Toward 'translating' *in vitro* dissolution to *in vivo* dissolution: a particle motion model to predict drug dissolution rate in the USP 2 paddle apparatus

B. Liu[a], M. Jamei[a], A. Rostami-Hodjegan[a,b] and D.B. Turner[a]

[a] Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; [b] Manchester Pharmacy School, The University of Manchester, U.K.

Bo.Liu@certara.com

INTRODUCTION

The USP 2 paddle apparatus is widely used in the pharmaceutical industry to measure *in vitro* drug release and dissolution rates (DR). For the purpose of anticipating *in vivo* dissolution/release rates media composition and stirring/agitation rates should mimic *in vivo* conditions as closely as possible. Typically *in vitro* studies are done in media representing the fasted stomach and the small intestine. However, *in vivo* conditions can exhibit high variability both between individuals and between occasions, have regional differences along the length of the GI tract and may change dynamically with time during the absorption process. Thus, even where *in vitro* dissolution conditions closely match typical or representative conditions *in vivo*, *in vitro* DR do not directly provide an indication of the potential variability in DR that may arise from the known physiological variability of luminal pH, luminal fluid volume, buffer capacity etc. One way to quantitatively anticipate such variability is through mechanistic PBPK models able to capture the impact of these relevant physiological parameters[1].

Fluid velocity can have significant impact upon DR and there is a well-known mis-match between typical conditions *in vitro* USP 2 and *in vivo*. A number of studies demonstrate that a) the simulated average fluid velocity is ~0.045 ms^{-1} in the USP 2 which is 30-40 times higher than that in the intestine (~0.0013 ms^{-1}), and 2) the simulated average shear rate is ~46 s^{-1} in the USP 2 which is ~5 times higher than the simulated average shear rate of 10 s^{-1} in the pylorus. This implies that to better predict *in vivo* DR it is necessary to 'translate' *in vitro* DR to better reflect *in vivo* conditions. The first step of this translation process is to build a mechanistic model of DR in the USP 2 apparatus.

Although computational fluid dynamics (CFD) methods can be used to predict FD and DR in the USP 2 paddle apparatus, running such models can take from several hours to several days, depending mainly upon the complexity of meshes. Such time scales are generally not acceptable within a pharmaceutical drug development setting. Various approaches have been taken to model drug particle dissolution in *in vitro* systems such as the classical Noyes-Whitney and Wang-Flanagan equations for particle dissolution[2]. However, these equations are not always applied with consideration of the effect of both hydrodynamics and (time-dependent) particle radius on a key parameter, the thickness of the diffusion layer (h_{eff}).

The aim herein is to model drug particle dissolution in the USP 2 paddle apparatus using a combination of particle motion and the Noyes-Whitney equations[3].

MATHEMATICAL MODEL AND EXPERIMENTAL METHODS

Model assumptions

1) All particles are suspended in the USP 2 vessel fluid (required).

2) The USP 2 vessel is divided into many cross-sectional surfaces across which suspended particles are equally distributed - particles do not move between surfaces.

3) The model only considers fluid velocities in the axial and tangential directions.

4) For a given rotation speed a single, representative fluid velocity can be obtained and is sufficient.

Mathematical equations

The following 8 equations are used to predict DR in the USP 2 paddle apparatus:

$$V_{\tan} = \frac{0.4 * V_{tip}}{2} \qquad V_{axial} = \frac{0.1 * V_{tip}}{2}$$

$$m_p \frac{dU_p}{dt} = F_{drag} + F_{gravity} + F_{buoy} \qquad U_{total} = V_{\tan} - U_p$$

$$\mathrm{Re} = \rho_f U_{total} \frac{d_p}{\mu_f} \qquad Sh = 2 + 0.6\,\mathrm{Re}^{1/2} Sc^{1/3}$$

$$\frac{1}{h_{eff}} = \frac{Sh}{d_p} \qquad \frac{dM_s}{dt} = -SD_{eff} \frac{1}{h_{eff}} (C_s - C_t)$$

V_{tip} - impeller tip speed;
$V_{\tan}$ - average tangential fluid velocity;
V_{axial} - average axial fluid velocity;
m_p - particle mass;
U_p - particle motion velocity;
F_{drag} - drag force;
$F_{gravity}$ - force due to gravity;
F_{buoy} - buoyancy force;
U_{total} - total relative velocity;
ρ_f - fluid density;
d_p - particle diameter;
t - time;
h_{eff} - thickness of the diffusion layer;
M_s - solid mass;
S - particle surface area;
D_{eff} - effective diffusion coefficient;
C_s - surface solubility;
C_t - bulk solubility;
Sh - Sherwood number;
Re - Reynolds number;
Sc - Schmidt number;
μ_f - apparent fluid viscosity;

Model drugs and dissolution conditions

The model was tested under different dissolution conditions using 3 model drugs. All tests were carried out at 37 °C.

Carbamazepine (CBZ), dose 200 mg. The dissolution test was carried out at 75 rpm in 900 mL of dissolution media (either water or 1% SLS) (in-house data).

Digoxin, dose 0.25 mg. The dissolution test was carried out at 100 rpm in 600 mL of 0.1 M HCl[5].

Danazol, dose 100 mg. The dissolution tests were carried out at 75 and 100 rpm in 500 mL FaSSIF media[4].

RESULTS AND DISCUSSION

The predicted and observed dissolution profiles of CBZ in water and 1% SLS (Fig. 1) are comparable at early time points. However, the predicted dissolution profile is slightly faster than the observed profile at the later stages of dissolution in both water and 1% SLS. This is most likely due to the disintegration of CBZ particle agglomerates.

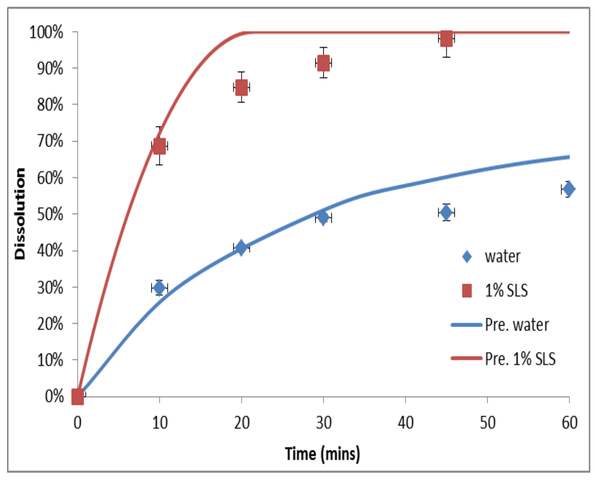

Figure 1: Observed (markers) and predicted (lines) CBZ dissolution at 75 rpm in 900 mL water and 1% SLS, respectively.

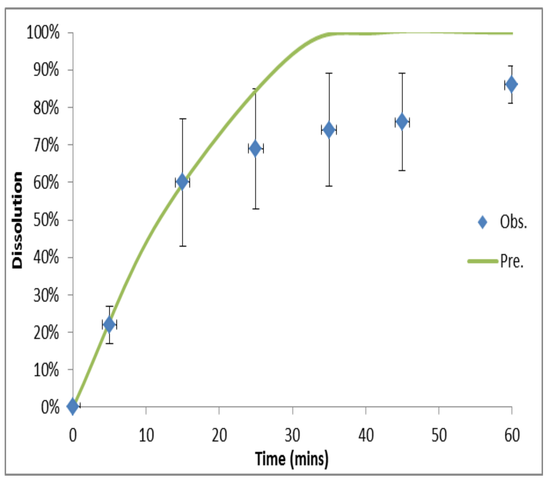

Figure 2: Observed and predicted digoxin dissolution profiles at 100 rpm in 600 mL 0.1 M HCl.

The prediction of digoxin DR is identical to the observed data (Fig. 2) at early time points but is over-predicted after about 25 minutes. Although sink conditions were ensured in the system, the observed dissolution tends to a level of around 80% release after 30 mins. This suggests that there are other unknown factors affecting digoxin dissolution which require further investigation.

The predicted danazol dissolution profile is similar to the observed profile at late stages (after 60 mins.) at both 50 and 100 rpm (Fig.3). The dissolution rate is over-predicted at early stages (0 - 30 mins.) perhaps because the current model does not consider particle agglomeration.

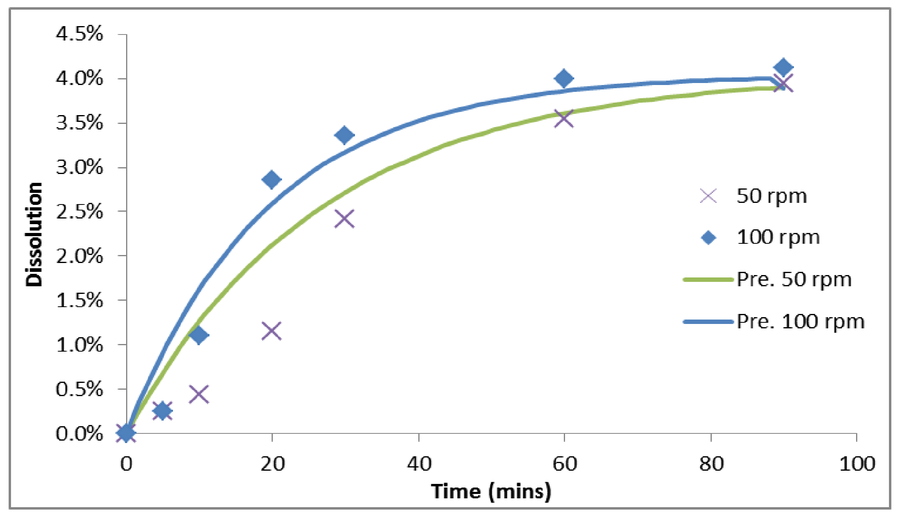

Figure 3: Observed (markers) and predicted (lines) danazol dissolution profiles at 50 and 100 rpm in 500 mL FaSSIF dissolution media. The maximum % dissolved is consistent with the reported equilibrium solubility of danazol in FaSSIF[6].

CONCLUSION

Overall, the described particle motion model is effective for predicting DR in the USP 2 paddle apparatus under different conditions. The next step is to incorporate this model into PBPK models of the GI tract in order to predict *in vivo* drug dissolution and validate against clinical data.

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