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Identification and Influence of Critical Coating Process Parameters on Drug Release from a Fully Formulated Aqueous Ethylcellulose Dispersion

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Introduction

Extended release (ER) of drugs using barrier membrane coated multi-particulate systems continues to grow in the market place. Ethylcellulose barrier membrane, applied organically or in the form of its aqueous dispersion, is the most popular used polymer for this application. The objective of this study was to identify and study the influence of critical film coating process parameters on drug release behavior and the output or response variables of that process.

Methodology

An aqueous ethylcellulose dispersion (Surelease® E-7-19050, Colorcon, USA) was applied on 18-20 mesh pellets drug layered with chlorpheniramine maleate (34 mgg-1) as a model drug. A two-level, full factorial, structured formal experimental design was developed using design of experiment (DoE) software. The effects of four coating process variables (inlet air temperature, atomizing air pressure, fluid delivery rate, and percent solids concentration) were investigated in a Glatt GPCG-3 fluid-bed equipped with a Wurster insert.

One non-numeric process related variable examined was post coating thermal (curing) treatment.

Table 1. Fluid-bed Coating Experimental Process Variables

Variable Name	Units	Range Low Level	Range High Level
Inlet Air Temperature	ºC	55	75
Spray rate	g min $^{-1}$	10	40
Atomizing Air Pressure	Bar	1	3
Surelease® Solids Content	%	10.0	22.5
Curing @ 60ºC	Hours	0	24

Table 1 shows the coating process ranges that were used to encompass typically recommended settings within the particular equipment utilized in this study. Other process coating variables were held constant.

Nineteen coating runs including three replicates, for purposes of determining experimental error, were carried out. A total batch weight of 2.5 kg drug layered pellets coated to a theoretical 10% weight gain was used in each coating trial.

Response variables examined were: product temperature, process air flow, process coating efficiency, agglomeration, and drug release.

Product temperature and process air flow response data were obtained from an average of recorded values obtained during each coating trial.

Dissolution testing was carried out for all coating trials to assess the effect of coating process conditions on drug release characteristics. Twelve-hour dissolution testing in a USP apparatus I (basket), distilled water at 37± 0.5 °C and 100 rpm was carried out for all samples. Additionally, samples were cured for 24 hours in an oven at 60°C and retested to study possible changes in drug release as a result of further coalescence of the latex coating.

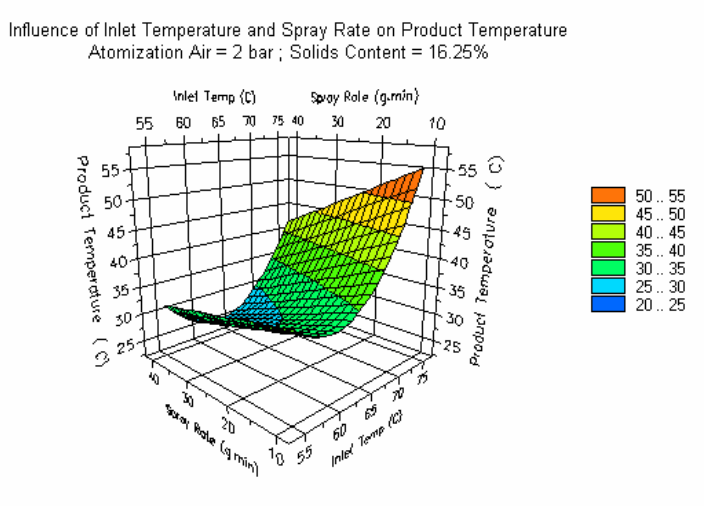
Dissolution profiles were compared using both time for fifty percent drug release (T_{50}) and a similarity factor (f_2).

Results and Discussions

Summary of Ranges in Values of Response Variables Obtained

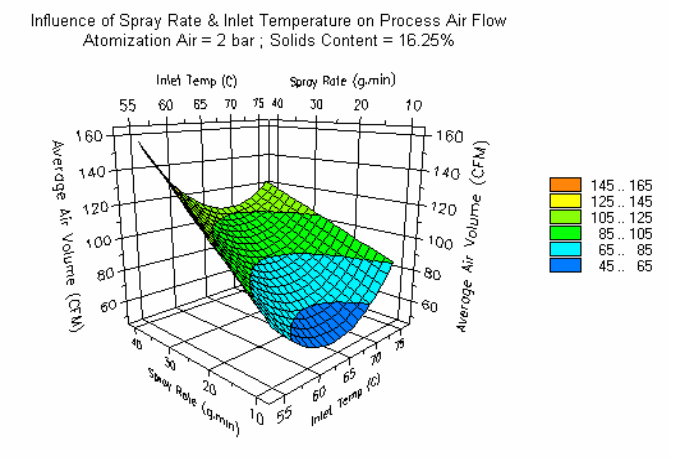
Response Variable	Units	Range
1. Product Temperature	°C	28-59
2. Process Air Flow	ft^3min^{-1}	67-174
3. Coating Process Efficiency	%	69.1-95.9
4. Agglomeration	%	0.0-16.0
5. Drug Release	% min^{-1}	59.9-97.4

Product Temperature



Product temperatures ranged from approximately 28°C – 59°C. Inlet air temperature and coating dispersion spray rate accounted for the majority of the effects on product temperature. Not surprisingly, an increase in process inlet temperature resulted in a higher product bed temperature. This response was greatest at lower coating dispersion spray rates.

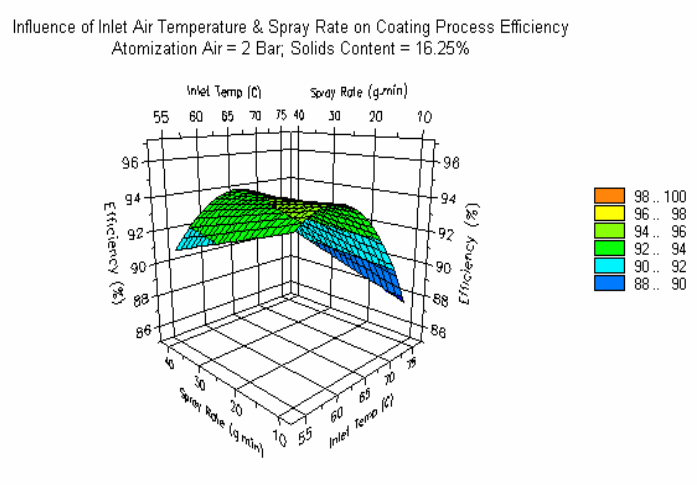
Process Air Flow



Depending on the process conditions employed, process air flow had to be adjusted to maintain a constant fluidizing pattern.

All processing conditions had some noticeable effect on process air flow. The major factor creating the need to adjust process air flow was the relative wetness of the product, and thus was impacted the greatest at high spray rates, spraying the coating suspension in its most dilute form, and employing the lowest atomizing air pressures.

Process Coating Efficiency

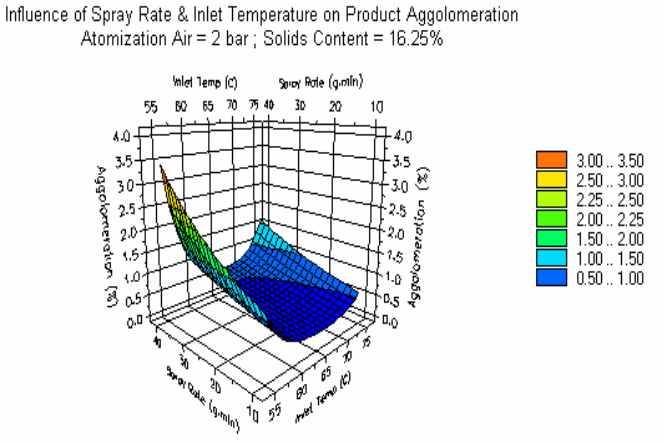


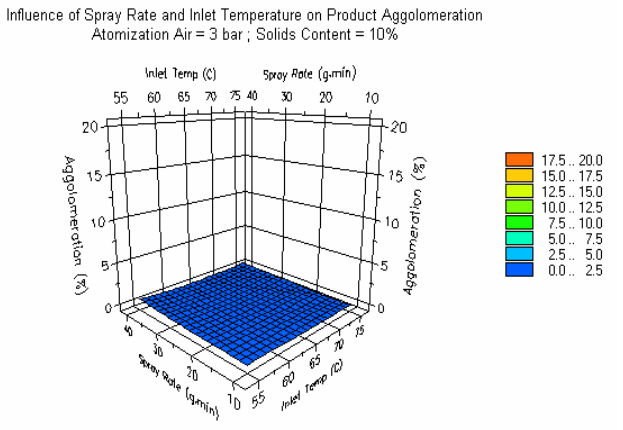
Coating process efficiencies in excess of 90% were obtained.

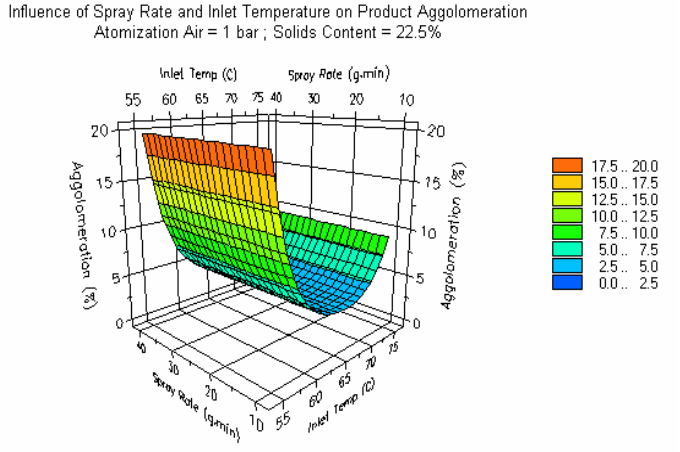
Virtually all the process variables examined in this study had an impact on process efficiency, and to a similar extent. The highest process efficiencies were achieved at a combination of the lowest inlet temperatures and slowest spray rates. As expected, increasing inlet temperature and decreasing spray rate resulted in lower process efficiency due to spray drying and attrition.

It must be noted that some of the trials with the highest efficiencies also were prone to agglomeration of the beads.

Agglomeration





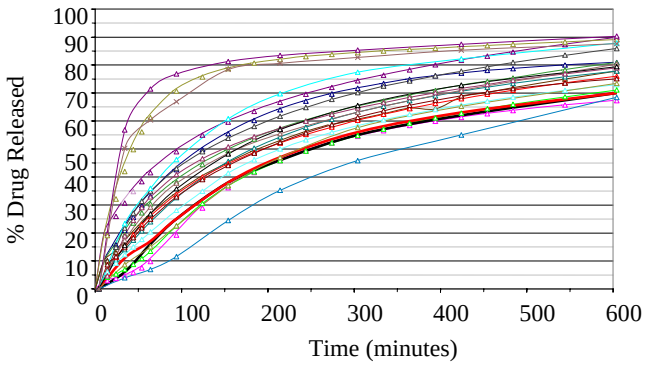


Both low atomization air pressure and high dispersion solids content were the main cause of agglomeration. Product agglomeration was worst at low atomization air pressures and high solids content. This may be due to larger dispersion droplet size caused by low air: liquid ratios and higher viscosity.

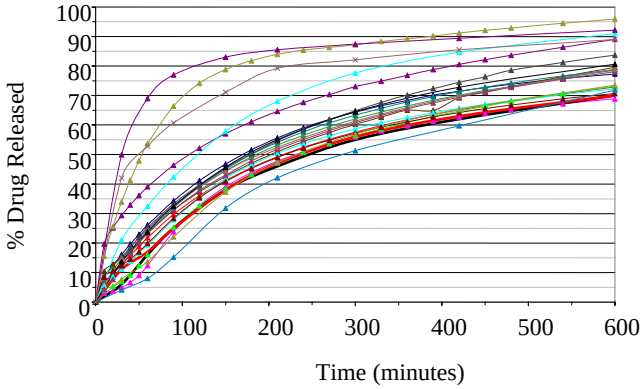
Product agglomeration could be minimized by coating at both moderate atomization air pressures and solids content.

Drug Release Characteristics

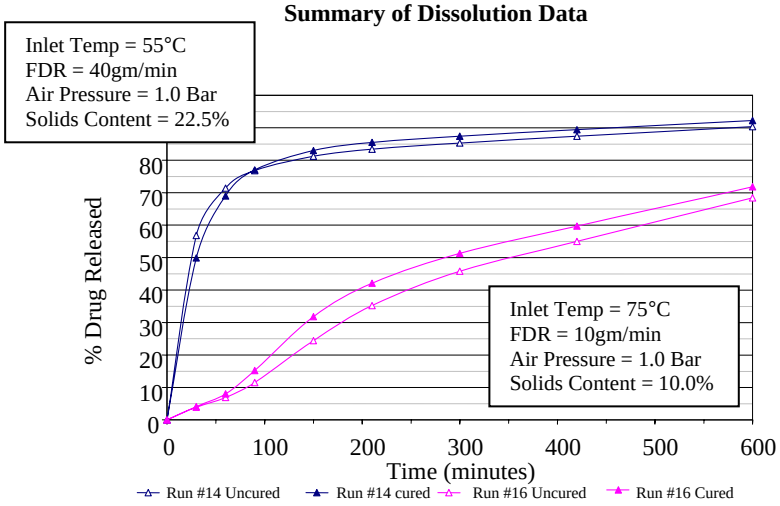
Summary of Dissolution Data for All Runs *(Uncured)*



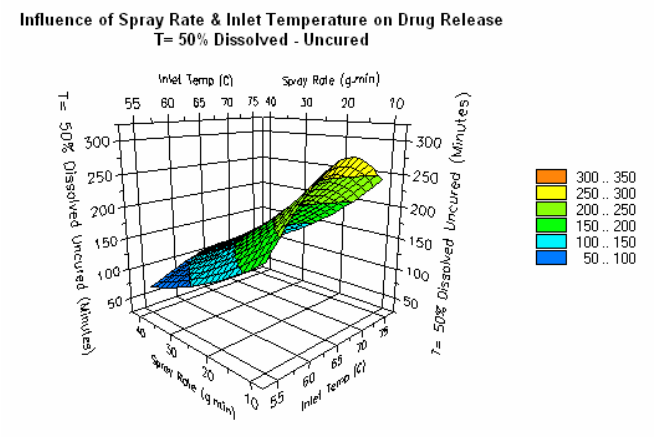
Summary of Dissolution Data for All Runs *(Cured)*

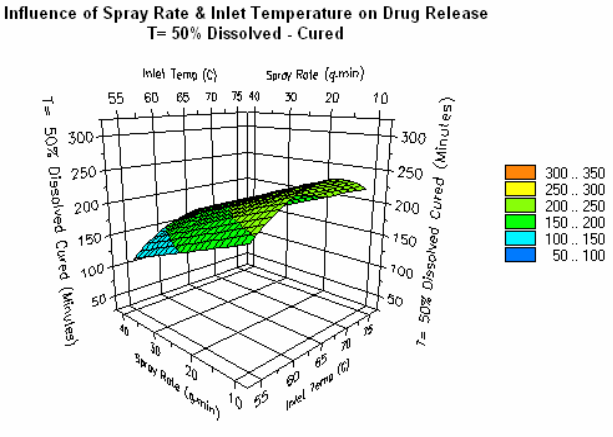


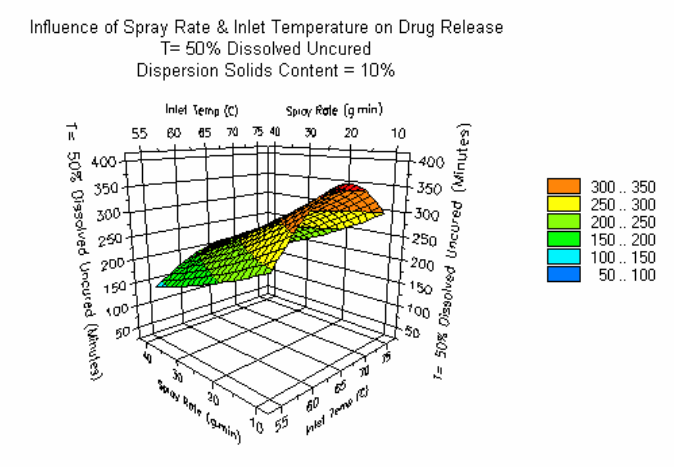
Fastest Drug Release versus Slowest Drug Release
Summary of Dissolution Data

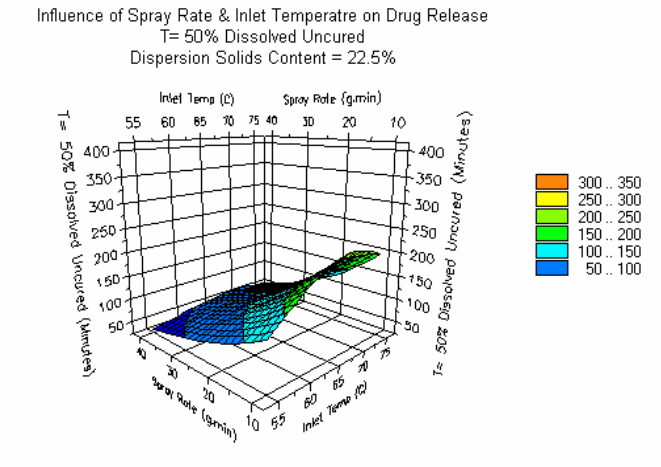


Drug Release (T_{50}) Versus Process Conditions







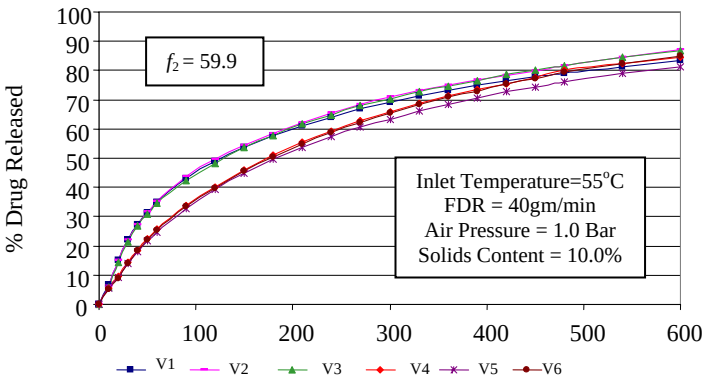


While all process conditions demonstrated some effect on drug release, dispersion solids content & dispersion application rate had the greatest effects, as shown above.

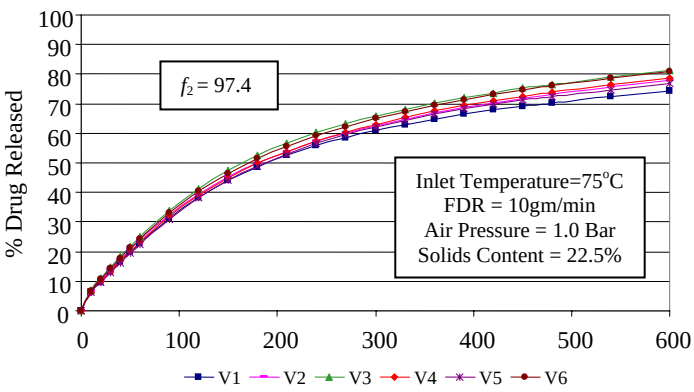
Application of the dispersion at higher spray rates or lower solids content resulted in faster drug release. This is presumably due to migration of the drug during the coating process.

Comparison of highest and lowest f_2 values obtained in DoE.

Design of Experiments - Run #8



Design of Experiments - Run #6



A comparison of highest and lowest f_2 values obtained for all coating trials and their processing conditions is illustrated above.

In spite of the illustrated effect of process conditions on drug release rates between runs, curing effects were not evident. (V1 - V3 Uncured, V4 - V6 Cured)

Conclusions

Within the scope of this study, a broad range of results was obtained, illustrating the usefulness of DoE in identification and optimization of critical coating process parameters.

While a broad range of f_2 values were obtained, the results indicate that curing did not have a significant effect on drug release. However coating process conditions, particularly dispersion solids content and application rate, did have an effect on drug release.

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