Effect of Surelease® Coating Conditions and Seal-coat on a Highly Soluble, Cationic Drug

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Purpose

This work studies the impact of coating process parameters, using Surelease®, Ethylcellulose Dispersion Type B NF and a seal-coat on the drug release rate of a highly soluble, cationic drug, metformin HCl. This study addresses the claims made by Zou et al that the ammonia contained in Surelease interacts with cationic drugs causing a reduction in dissolution rate.[1]

Methods

Drug loaded sugar spheres were prepared in a Huttlin Unilab fluid bed. A 6 kg batch of 18/20 mesh Suglets®, sugar spheres were layered with a dispersion of 70% metformin HCl and 30% Opadry® film coating system, 02A clear prepared to a 20% w/w solids level. A 40% weight gain (WG) was applied yielding a batch of 8.4 kg and a drug concentration of 20.0%. This batch was divided into 1.2 kg batches that were then subsequently coated in Glatt GPCG-3 (fitted with a 7" Wurster insert). Two batches were first seal-coated with Opadry 02A Clear, prepared at an 8% solids level, to create a barrier between the drug and the Surelease coating. A 20% WG of the seal-coating was applied. All seven batches were coated with Surelease E-7-19040 to a 20% WG; two batches with seal-coat and five without. The theoretical assay of the five batches without seal-coat were 16.7% drug and the two batches with seal-coat were 13.9% drug.

Process parameters were varied for the Surelease coatings, Table 1. A target process was established with a product bed temperature of 45ºC with an inlet temperature of 60ºC, resulting in a spray rate of 10 g/min. After coating the batches were divided, with one half oven cured at 60ºC for 24 hours. Samples from batches were tested for particle size at each stage of the process using a Camsizer P4 dynamic image analyzer to understand the growth of the beads at each process stage. All samples were tested for assay and dissolution using USP apparatus I, at 100 rpm in purified water for 18 hours.

Table 1. Process Parameters

Batch	Seal-coat	Product Temp (°C)	Inlet Temp (°C)	Spray Rate (g/ min)	Process Description
MF2	None	45	60	10	Target
MF3	None	40	55	10	Cold/ Wet
MF4	None	40	60	15	Cold/ Wet
MF5	None	50	65	10	Hot/ Dry
MF6	None	50	60	5	Hot/ Dry
MF7	Yes	45	60	10	Target
MF8	Yes	40	60	15	Cold/ Wet

Results

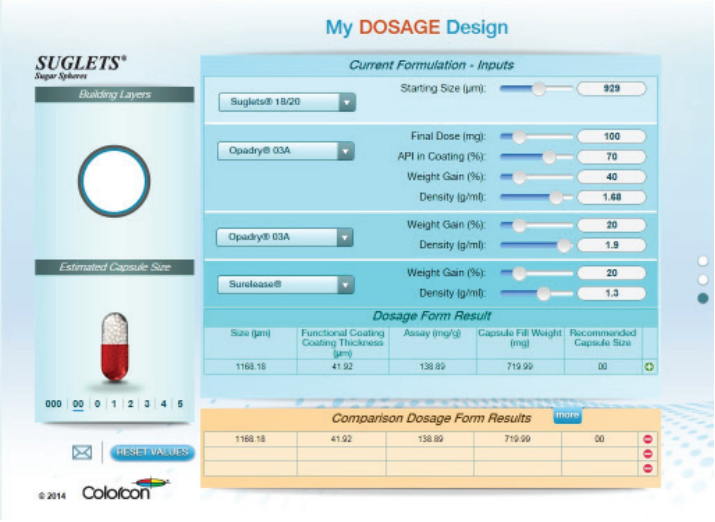
Camsizer results are summarized in Table 2. *My Dosage Design*™, a multiparticulate design calculator developed by Colorcon, was used to confirm the coating layers applied and the resulting thickness, Figure 1. This tool helps formulators understand the impact of substrate size and theoretical film thickness of an applied coating. Surface area to volume ratio can be studied when changing substrate size in order to maintain consistent dissolution with different size beads.[2]

Table 2. Camsizer Analysis from Various Stages of Processing

Batch Stage	D(0.1) (microns)	D(0.5) (microns)	D(0.9) (microns)	Sphericity	Span	Film Thickness (microns)
Suglets 18/20	863	929	981	0.971	0.127	NA
Drug Layered (MF1)	969	1030	1084	0.974	0.112	50.5
Seal-coated	1015	1083	1143	0.971	0.118	26.5
Surelease Coated (MF7)	1094	1169	1238	0.978	0.123	43.0

My Dosage Design™ prompts the user to select the starting bead size, allowing exploration of the theoretical range of sizes for a given product. The tool then allows the formulator to add the drug layer with variations for final dose, percent drug and percent weight gain to be applied to the starting bead and density of the layer. The remaining sections cover a seal-coat if applied and the final functional coat. Some standard Colorcon coating products can be selected or a custom system can be designated.

Figure 1. *My Dosage Design*™



The fluid bed process was satisfactory for all batches and irrespective of the coating layer applied, no agglomeration was seen in any batch. Attrition of the beads was not seen at any process stage. Following curing, some beads were lightly agglomerated but broke apart very easily. Dissolution of beads, without the barrier membrane coating, released 100% of the drug within 10 min. A slightly lower dissolution was seen for the batch with seal-coat at the 5 min time-point.

Dissolution from the uncured batches showed similar release profiles, extending release of the drug past 18 hours. Drug release for batches without the seal-coat were nearly identical, showing a range of f_2 values from 68 - 99. The two batches with the seal-coat showed slower drug release, but with a very similar profile; they showed an additional lag in release for the initial time points. This may be attributed to the talc in the seal-coat producing a more hydrophobic coating and delaying the drug release beneath the barrier membrane. The batches with seal-coat showed a range of f_2 values from 58 – 74, compared to batches without seal-coat. The release from the two seal-coated batches was very similar to each other with an f_2 value of 93.

Upon curing of the batches, some slight changes in drug release were seen. In the cold/ wet processes, the f_2 value between uncured and cured batches was lowest, 69 - 70. The batches processed at target or hot/ dry conditions showed less change upon curing, with higher f_2 values 85 - 93. Batches without seal-coat, processed at cold/ wet conditions, showed a slight slowing of the profile but only in the 1 - 7 h range. After the 7 h time point, release profiles did not change. Interestingly, when the seal-coat was applied and the process was cold/ wet, there was practically no change in dissolution, producing f_2 value of 98. Figures 2 to 8 show the drug release for each batch before and after curing.

Figure 2. Target Conditions, (Spray Rate 10g/ min, Product 45ºC, Inlet 60ºC)

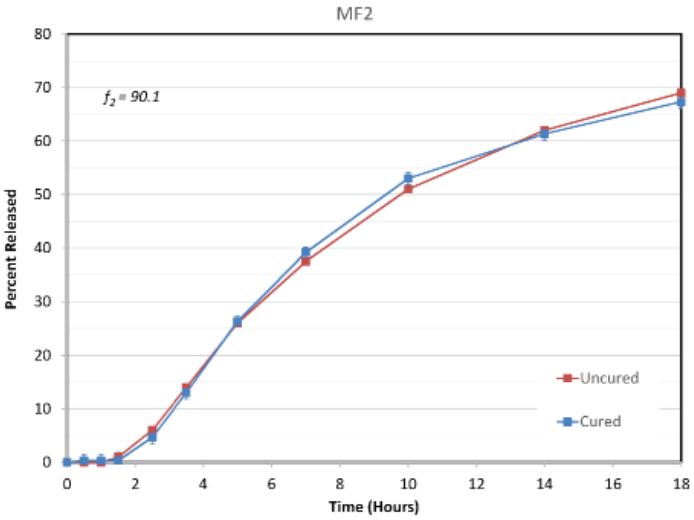


Figure 3. Cold/ Wet Conditions, (Spray Rate 10g/ min, Product 40ºC, Inlet 55ºC)

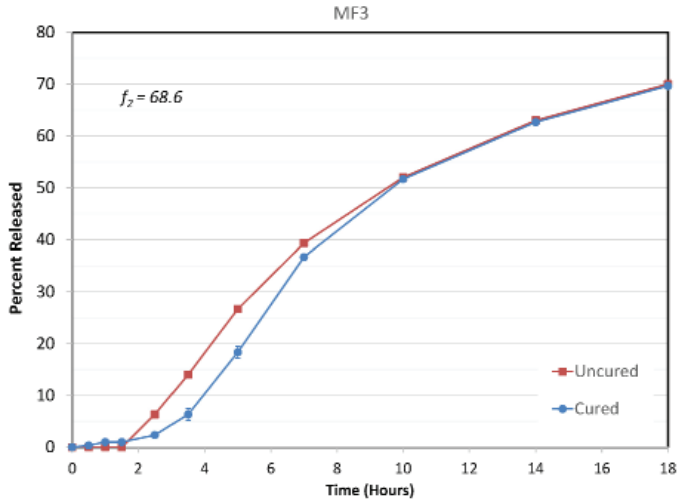


Figure 4. Cold/ Wet Conditions, (Spray Rate 15/ min, Product 40ºC, Inlet 60ºC)

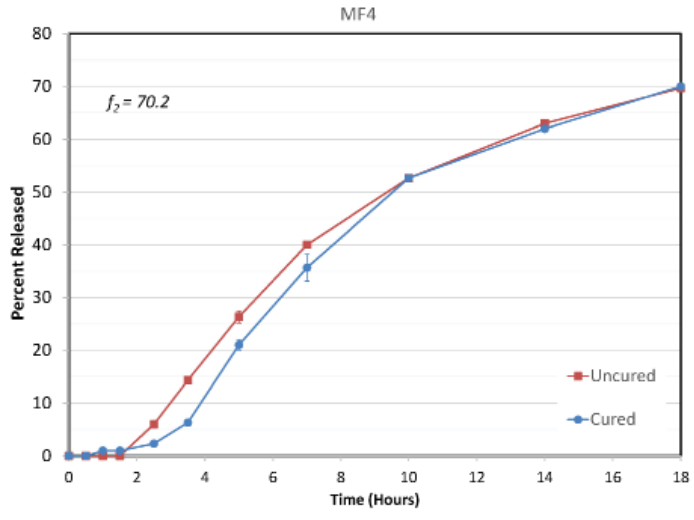


Figure 5. Hot/ Dry Conditions, (Spray Rate 10g/ min, Product 50ºC, Inlet 65ºC)

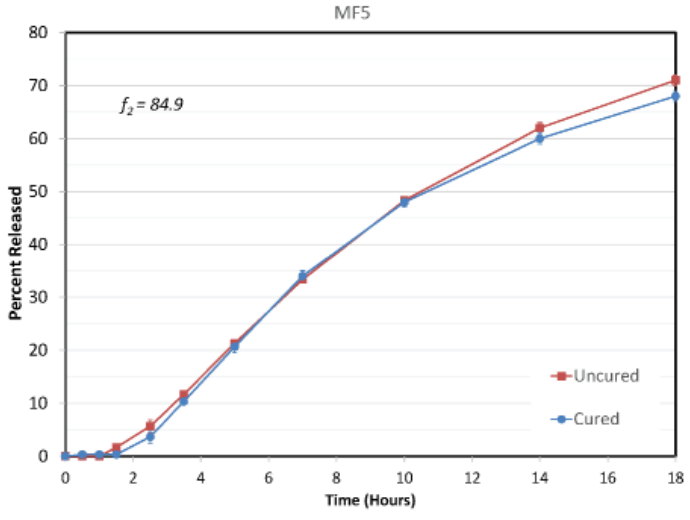


Figure 6. Hot/ Dry Conditions, (Spray Rate 5g/ min, Product 50ºC, Inlet 60ºC)

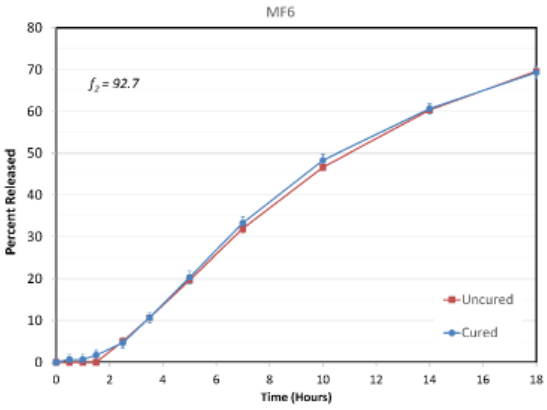


Figure 7. Seal-coat at Target Conditions, (Spray Rate 10g/ min, Product 45ºC, Inlet 60ºC)

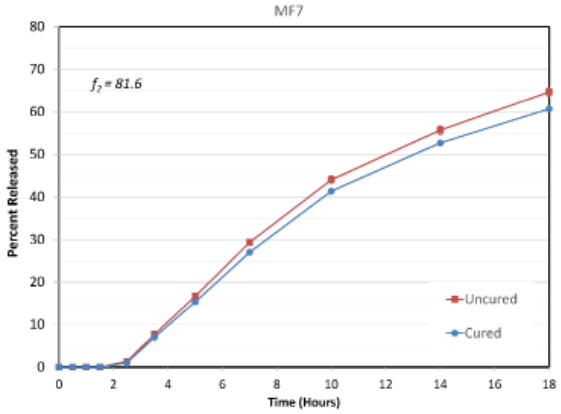
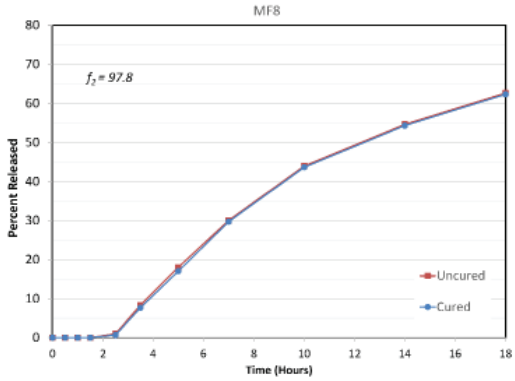


Figure 8. Seal-coat at Cold/ Wet Conditions, (Spray Rate 15g/ min, Product 40ºC, Inlet 60ºC



Conclusions

A robust process was developed using Surelease to produce a sustained drug release multiparticulate dosage for a highly soluble, cationic drug. No slowdown in dissolution was seen, even with cold and wet process conditions. No rupture of the barrier membrane was seen after curing of the beads. Issues reported by Zou et al[1] may have been due to inappropriate coating parameters and/or substrate and were not observed in this study. The results observed by Zou et al[1] may also be due to trapped ammonia in the film/substrate, forming a complex with the drug thereby affecting drug release profiles[3]. Processing of Surelease at target, or hot/dry conditions, resulted in consistent drug release profiles and unimpacted by curing. When processing in cold/wet conditions, coalescence of the film may not be fully complete and curing may be required. The lowest similarity value after curing, f_2=69, was seen in the batch without a seal-coat and with low inlet temperature. Seal-coating the beads after drug layering produced the highest similarity before and after curing, essentially eliminating the need to cure.

References

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2. LaBella G., Hansell J., Vass S., Why choose small spheres? Abstracts of Posters, Meeting of the Controlled Release Society, Seattle, WA, July 2016.
3. Sadeghi F., Ford J.L., Rubinstein M.H. and Rajabi-Siahboomi A.R., The influence of drug type on the release profiles from Surelease-coated pellets, Int. *J. Pharm.* (2003) 254, 123 – 135.

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