

Predictive Modeling and Validation of Tamoxifen Release from EVA Copolymers

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ABSTRACT SUMMARY

Hansen Solubility Parameter values were calculated for a divergent array of active pharmaceutical ingredients (API) and compared to those of ethylene vinyl acetate (EVA) copolymers to predict API solubility in EVA. Four API were selected for measurement of actual solubility in and diffusion coefficient through EVA films using Franz diffusion cells. Predicted release profiles were generated from that solubility and diffusion data for selected API-polymer combinations.

A formulation of Tamoxifen with EVA having 28% VA content was melt compounded then molded into a cylindrical rod. *In vitro* elution results agreed very well with the predicted profile, validating this methodology for screening selection and initial formulation design for controlled drug delivery from EVA copolymers.

INTRODUCTION

EVA has been used commercially in a number of diffusion-controlled drug delivery applications including ocular implants, intra- vaginal rings, and subcutaneous implants. It would be of benefit to have a generalized method to screen API for potential use with EVA excipients, so we set out to apply the basic principles of solubility prediction and diffusion measurement to predictive modeling of controlled release based on drug permeation through the amorphous phase of the polymer.

Hansen Solubility Parameter values were calculated for 32 API using the Yamamoto Molecular Breaking method as implemented in the commercial software HSPiP version 3.1.23. The array of small molecule API represented a wide experimental design space of water solubility, log P, molecular weight, and melting point. Tamoxifen, Olanzapine, D-Norgestrel, and Valsartan were thus selected for experimental determination of solubility and diffusion coefficient in EVA based on the sum of squared deviations method from the three-dimensional Hansen parameters for EVA.

EXPERIMENTAL METHODS

EVA films (9% and 28% nominal VA contents) of 103 – 109 μ thickness (std. dev. 7 μ) were conditioned in the medium (25 mM sodium acetate with 2% Solutol HS15; pH 4.2) and mounted in vertical Franz cells (PermeGear Model V9A). One ml of API dispersion in the medium was loaded on the donor side with 15 ml of the same medium on the receptor side, all maintained at 37°C. Assay was via UV-Vis on 500 μ l sample aliquots with replacement using fresh medium.

Diffusion profiles were plotted and the linear portion representing steady state was used to calculate P, S, and D according to the time-lag method of Baker and Lonsdale¹ as demonstrated for EVA by Van Laarhoven.²

For the combination of Tamoxifen and 28% VA EVA, a test sample was prepared by melt compounding at 110°C for five minutes in Haake Rheocord 9000 bowl mixer at 30 rpm. The compound was cryo-ground then injection molded into a single cavity O-ring mold to form 4 mm thick, 54 mm O.D. rings containing 100 mg Tamoxifen.

Three 4 cm long rods were cut from separate rings for *in vitro* elution testing using the same medium as used for the Franz cell measurements. The jars were maintained at 37°C on a shaker at 60 rpm and the entire 100 ml of medium was removed daily with replacement to ensure sink conditions, with 200 ml used across weekends. Assay was as before.

RESULTS AND DISCUSSION

Only Tamoxifen showed sufficient permeation rate through the 9% VA EVA to obtain satisfactory data linearity from which to determine P, S, and D. Using 28% VA EVA, satisfactory linear data was obtained for all the APIs except D-Norgestrel. Results for Valsartan are shown in Figure 1 and Table 1 summarizes the S and D values for drug-polymer combinations exhibiting good linear data quality to enable their calculation.

Predicted release profiles were calculated using

the S and D values in conjunction with a proprietary diffusion model developed by Particle Sciences, Inc., called PSDM, which takes into account device geometric design, drug loading level, and saturation state of the drug in polymer (solution versus dispersion).

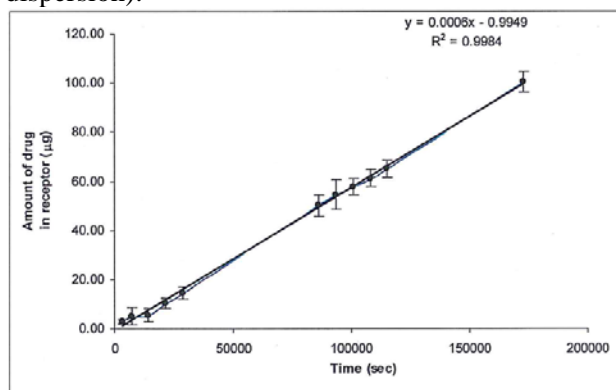


Figure 1 Valsartan diffusion through 28% VA EVA

Table 1 Summary of Solubility and Diffusion Coefficients

API	Solubility (wt%)	Diffusion Coefficient (cm ² /sec)
In 9% VA EVA:		
Tamoxifen	0.31	2.21×10^{-9}
In 28% VA EVA:		
Valsartan	0.015	1.37×10^{-8}
Tamoxifen	0.85	8.00×10^{-9}
Olanzapine	0.40	1.56×10^{-9}

The measured average daily release of Tamoxifen from a 4 cm rod comprised of 28% VA EVA containing approximately 26 mg Tamoxifen is shown in Figure 2, compared to model predictions based on both solution and dispersion conditions, since the drug loading was above the measured solubility. The two model conditions converge as expected as the rod is depleted, and the observed profile agrees very well. This suggests that melt compounding may have resulted in formation of a supersaturated solid solution of the drug in the polymer exceeding the drug solubility as estimated by the permeation time-lag method. The cumulative release profile is shown in Figure 3 and represents about 80% release of the drug in 22 days.

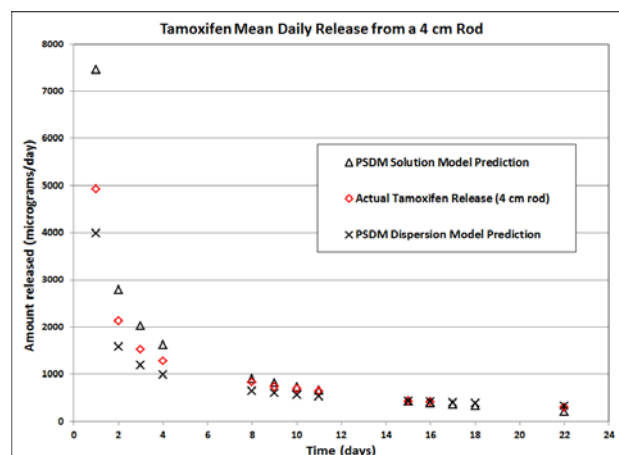


Figure 2 Daily release of Tamoxifen from 28% VA EVA

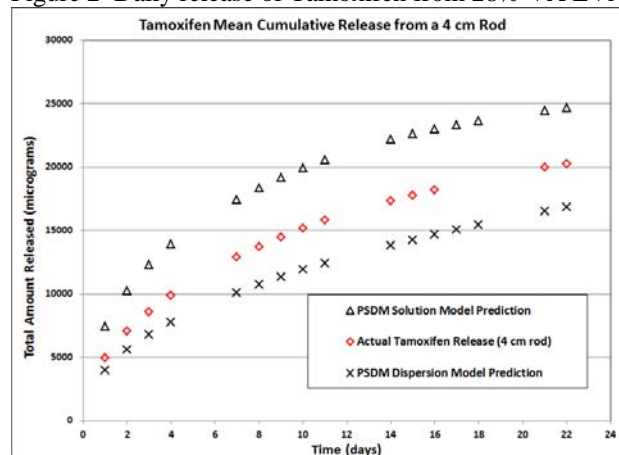


Figure 3 Cumulative release of Tamoxifen from 28% VA

CONCLUSION

A method was demonstrated using Hansen solubility parameter concepts coupled with Franz cell-derived solubility and diffusion coefficients in a predictive model to first screen active pharmaceutical ingredients for adequate solubility and permeability in ethylene vinyl acetate copolymers and then to accurately predict the release profile of the drug from the polymer matrix based on diffusion-controlled release. This approach, coupled with the demonstrated feasibility of ethylene vinyl acetate copolymers for low temperature melt extrusion and the known biocompatibility of the polymer, offers a framework for rapid and accurate feasibility assessment and prediction of behavior of drug eluting formulations for use in drug delivery systems.

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