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Extended-release Venlafaxine Pellets: Scaling Up the Coating Process

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Introduction

This study investigated the influence of coating process scale when applying an organic solvent–based modified-release coating to multiparticulates using a Wurster process. In addition, the study investigated potential changes in film structure on process scale up that might ultimately influence drug-release rates. These potential changes result from the presence of a water-soluble pore-forming polymer that undergoes phase separation as the coating dries [1].

Methods

Multiparticulates containing venlafaxine HCl were prepared using a fluid-bed drug-layering process. Venlafaxine is an antidepressant. These drug-loaded pellets were subsequently film coated using a modified-release coating system, based on Aqualon™ N50 ethylcellulose (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 Klucel™ EF hydroxypropylcellulose (HPC) as a pore-forming agent, in an EC:HPC ratio of 3.5:1. Coating process studies were conducted using MiniGlatt, GEA MP-1 and Vector VFC 30MX fluid-bed coaters, 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 %.

Table 1. Coating Process Conditions Used for Extended-release Coating

Parameter	Mini-Glatt	GEA MP-1	Vector VFC 30MX
Batch Weight (kg), Seal Coated, Drug Loaded Pellets	0.25	3	22
Solid Content of Coating Solution (% w/w)	10	10	10
Target Weight Gain (% w/w)	12.5	12.5	12.5
Process Airflow ($m^3\ h^{-1}$)	26–27	45	1360
Spray Rate (g min^{-1})	2.5	15.8	232.2
Atomization Air Pressure (bar)	1.5	1.2	3
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

Previously [2], various pore-forming agents were evaluated in extended-release coatings based on ethylcellulose (Aqualon N50 EC), with typical results shown in Figure 1. In the present study, hydroxypropylcellulose (HPC) was chosen as the pore-forming agent because of its potential ability to

Note: This work was presented at the annual meeting of the American Association of Pharmaceutical Scientists, October 25–29, 2015, Orlando, Florida.

create discrete pores as a result of phase-separation characteristics when added to ethylcellulose coatings, as depicted in the photomicrographs in Figure 2 (dried coatings soaked in water for two hours). It had been suggested previously [1] that phase separation and, thus, pore size, may be influenced by coating drying rate.

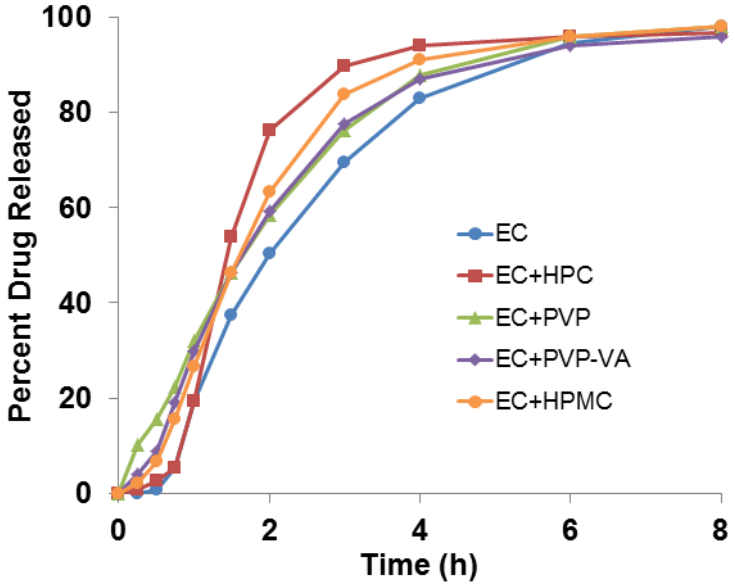
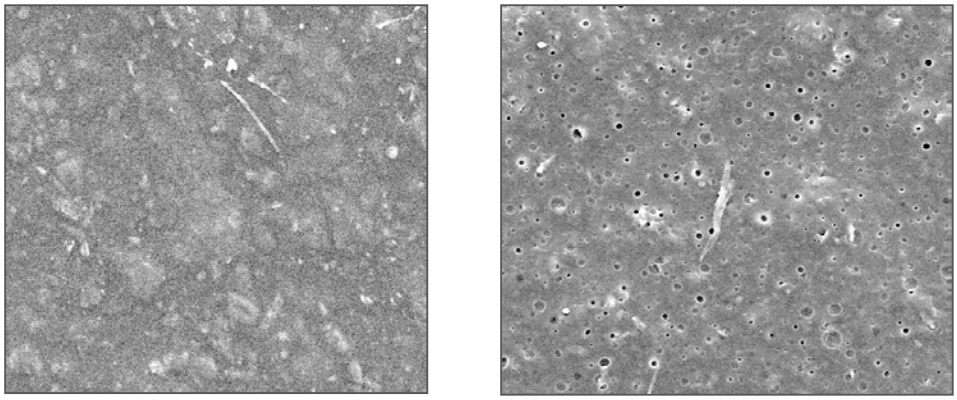


Figure 1. Influence of Pore-forming Agents (EC-PFA Ratio 3.5:1) on Drug Release from Venlafaxine Pellets Coated with Ethylcellulose Coatings (10% weight gain)



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

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

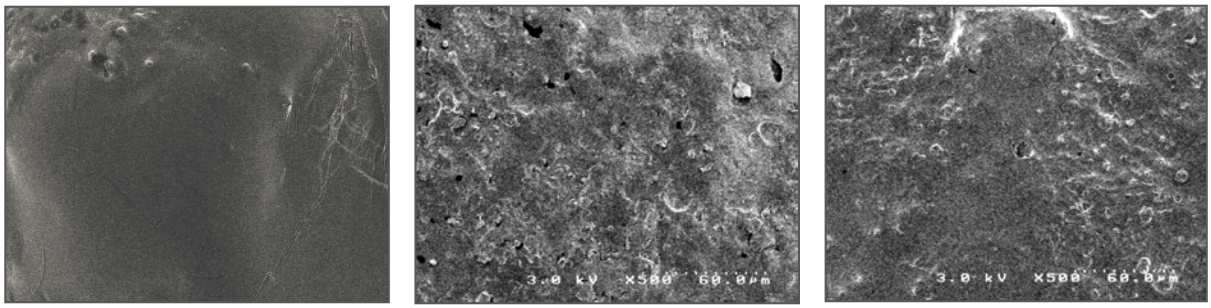
Coated pellets were subjected to dissolution testing using USP Apparatus I, with deionized (DI) water as the dissolution medium. The structure of the coating in each case, obtained from coated pellets at the conclusion of the process and after soaking in DI water for up to 2 hours, was examined using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

Results and Discussions

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

Mini-Glatt **GEA MP-1** **Vector VFC 30MX**

Figure 3. Photomicrographs of Coated Venlafaxine Pellets



Mini-Glatt **GEA MP-1** **Vector VFC 30MX**

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

Although by no means clear cut, these photomicrographs provide some evidence that the pore structure in pellets prepared using either the GEA MP-1 of the Vector VFC 30MX process was different from that in pellets coated using the Mini-Glatt process (where the presence of pores is not visually evident).

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

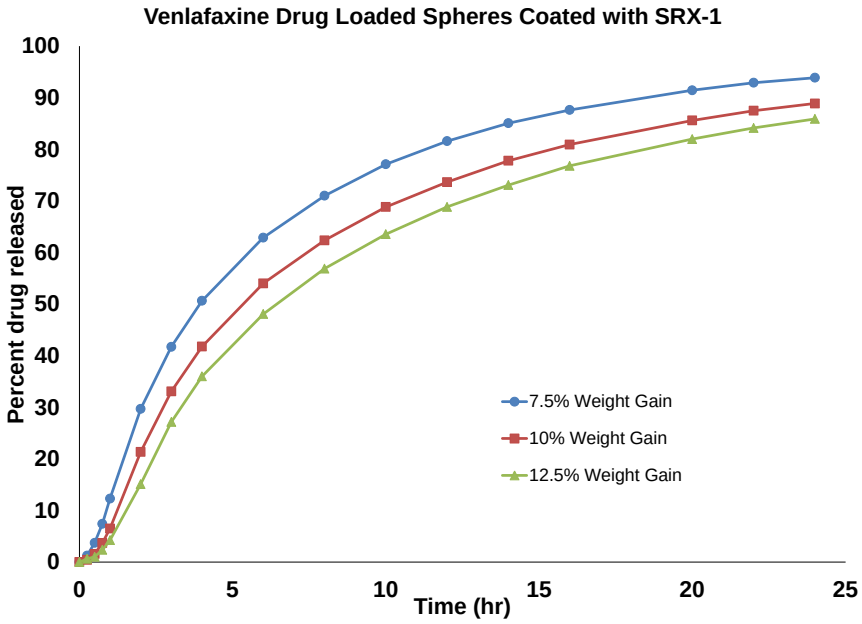


Figure 5. Initial Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC Coating (No Pore Former) Using the Mini-Glatt

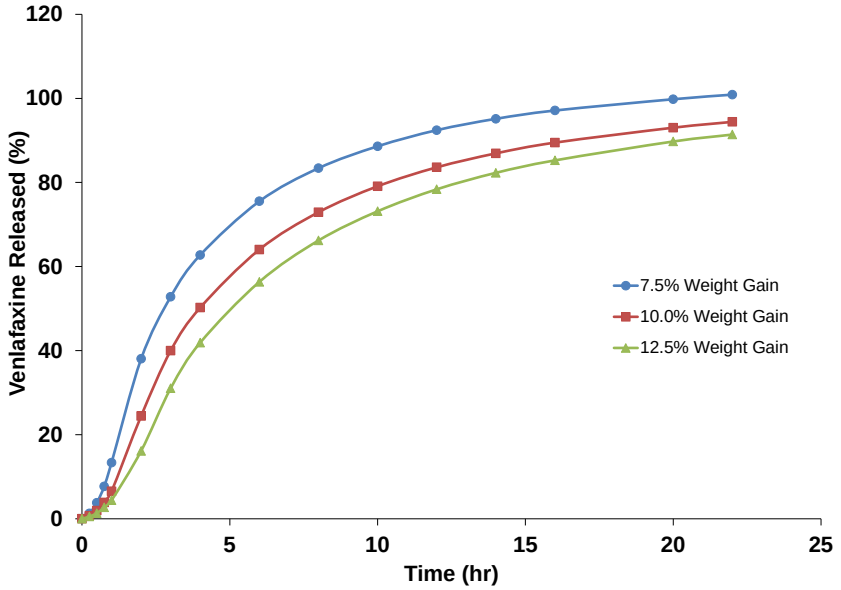


Figure 6. Initial Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC + HPC (3.5:1 Polymer Ratio) Coating Using the Mini-Glatt

On the basis of these data, the 7.5% weight gain level was chosen for all subsequent 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 at 7.5% weight gain with an EC coating (no pore former) at each of the processing scales. 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.

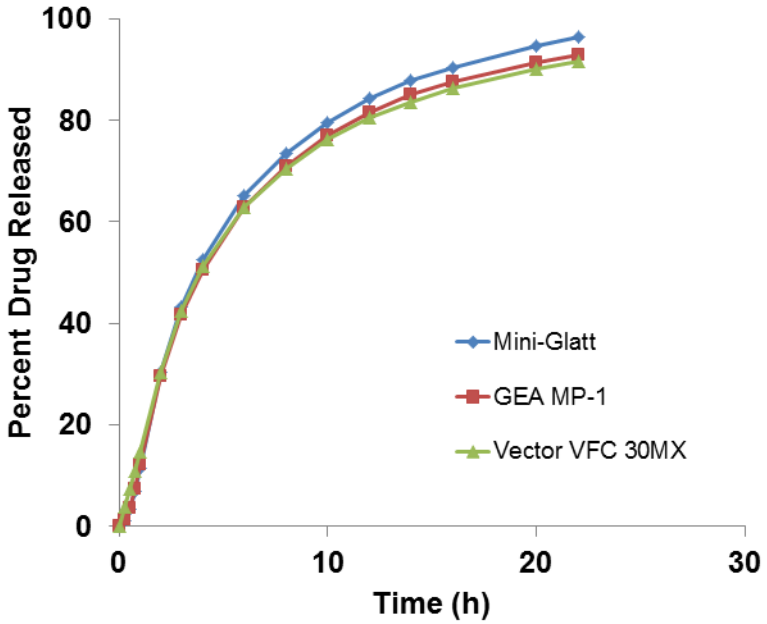


Figure 7. Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC Coating (No Pore Former) on Various Processing Scales

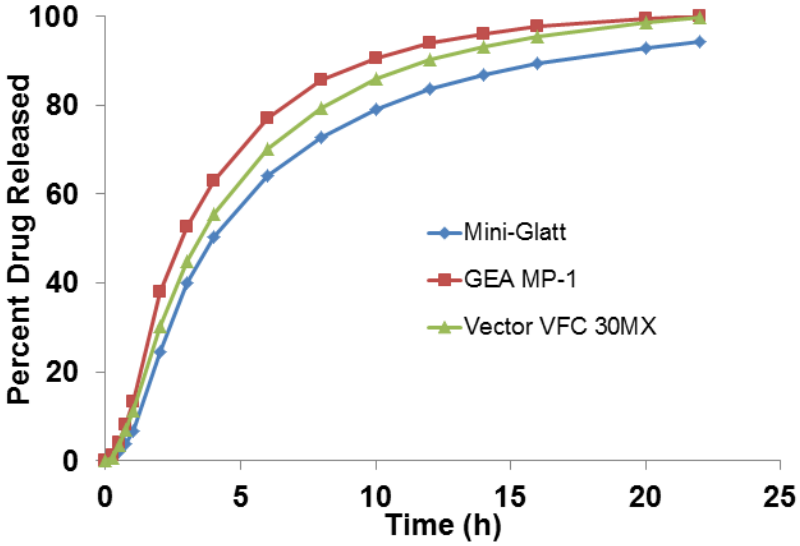


Figure 8 Dissolution Results Obtained When Coating Venlafaxine Pellets with an EC Coating Containing a Pore Former (EC:HPC ratio 3.5:1) on Various Processing Scales

In the absence of a pore-forming agent (in this case 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 f2 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. Release rates are faster for pellets coated on both the lab (GEA MP-1) and pilot (Vector VFC 30MX) scale 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 F2 values of 37 and 49, respectively, confirming the lack of statistical similarity.

The release profiles obtained from the Mini-Glatt are different from the two obtained at intermediate and large scale, as indicated by the calculated f2 values. The photomicrographs shown in Figure 4 provide some evidence that the pore diameters and quantity of pores in the coatings are larger for the pellets coated at larger scale, in contrast to those coated in the Mini-Glatt. A potential explanation may be the increased extent of phase separation, which can be caused by differences in coating process conditions that impact the drying rate of the applied coatings. This, in turn, can lead to differences in the degree of phase separation and the size of the hydrophilic domains (that ultimately create pores during dissolution testing).

Although the photomicrographs shown in Figure 4 (taken after a two-hour soak test) are far from conclusive, there is some evidence that pellets coated on the two larger processing scales possess more visible pores than those coated on the Mini-Glatt. This result is consistent with the likelihood that the process conditions on the two larger scale processes exhibited sufficient differences in drying conditions (compared with those achieved on the Mini-Glatt) that different extents of phase separation occurred as the coatings dried, leading to formation of larger pores with a consequent impact on drug release characteristics.

Conclusions

The results of 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. 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.

References

(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)