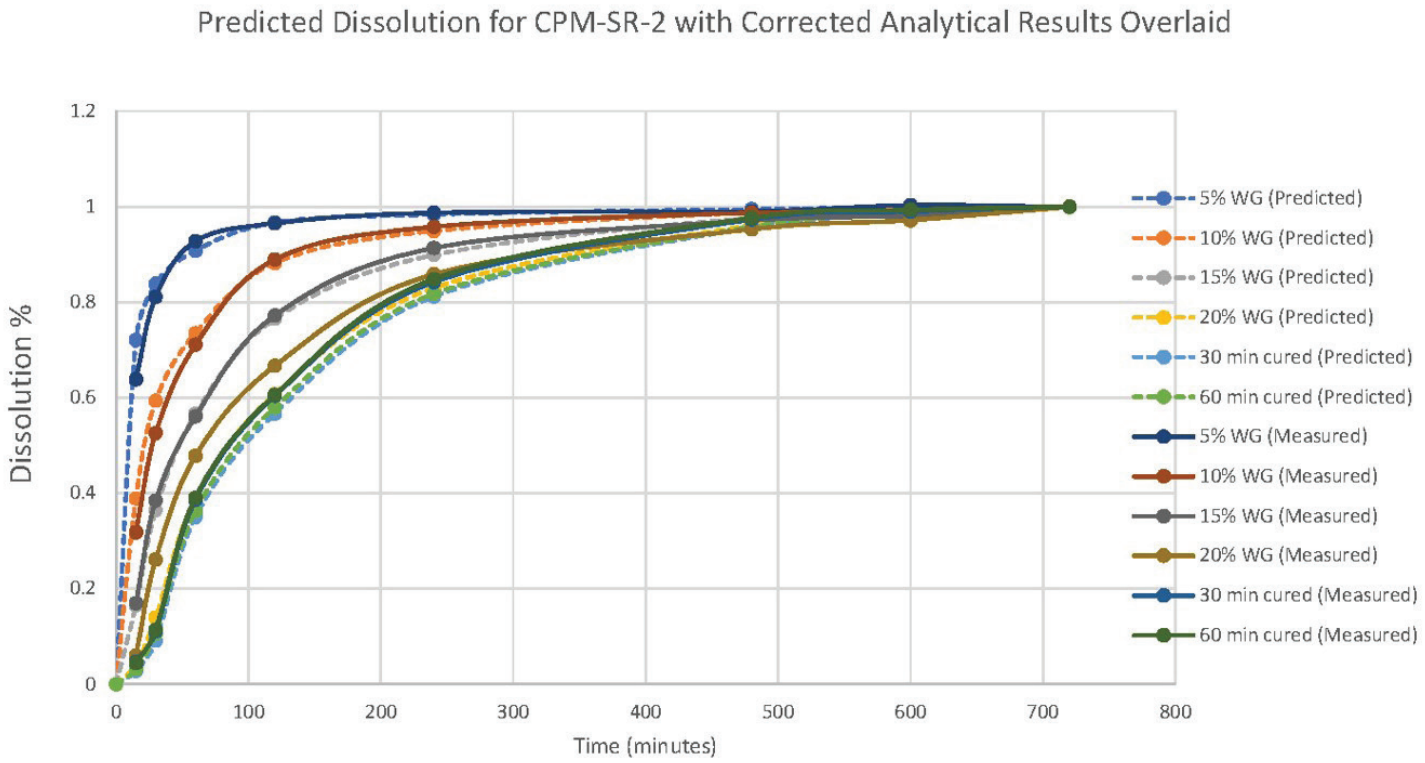
This data predicts the dissolution curves shown in Figure 7. Figure 7 overlays the analytical measured dissolution data, denoted (A), with the predicted (P) dissolution performance. From this graph, we can draw a conclusion as to the success of the experiments.

Table 3: Predicted Dissolution of CPM-SR-2 Based on CPM-SR-1 Film Thickness Value

SR2		Predicted Dissolution at (mins)								
Sample Point	Film Thickness (µm)	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%

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 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 7: Predicted (P) vs Analytical (A) Dissolution of CPM-SR-2



Conclusions

Suglets, sugar spheres, were drug layered with chlorpheniramine maleate, then coated with Surelease:Opadry (80:20) and Opadry EC functional coatings in a Glatt GPCG-2 lab-scale fluid bed system to obtain modified release characteristics. Particle size measurement was performed using an Innopharma Technology Eyecon$_2$ (in-line) and Camsizer (off-line) particle analyzer. Particle size growth was predicted by My Dosage Design tool. This study demonstrates the feasibility of predicting dissolution drug release profiles on multiparticulates in a Wurster coating process, using in-line measured coating thickness derived from the growth in the material particle size distribution and theoretical based film thickness calculator, My Dosage Design™.

References

1. G Labella, J Hansell, S Vass, “Why Choose Small Sugar Spheres?” Controlled Release Society Annual Meeting, 2016.
2. P Patel, E Godek, C O’Callaghan, “Real-Time Prediction of Polymer-Coated Multiparticulate Dissolution using Process Analytical Technology,” IFPAC 2016.

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