# Hybrid CFD-PBPK Model for Prediction of Systemic PK Following Nasal Insufflation of Milled Oxycodone Hydrochloride Extended-Release Tablets

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## PURPOSE

Identifying a reliable in vitro method for assessing abuse deterrence non-inferiority via the intranasal route can facilitate drug development of generic opioid drug products with abuse deterrent properties. A hybrid computational fluid dynamics (CFD) and physiologically-based pharmacokinetic (PBPK) model may assist in identifying a reliable in vitro method. Therefore, a hybrid CFD-PBPK model was developed to predict systemic exposure following insufflation of manipulated oxycodone hydrochloride (HCl) extended-release (ER) tablets. This model assessed the biopredictive capability of a previously developed dissolution method.

## METHODS

- Nasal vestibule and nasal cavity deposition fractions (DFs) following nasal insufflation of finely (between 106 – 500 µm) and coarsely (between 500 – 1000 µm) milled formulations were predicted using a three-dimensional (3D) CFD model based on methods established in Walenga et al.,[1] using the commercial software package ANSYS Fluent 2019 R2 (ANSYS, Inc., Canonsburg, PA, USA).
- These predictions were used as inputs to a hybrid CFD-PBPK model that was based in part on the model developed by Rygg et al.[2-4]
- Another PBPK model was developed using GastroPlus™ 9.7 (Simulations Plus, Inc., Lancaster CA, USA) for intravenous (IV) and oral absorption of oxycodone HCl, where available IV and oral data were used to parameterize the model.
- The distribution and elimination constants obtained in the GastroPlus model were used as inputs to the CFD-PBPK model, and the Pulmonary Compartmental and Absorption and Transit (PCAT™) model was used to estimate the nasal absorption constant and permeability.
- Dissolution data were collected for the milled drug product used in the in vivo pharmacokinetic (PK) study described in Boyce et al.[5] As shown in Figure 1, the dissolution method developed by Feng et al.[6] was used where eight layers of milled drug product were distributed throughout the United States Pharmacopeia (USP) Apparatus 4 vessel.
- These data served as nasal dissolution inputs for the simulations of nasal insufflation of finely milled immediate-release (IR) and ER tablet formulations, as well as coarsely milled ER tablets, all in the 30 mg strength.
- Mucociliary clearance rate for the IR formulation, similar to that from Soane et al.,[7] was adjusted for the ER formulations to closely match the PK data.[5]
- Prediction values were compared to observed in vivo PK data on a percentage basis.
- The influence of dissolution method was explored by using data from Feng et al.[6] where three or five layers of milled drug product were distributed throughout the USP Apparatus 4 vessel.

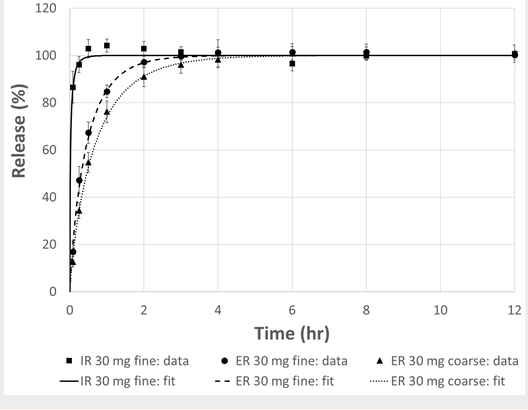


**Figure 1**. Dissolution data collected (mean ± standard deviation, n = 6) using the method described in Feng et al.,[6] with a USP Apparatus 4 with eight layers of milled powder distributed in the vessel, for finely milled oxycodone HCl IR and ER tablets and for coarsely milled oxycodone HCl ER tablet. The formulations measured are the brand-name products, where the strength is 30 mg for all formulations. The Weibull function fits to the data that were used for modeling are also shown.

## RESULTS

- DF predictions in the nasal cavity and nasal vestibule for the coarsely milled ER formulation are displayed in Figure 2. For the finely milled IR and ER formulations, the DF predictions for both cases (not shown) were 99.9% in the nasal cavity and 0.1% in the nasal vestibule.
- Predictions of PK using the CFD-PBPK model are shown in Table 1 and Figure 3 for the IR and ER formulations.
- The ranges of relative percentage differences between predicted and mean maximum peak concentration ($C_{max}$) and area under the plasma concentration-time curve up to the last recorded data point ($AUC_{0-t}$) were between -0.5% and 3.2% for $C_{max}$ and 3.3% and 5.4% for $AUC_{0-t}$.
- Mucociliary clearance of particles was predicted as shown in Figure 4 for the three formulations, where the predicted time at which 50% of the particles remain and the percentage of particles retained were 21 min and 24% for the IR formulation, 71 min and 23% for finely milled ER formulation, and 25 min and 15% for the coarsely milled ER formulation.
- The effect of dissolution method on PK predictions is displayed in Figure 5 for the finely milled IR and ER formulations and the coarsely milled ER formulation.

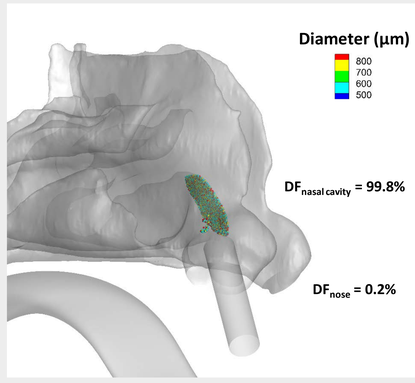


**Figure 2.** Predictions of DF following insufflation of the coarsely milled ER formulation in the nasal cavity and nasal vestibule using the 3D CFD model, where the particles are color-coded according to particle diameter.

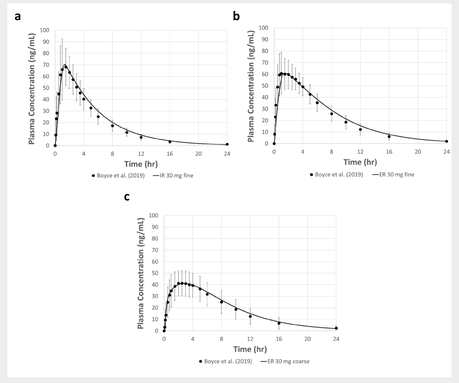


**Figure 3.** Plasma concentration PK predictions (lines) and in vivo data[5] as observed mean data ± standard deviation (dots and error bars, with n = 36 for all formulations) following nasal insufflation of a) finely milled powder of oxycodone HCl IR tablet in the 30 mg strength, b) finely milled powder of oxycodone HCl ER tablet in the 30 mg strength, and c) coarsely milled powder of oxycodone HCl ER tablet in the 30 mg strength.

**Table 1**. Mean observed in vivo PK parameters[5] and predicted values for finely milled oxycodone HCl IR and ER tablets and for coarsely milled oxycodone HCl ER tablet, all in the 30 mg strength, with relative percentage differences (Δ) for $C_{max}$ and $AUC_{0-t}$.

| | $C_{max}$ (ng/mL) | | Δ (%) | $AUC_{0-t}$ (ng-h/mL) | | Δ (%) | $t_{max}$ (h) | |
|---|---|---|---|---|---|---|---|---|
| | In vivo | Predicted | | In vivo | Predicted | | In vivo | Predicted |
| IR 30 mg fine | 68.2 | 70.4 | 3.2 | 407.1 | 429.0 | 5.4 | 1.5 | 1.4 |
| ER 30 mg fine | 60.8 | 60.8 | 0.0 | 503.4 | 519.8 | 3.3 | 1.0 | 1.4 |
| ER 30 mg coarse | 41.2 | 41.0 | -0.5 | 419.1 | 436.4 | 4.1 | 2.0 | 2.8 |

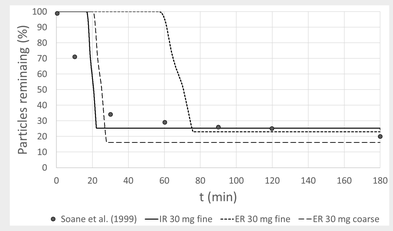


**Figure 4.** Percentage of particles predicted to remain in the nasal cavity following nasal insufflation of finely milled powder of oxycodone HCl IR tablet in the 30 mg strength, finely milled powder of oxycodone HCl ER tablet in the 30 mg strength, and coarsely milled powder of oxycodone HCl ER tablet in the 30 mg strength. Prediction data are compared with in vivo data from Soane et al.,[7] which represent mucociliary clearance without formulation effect.

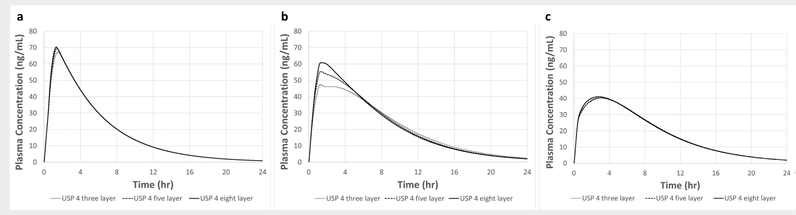


**Figure 5.** Plasma concentration PK predictions following nasal insufflation of a) finely milled powder of oxycodone HCl IR tablet in the 30 mg strength, b) finely milled powder of oxycodone HCl ER tablet in the 30 mg strength, and c) coarsely milled powder of oxycodone HCl ER tablet in the 30 mg strength. The dissolution input data were adjusted to reflect in vitro data from Feng et al.[6] collected using the USP Apparatus 4 with either three, five, or eight layers of milled drug product distributed through the vessel.

## CONCLUSIONS

A hybrid CFD-PBPK model was developed to predict systemic exposure following insufflation of manipulated IR and ER tablets with AD properties. Predictions were dependent on both nasal dissolution and mucociliary clearance, where in vitro measured dissolution was significantly slower for the ER formulations. Mucociliary clearance was predicted to be about three and a half times slower for the finely milled ER tablets as compared with finely milled IR tablets and coarsely milled ER tablets. A sensitivity analysis was conducted to investigate the effect of different USP Apparatus 4 dissolution methods on PK predictions, where results showed very little change for the IR formulation and the coarsely milled ER formulation, but noticeable differences for the finely milled ER formulation that may be due to the predicted reduction in mucociliary clearance rate. Altogether, while the dissolution method described by Feng et al.[6] may be a useful component of an in vitro-only method that characterizes abuse deterrence of nasally insufflated oxycodone HCl ER tablets, another component would be needed to reflect formulation effects on mucociliary clearance. Future research may include development of an in vitro method that mimics nasal mucociliary clearance and characterizes mucociliary clearance due to deposited particles.

## REFERENCES

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