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EXTENDED-RELEASE VENLAFAXINE PELLETS: SCALING UP THE COATING PROCESS

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INTRODUCTION

This study was undertaken to investigate the influence of coating process scale when applying an organic solvent based modified release coating to multiparticulates using a Wurster process. In addition, the intent was to investigate potential changes that occur in film structure on process scale up, and thus might ultimately influence drug release rates, as the result of the presence of a water soluble pore forming polymer that has previously been considered to undergo phase separation as the coating dries [(1)].

METHODS

Multiparticulates containing venlafaxine HCL were prepared using a fluid-bed drug-layering process. These drug-loaded pellets were subsequently film coated using a modified-release coating system, based on ethylcellulose (Aqualon™ N50 EC), and applied from a hydro alcoholic solvent (90:10 ethanol/water), using a Wurster process. In some cases, the only polymer used was ethylcellulose, and in others, the coating formulation also contained hydroxypropylcellulose (Klucel EF HPC) (EC/HPC ratio 3.5:1) as a pore forming agent. Coating process studies were conducted using a MiniGlatt, a GEA MP1, and a Vector VFC 30MX fluid bed coater, each fitted with a Wurster insert. The coating process conditions used are summarized in Table 1. In each case, the target weight gain was 12.5%, with samples being removed for testing at intermediate weight gains of 7.5 and 10.0 % respectively.

	Trial 1	Trial 2	Trial 3
Coating Equipment	Mini-Glatt	GEA MP-1	Vector VFC 30MX
Batch Weight (kg), Seal Coated, Drug Loaded, Pellets	0.25	3.0	22.0
Solid Content of Coating Soln. (% w/w)	10.0	10.0	10.0
Target Weight Gain (% w/w)	12.5	12.5	12.5
Process Airflow ($m^3 h^{-1}$)	26-27	45.0	1360.0
Spray Rate (g min^{-1})	2.5	15.8	232.2
Atomization Air Pressure (bar)	1.5	1.2	3.0
Inlet Temperature (°C)	37	48.3	44.2
Bed Temperature (°C)	26	30.4	32.1
Exhaust Temperature (°C)	-	32.1	31.7
Coating Process Time (min)	105	160	170

Table 1 Coating Process Conditions Used for Extended-release Coating

Previously [(2)], various pore-forming agents had been evaluated in extended-release coatings based on ethylcellulose (EC), with typical results obtained shown in Figure 1. In the present study, hydroxypropylcellulose (HPC) was chosen as the pore-forming agent because of its potential ability, as a result of phase-separation characteristics in ethylcellulose coatings, to create discrete pores, as depicted in the photomicrographs shown in Figure 2 (dried coatings soaked in water for two hours), and the suggestion previously reported [(1)] that phase separation, and thus pore size, may well be influenced by the drying rate achieved in the coating process.

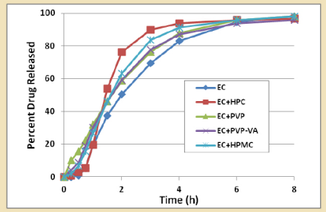
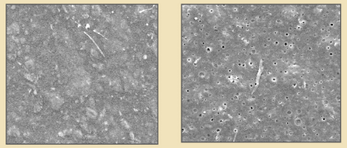


Figure 1 Influence of Pore-forming Agents (EC-PFA Ratio 3.5:1) on Drug Release from Venlafaxine Pellets Coated with Ethylcellulose Coatings (10% weight gain)



1. EC Only **2. EC + HPC (3.5:1)**

Figure 2 Influence of Pore-forming Agents on the Structure of Ethylcellulose Films

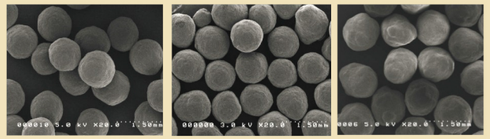
Coated pellets were subjected to dissolution testing using USP Apparatus 1, with DI water as the dissolution medium.
The structure of the coating in each case, obtained from coated pellets, at the conclusion of the coating process and after soaking in DI water for up to 2 hours, was examined using scanning electron microscopy.

RESULTS AND DISCUSSION

The photomicrographs shown in Figure 3 are taken from typical coated pellets sampled at the conclusion of each coating trial. No evidence of potential coating defects was observed.

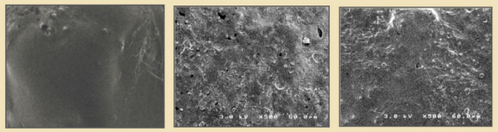
The photomicrographs shown in Figure 4 were prepared from samples of coated pellets, where the coating contained a pore former, and had been subjected to a two-hour soak test.

Although by no means clear-cut, the photomicrographs in Figure 4 provide some evidence that the pore structure obtained with pellets prepared using either the GEA MP-1 of the Vector VFC 30MX process was different from that for pellets coated using the Mini-Glatt process.



A. Mini-Glatt **B. GEA MP-1** **C. Vector VFC 30MX**

Figure 3 Photomicrographs of Coated Venlafaxine Pellets



A. Mini-Glatt **B. GEA MP-1** **C. Vector VFC 30MX**

Figure 4 Photomicrographs of Coated Venlafaxine Pellets (With Pore Former and After Soak Test)

Dissolution Results: Ultimately, coating weight gain targets for the scale-up coating trials were based on dissolution data obtained initially from coating trials performed using the Mini-Glatt. Typical dissolution results obtained for these small-scale trials are shown in Figures 5 and 6.

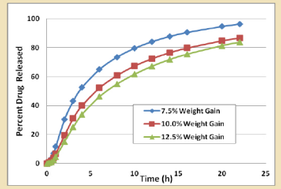


Figure 5 Initial Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC Coating (No Pore Former) Using the Mini-Glatt

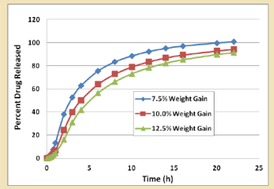


Figure 6 Initial Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC + HPC (3.5:1 Polymer Ratio) Coating Using the Mini-Glatt

On the basis of these data, it was decided to use the 7.5% coating level for all subsequent data comparisons between the different processing scales, because this coating level achieved approximately 100% drug release (albeit after 22 hours).

The data shown in Figure 7 are the dissolution results obtained for venlafaxine pellets coated (7.5 % w/w coating) with an EC coating (no pore former) at each processing scale Similarly, the data shown in Figure 8 illustrate the results when a pore forming agent, HPC, was included at an EC:HPC ratio of 3.5:1.

In the absence of a pore-forming agent (HPC), the data are remarkably consistent for pellets coated at all three processing scales. Using the data obtained for the Mini-Glatt coating trials as the reference, the profiles for the GEA MP-1 and Vector VFC 30MX had F_2 values of 68 and 72 respectively, confirming the similarity in dissolution profiles. The slightly slower drug-release profiles for pellets coated on the lab (GEA MP-1) and pilot (Vector VFC 30MX) processing scales, compared with those produced on the Mini-Glatt, are consistent with the common observation that process efficiency can often improve when scaling up multiparticulate fluid-bed coating processes, thus leading to the deposition of slightly higher amounts of coating material.

In contrast, when the HPC pore-forming agent is present, there are observable differences in the drug-release profiles obtained, with release rates being faster for pellets coated on both the lab (GEA MP-1) and pilot (Vector VFC 30MX) equipment. Again using the data from the Mini-Glatt coating trials as the reference, the profiles for the GEA MP-1 and Vector VFC 30MX had F_2 values of 37 and 49 respectively, confirming the lack of statistical similarity.

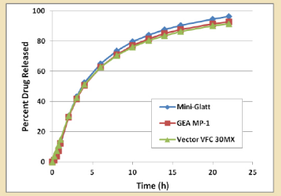


Figure 7 Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC Coating (No Pore Former)

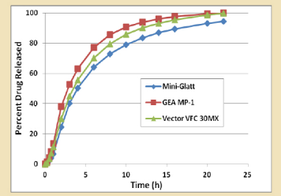


Figure 8 Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC Coating Containing a Pore Former (EC:HPC ratio 3.5:1)

Although the photomicrographs shown in Figure 4 (taken after a two-hour soak test) are far from conclusive, there is some evidence to suggest that pellets coated on the two larger processing scales possess more visible pores than those coated on the Mini-Glatt, a result that is consistent with the likelihood that the drying conditions achieved on these two larger-scale processes produced different extents of phase separation, resulting in larger pores and, thus, faster drug-release rates.

CONCLUSIONS

The results obtained in this study confirm that consistent results (in terms of drug release) can be obtained when scaling up fluid-bed coating processes involving the application of plain ethylcellulose modified-release film coatings.
However, the data presented also confirm that the level of complexity, in terms of impact of coating process conditions on ultimate coating structure, increases when water-soluble pore-forming polymers are included in the coating formulation. As a result, it is clear that further studies are required to achieve appropriate optimization of the coating process so that consistent drug release rates can be achieved on all processing scales.

BIBLIOGRAPHY

(1)"Effect of the manufacturing conditions on the structure and permeability of polymer films intended for coating undergoing phase separation," Marucci, et al, Eur. J. Pharm. & Biopharm., 83 (2013), pp 301-306
(2) "Controlled-Release Multi-Unit Pellets (MUPS) Tablets: Effect of Coating & Cushioning Agents." Pinto, et al, Poster T2164 presented at AAPS Annual Conference, San Antonio, TX (Nov 2013)