

PTR-103

Extended-release Venlafaxine Pellets: Influence of Coating Process Conditions

Stuart C. Porter, Bradley Beissner, Ron Hach and Kapish Karan

Introduction

Published data [1] suggest that coating process conditions can influence the structure of ethylcellulose (EC) coatings containing water-soluble pore-forming agents, which have been deposited from hydro-alcoholic solvent systems. Previous work indicated that differences in venlafaxine HCl release rates from pellets coated with such a coating formulation occur when applied on different processing scales. These differences may well be related to differences in process conditions at each scale, particularly those that may affect drying rate of the coating. This present work was intended to gain better insight into effects of process conditions on venlafaxine HCl release from pellets coated with an EC coating containing pore formers, and to identify processing conditions that might minimize differences in drug release rates when coating at different processing scales. Results obtained using a mini-Glatt Wurster coater (typically used for early product/process development) have been compared with those obtained using a GEA MP-1 machine fitted with a Wurster insert.

Methods

Pellets containing venlafaxine HCl were coated with an EC film coating (10% weight gain). Venlafaxine is an antidepressant. The coating contained hydroxypropylcellulose (HPC) as a pore former and was applied from a hydro-alcoholic solvent system, yielding a composite coated pellet (see Figure 1). Coatings were applied using GEA MP-1 fluid bed coater (see Figure 2) fitted with a Wurster column insert. A statistical design of experiments (D.o.E.) approach was used (see Figure 3 and Table 1). The D.o.E. approach (central composite design, employing 8 corner points, 6 axis points and one center point consisting of 6 replicates) involved examining the effect of process air volume, inlet temperature, and spray rate on ultimate drug release.

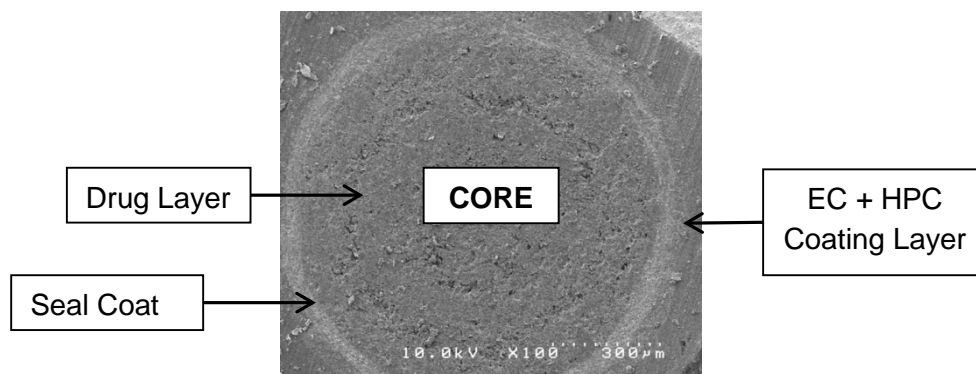
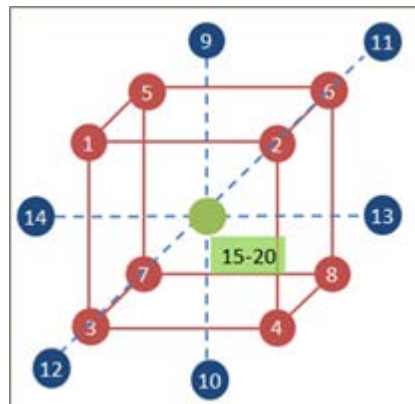


Figure 1. Structure of Coated Pellets

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



Figure 2. Set Up for GEA MP-1 Wurster Coater



- . 8 corner points (in red)
- . 6 axis points (in blue)
- . 1 central point with 6 replicates (in green)

Figure 3. Central Composite Plan of Experiments

Process Variable	Range Settings
Air Volume ($\text{m}^3 \text{h}^{-1}$)	35–55
Inlet Temperature ($^{\circ}\text{C}$)	35–55
Spray Rate (g min^{-1})	10–20

Table 1. Summary of Coating Process Conditions Used in GEA MP-1

All dissolution testing was carried out using USP Apparatus I, employing phosphate buffer, pH = 6.8 as the dissolution medium, and using a stirring speed of 100 rpm. In each case, all drug release results obtained were compared with those obtained using a Mini-Glatt fluid-bed coater (designated as the standard).

Results and Discussion

Previously [2], it had been shown that although drug release data for venlafaxine pellets coated with an EC coating without pore former showed good correlation between data obtained from a Mini-Glatt fluid-bed coater and those from a larger GEA MP-1 machine, the correlation between data produced from pellets coated on each processing scale when an HPC pore former was used was less than satisfactory (see Figure 4 for typical results). When a pore former was present, the lack of correlation was thought to be due to different drying rates influencing the degree of phase separation (between EC and HPC) and, hence, the size of pores formed, as the HPC is gradually leached from the coating during dissolution testing (an effect confirmed to some degree by subsequent SEM analysis).

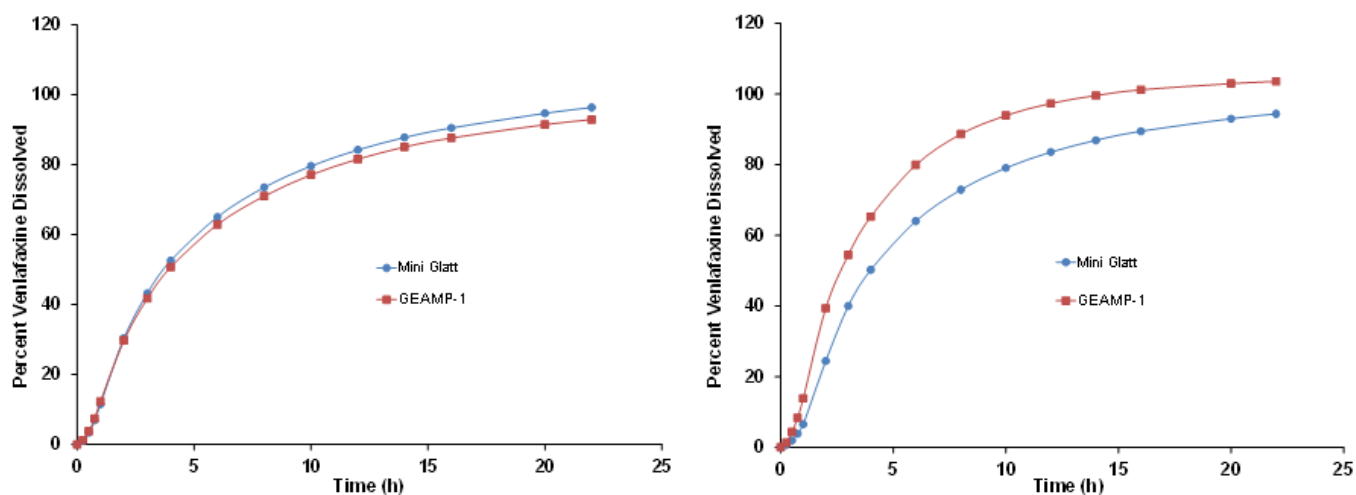


Figure 4. Comparative drug-release data obtained in earlier study; left, pore former; right, no pore former

In the present study, a broad range of drug release data were obtained, and selections from the completed data set are shown in Figure 5. Although these data indicate that changing coating process conditions can impact drug release, the variations from run to run in observed drug release characteristics were not as substantial as those indicated previously in Figure 4.

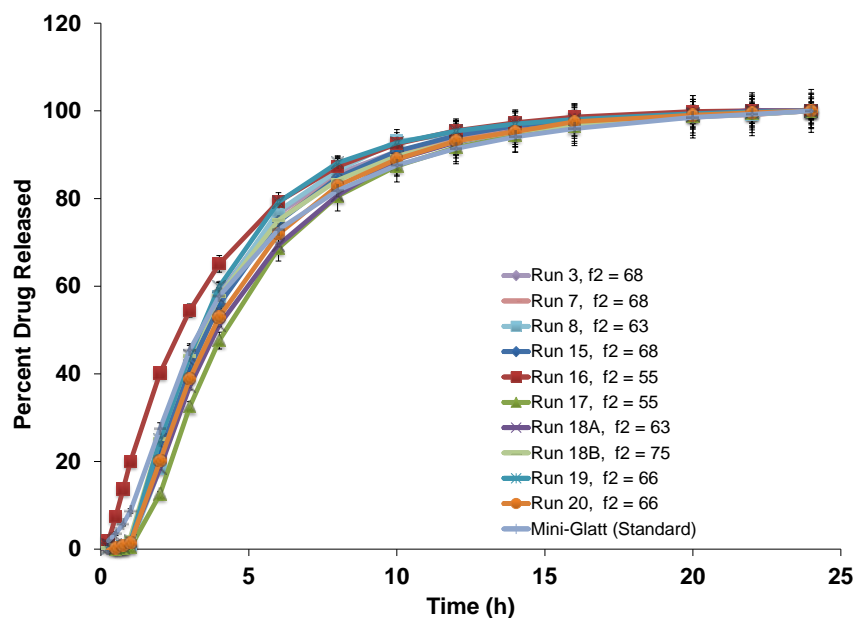


Figure 5. Summary of Typical Drug Release Data Obtained in Present Study

Also, in each case, the f_2 values obtained (comparing data from each run with a standard obtained for pellets coated using the Mini-Glatt) are all above 50, suggesting statistical similarity. However, the closeness of fit for these results may be impacted by the fact that the data for time points > 15 to 20 hours were almost identical for each run, which was not the case in the previous study [2]. Such similarity in the later stages of the dissolution profiles may well have contributed to greater statistical similarity (as indicated by f_2 values) in the overall drug release profile.

The data presented in Figure 6 illustrate the worst-case scenarios in terms of comparison of results with the standard obtained for pellets coated using the Mini-Glatt.

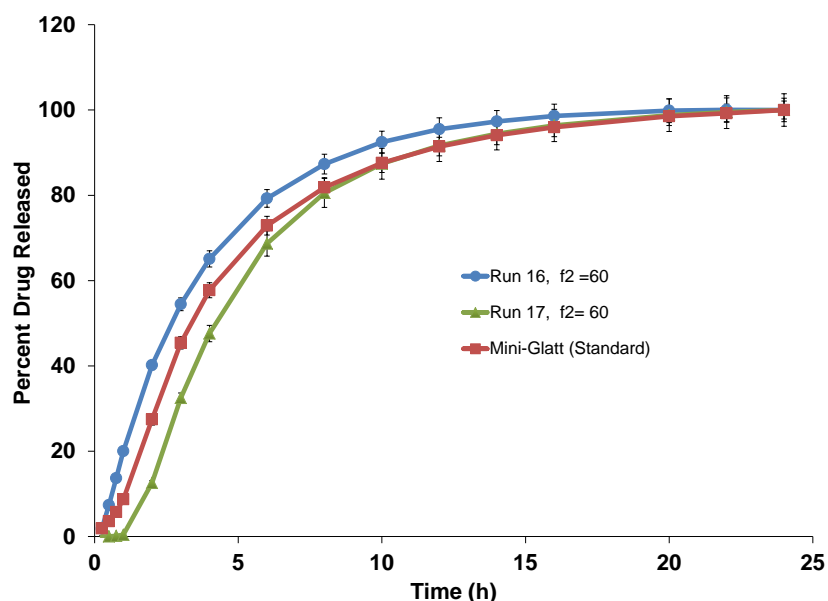


Figure 6. Dissolution Results Exhibiting Greatest Dissimilarity to the Standard

Although the f_2 values again illustrate that these data are marginally statistically similar to those obtained with the standard using the Mini-Glatt, the variability obtained in the first 10 hours of the dissolution profiles brings this apparent similarity into question.

In contrast, the data shown in Figure 7, which illustrate the best fit to the standard, where the f_2 value is 75, confirm that selecting suitable process conditions can produce comparable results on each scale. These data indicate that it is possible to achieve consistent scale-up results that optimize coating process conditions, even when using a coating formulation with the potentially complicating factor of a pore forming agent.

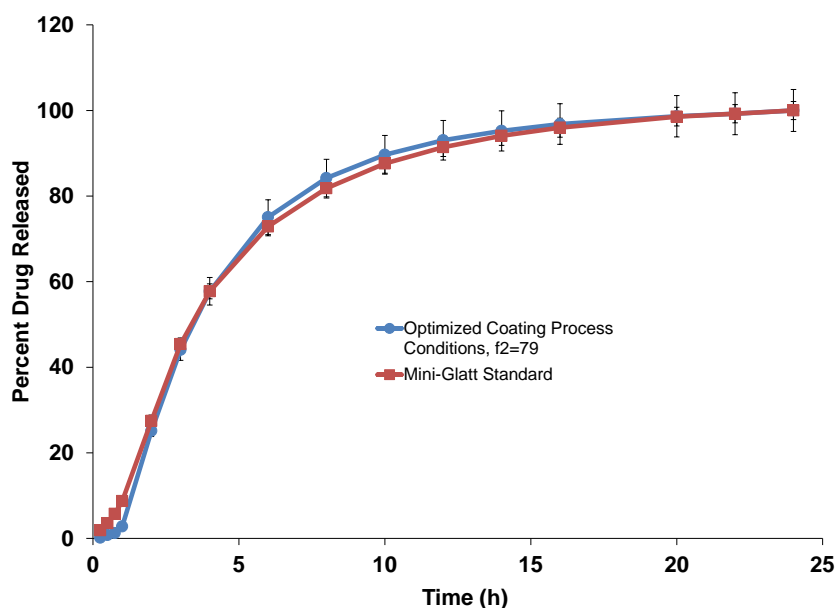


Figure 7. Data Comparing Results for Optimized Process Conditions with Those of the Standard

The process conditions summarized in Table 2 compare those conditions used for the optimized coating process with those used for the two worst-case scenarios.

**Table 2. Summary of Key Processing Conditions
Process Parameter Values**

Run #	Air Volume ($\text{m}^3 \text{h}^{-1}$)	Inlet Temp. ($^{\circ}\text{C}$)	Spray Rate (g min^{-1})
16	45	45	15
17	40	40	12
Optimal Conditions	36.6	45	15

These process data suggest that only minor adjustments in coating process conditions are required to achieve optimal results with the processing equipment employed in this study, and that process air flow volume is a more notable factor.

Conclusions

The focus of this study was to gain a better understanding of how coating process conditions affect drug release from venlafaxine HCl pellets coated with an EC coating containing a pore former, and to allow greater similarity to be achieved for results obtained on different processing scales. This objective was certainly achieved within the limits of the scope of the study undertaken. Further validation of the results needs to be obtained by undertaking confirmation studies for the process scales used, as well as conducting further studies on larger 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) Extended-release Venlafaxine Pellets: Scaling Up the Coating Process, Poster T2226 presented at AAPS Annual Conference, San Diego, CA (Nov 2014)