Supplementary materials for:

Parameterization of Physiologically Based Biopharmaceutics Models: Workshop Summary Report

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1. POINTS TO CONSIDER WHEN MEASURING DRUG SOLUBILITY

This section highlights important aspects to facilitate robust solubility inputs into PBBMs for crystalline or amorphous drug substance (DS) in an immediate release (IR) drug product. Points to consider focus on experimental measurement considerations rather than direct input methods into PBBM software, which may vary by software platform.

1.1 CRYSTALLINE DS

Applies to thermodynamically stable form, metastable polymorphs, solvates, hydrates, salts, cocrystals.

1.1.1. Important solubility data for neat DS (i.e., in absence of formulation components)

1.1.1.1. Thermodynamic solubility vs. pH

Experimentally determine DS thermodynamic solubility versus bulk final pH

- Use aqueous media without solubilizing components (e.g., no bile salts, surfactants)
- Perform at 37ºC (body temperature)
- Adjust to desired ionic strength (e.g., isotonic with body fluids) and consider ionic strength impact on e.g., pKa(s)
- Consider impact of medium components on ‘salt limiting’ solubility product and relevance to in vivo situation

- Consider potential for 'artifacts' due to unintended interaction of drug with medium components (e.g., drug-phosphate complexes), DS degradation in medium, or DS self-aggregation.[1-3]
- Consider potential phase conversions and impacts on solubility values (e.g., if metastable polymorph, salt, cocrystal, partially amorphous DS is under evaluation). Recover the solid phase after equilibration and compare its XRPD pattern with that of the ingoing solid to see if a phase change has occurred.
- pH measurement range, number of experimental datapoints (e.g., pH values), and pH values selected should allow for generation of an accurate profile in the GI pH range of approximately 1-8.
    - Experimental points should capture multiple degrees of ionization (e.g., 0% ionized, 50% ionized, 90% ionized)
    - Measurements at pH values > 8 may be needed to capture DS intrinsic solubility (e.g., weak base with highest pKa > ~5)
    - Consider determining solubility in purified water and measuring final pH to determine pH at which API is effectively neutral.
- Use final pH of the saturated solution to generate a pH-solubility curve.
- Ensure measurement duration is sufficiently long to ensure equilibration has occurred. Consider collecting multiple time points to ensure a stable result.

Determine pKa values using experimental technique(s) and/or predict using computational method(s). Overlay/fit theoretical solubility vs. pH profile (e.g., Henderson-Hasselbalch (H-H) equations) with experimental profile

- Determine if experimental profile makes 'theoretical sense' (e.g., matches the shape of the H-H equations) with necessary and reasonable adjustments to pKa(s) and/or 'salt limiting' solubility product(s). If yes, move forward with profile, if no, investigate for potential measurement errors or testing artifacts.

Consider 'corroborating' profile using solubility measurements and/or non-sink dissolution testing in multiple medium types (e.g., buffer species, ionic strength) to ensure solubility vs. pH profile is robust and relevant to in vivo and in vitro fluids/buffers.

1.1.1.2. Solubility vs. mixed lipidic aggregate (e.g., bile salt) concentration

Experimentally determine DS apparent thermodynamic solubility versus mixed lipidic aggregate concentration, e.g., 'solubilization ratio (SR)' or 'bile micelle partition coefficient (Kbm)'

- Measure DS solubility in presence and absence of 'mixed lipidic aggregates' (e.g., bile salts, vesicles)
    - Source of mixed lipidic aggregates could be e.g., FaSSIF/FeSSIF powder, which contains sodium taurocholate and lecithin. Other sources could include different FaSSIF/FeSSIF versions, more specialized synthetic media, or aspirated in vivo

fluids. A diversity in mixed lipidic aggregate types could be explored to understand the potential impact on SR.

- Measure solubility using multiple concentrations of FaSSIF/FeSSIF powder, e.g., 0 mM, 3 mM, 13 mM where all other components remain unchanged to account for potential non-linearity, e.g., concentration-dependent SR.
- The 'blank medium' e.g., 0 mM FaSSIF/FeSSIF should be identical in composition (e.g., buffer species, buffer concentration) to the FaSSIF/FeSSIF containing medium except for the absence of FaSSIF/FeSSIF powder.
- Recover the solid phase after equilibration and compare its XRPD pattern with that of the ingoing solid to see if a phase change has occurred.
- Consider impact of degree of ionization on SR to account for differences in affinity for ionized vs. nonionized drug to mixed lipidic aggregates (e.g., negative affinity of negatively charged weak acids with negatively charged mixed lipidic aggregates). In such cases SR of both non-ionized and highly ionized DS should potentially be measured (e.g., in media with multiple pH values) if deemed important/relevant.

- Calculate SR using in house or commercial tools, noting impact of drug concentration, ionization, mixed lipidic aggregate type, and medium composition (e.g., ionic strength) where appropriate.

1.1.1.3. Solid particle surface solubility

Estimate solid particle surface pH and solubility for DSs with weakly acidic and/or basic moieties.

- Consider calculating/predicting solid particle surface pH using computational approaches.[4-9]
- Consider estimating solid particle surface pH experimentally using «slurry measurements».
  - Measure the pH of a saturated solution of DS in the medium of interest (e.g., gastric fluid, intestinal fluid) as an estimate of solid particle surface pH.[10]
  - Recover the solid phase after equilibration and compare its XRPD pattern with that of the ingoing solid to see if a phase change has occurred.
  - The medium composition should represent the properties of the in vivo gastrointestinal fluid of interest (e.g., buffer species and concentration) since these properties are likely to influence the results for drugs with the tendency to alter solid particle surface pH.

If solid particle surface pH differs significantly from the pH of the medium in the absence of the DS, solid particle surface solubility vs. pH may differ significantly from the standard solubility versus pH profile. In this event, consider adding solid particle surface solubility vs. pH to the PBBM to be used in dissolution rate calculations. Evaluate the sensitivity of

dissolution rate and oral absorption rate to the input of standard solubility versus pH or solid particle solubility versus pH.

1.1.1.4. Solubility in fat/lipids/meal components (for fed state simulations)

Determine the apparent solubility of DS in meal components.

- Consider measuring or estimating apparent solubility of drug in presence of meal components (e.g., fats, cholesterol)
  - Precedented media for measuring drug solubilization in meal components include milk, homogenized meals, FEDGAS®
  - Consider options for sampling, sample preparation, and analytical techniques that allow for differentiation between free drug, and drug associated with different components to facilitate understanding of the solubilization mechanism.
- Consider incorporating apparent solubility of drug in presence of meal components in the PBBM (e.g., in fed stomach)

1.1.1.5. Kinetic solubility of metastable solid forms

Determine kinetic solubility if DS is not the thermodynamically stable solid form.

- During equilibrium solubility measurements recover the solid phase after equilibration and compare its XRPD pattern with that of the ingoing solid to see if a phase change has occurred.
  - Consider investigating potential for phase conversion under a range of expected conditions (e.g., supersaturation ratio, medium properties, and composition) representative of in vivo conditions.
- In addition to investigating potential for phase change using a standard equilibrium solubility measurement for which only one measurement is collected at the end of the experiment, consider monitoring the concentration versus time profile (e.g., non-sink dissolution test) to aid in detecting the phase change. Consider performing a 'transfer' dissolution test where the DS is exposed to medium changes (e.g., gastric-to-intestinal transfer).
- If no phase change occurs the equilibrium solubility of the metastable solid form may be most suitable for the PBBM.
- If phase changes do occur, it may be necessary to account for solubilities of multiple solid forms in the PBBM.

1.1.2. Important solubility data for crystalline DS in an IR drug product

Determine if formulation component(s) (e.g., acidic or basic pH modifier, surfactant, cyclodextrin, polymer) change DS solubility compared to DS alone.

- Consider mechanism for change in DS solubility based on excipient type (e.g., change in DS phase behavior, ionization, solubilization/complexation).
- Based on known or suspected mechanism, design experiments to measure DS solubility in the presence of excipient(s) that facilitate accurate representation of DS solubility versus pH and DS SR, as well as solubility in food components and surface pH, if applicable.
- Consider testing multiple excipient concentrations relative to the DS concentration (e.g., to account for the range in GI volumes and excipient relative to DS level in the formulation).
- If excipients do not change DS solubility values, build PBBM using values determined for DS alone. If excipient(s) do change DS solubility versus pH and/or DS SR, make necessary adjustments to solubility inputs.

1.2 AMORPHOUS DS OR AMORPHOUS DS IN IR DRUG PRODUCT

1.2.1 Solubility vs. pH

Experimentally determine amorphous solubility (kinetic solubility) vs. pH.

- Test can be performed using a 'solvent-shift' method or by starting with amorphous DS. Minimize concentration of organic solvent in aqueous medium and avoid UV absorbing solvents.

During solvent shift test monitor UV signal at DS absorbing and non-absorbing wavelength to determine onset of liquid-liquid phase separation (LLPS) (e.g., amorphous solubility).[11, 12]

- If precipitation is too rapid to measure LLPS (e.g., drug is a rapid crystallizer), consider conducting experiments in presence of stabilizing polymer, such as by pre-suspending or pre-dissolving polymer in the medium or using an amorphous solid dispersion (ASD) as the initial solid phase to allow measurement(s) of amorphous solubility.
    - Consider the potential impact of ASD polymer/excipients on the amorphous solubility value (e.g., may increase or decrease amorphous solubility relative to DS alone). For example, presence of polymer could shift phase diagram, or could contribute to 'dissolved species' in excess of the amorphous solubility (e.g., nano-sized drug-polymer colloids). In some cases, the supersaturation ratio may be too great to measure the amorphous solubility prior to precipitation.
    - Amorphous solubility measurements obtained should be relevant to dosage form of interest (e.g., using same types/amounts of excipients in ASD or ASD in IR tablet) for use in PBBM. If precipitation/crystallization is too rapid to measure, then it may not be a meaningful input to the PBBM (or a useful dosage form).
    - If amorphous solubility test is performed by pre-suspending or pre-dissolving polymer in the medium, then consider 'corroborating' amorphous solubility values(s) using the amorphous dosage form of interest (e.g., ASD) to replicate behavior when drug and excipients are co-dissolving.

- Additional considerations specified under the crystalline solubility versus pH measurement section above also apply (e.g., related to media properties, artifacts, etc.)

Determine pKa values using experimental technique(s) and/or predict using computational method(s).

Overlay/fit theoretical amorphous solubility vs. pH profile (e.g., Henderson-Hasselbalch (H-H) equations) with experimental profile.

- Determine if experimental profile makes 'theoretical sense' (e.g., matches the shape of the H-H equations) with necessary and reasonable adjustments to pKa(s) and/or 'salt limiting' solubility product(s). If yes, move forward with profile, if no, investigate for potential measurement errors or testing artifacts.

Consider 'corroborating' profile using solubility measurements and/or non-sink dissolution testing in multiple medium types (e.g., buffer species, ionic strength) to ensure solubility vs. pH profile is robust and relevant to in vivo and in vitro fluids/buffers.

If precipitation/crystallization is expected to occur, it is likely necessary to account for solubilities of multiple solid forms in the PBBM (e.g., amorphous solubility and crystalline solubility).

1.2.2 Amorphous solubility vs. mixed lipidic aggregate (e.g., bile salt) concentration

Measure amorphous solubility versus mixed lipidic aggregate concentration, e.g., 'solubilization ratio (SR)' or 'bile micelle partition coefficient (Kbm)'.[1-3]

Use solvent-shift UV assay or start with amorphous DS or ASD using the same considerations as above for measuring amorphous solubility vs. pH.

Otherwise, the same considerations apply as for crystalline DS described above.

1.2.3 Solid particle surface solubility

Follow considerations for crystalline DS. Ensure relevant excipients are present/prevent and monitor crystallization as necessary (e.g., if drug is a rapid crystallizer).

1.2.4 Solubility in fat/lipids/meal components (for fed state simulations)

Follow considerations for crystalline DS. Ensure relevant excipients are present/prevent and monitor crystallization as necessary (e.g., if drug is a rapid crystallizer).

1.2.5 Accounting for nano-sized drug polymer colloids

Consider potential for formation of nanosized drug polymer colloids of amorphous DS dissolving in the presence of polymer (e.g., polymer suspended/dissolved in the medium or polymer in the dosage form).

Concentration and size of drug-polymer colloids can be determined by analyzing drug concentrations after microcentrifugation and ultracentrifugation (or alternatively via filtration), or by monitoring light scattering during in situ UV measurements. Both techniques should be performed in combination with dynamic light scattering.[13]

Consider potential impacts of nano-sized drug polymer colloids on absorption and methods for incorporating their impact on 'dissolved concentrations' in the PBBM. For example, consider impacts on predictions when including them in the amorphous solubility value, or instead accounting for their potential increase in e.g., rate of permeation via 'nano-modified Peff'.[14]

2. COMPARISON OF DISSOLUTION MODELS: ACALABRUTINIB EXAMPLE

To illustrate how different dissolution integration methods compare, two batches of acalabrutinib tested in clinical trials in the fasted state and following treatment with omeprazole were selected. These batches were already described in the literature.[8, 15] Batch L0505009 is a 100 mg acalabrutinib capsule representative of the commercial acalabrutinib capsule formulation. The drug is formulated with standard excipients and dry granulated prior to encapsulation. This drug product was tested in study ACE-HV-112 in three periods with different healthy volunteers in the fasted state and following omeprazole treatments[1]. In addition, 100 mg batch NVTF is also shown. This batch is a phase 1 clinical batch using drug in a binary blend which is then encapsulated. This batch was tested in healthy volunteers in the fasted state and following omeprazole treatment in study ACE-HV-004[2]. For these product batches, three mechanistic drug product dissolution models (the P-PSD fitted with the Excel tools described by Pepin et al.,[8] the use of the software DDDPlus® (Simulations Plus) and the Z-factor described by Takano et al.[16]) and a bottom-up approach using DS PSD were compared.

In terms of modeling performance, two indicators are calculated: average fold error (AFE) and absolute average fold error (AAFE) as shown in Table 1. Average fold error (AFE) is defined by following equation:

$$AFE = 10^{\frac{1}{n}\sum \log \frac{Pred_i}{Obs_i}}$$

The AFE is an indicator of the prediction bias. A method that predicted all observed values with no bias would have a value of 1; under-predictions are shown by an AFE below 1 and over-predictions by AFE values above 1. AFE values vary between 0 and infinity. In the context of dissolution prediction performance, a prediction may be considered satisfactory if the AFE is between 0.85-1.25, passable if AFE within [0.6-0.85] or [1.25-1.4], and poor if AFE within [0-0.6] or above 1.4.

Absolute average fold error (AAFE) is defined by following equation:

$$AAFE = 10^{\frac{1}{n}\sum \left|\log \frac{Pred_i}{Obs_i}\right|}$$

The AAFE converts negative log fold errors to positive values before averaging, measuring the spread of the predictions. AAFE values vary between 1 and infinity. A method that predicted all observed values perfectly would have a value of 1; one that made predictions that were on average 2-fold off (100% above or 50% below) would have a value of 2 and so forth. In the context of dissolution prediction performance, a prediction may be considered satisfactory if the AAFE was less than 1.3, passable if the AAFE was comprised between 1.3 and 1.5, and poor for AAFE above 1.5.

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[1] https://www.astrazenecaclinicaltrials.com/study/ACE-HV-112/
[2] https://www.astrazenecaclinicaltrials.com/study/ACE-HV-004/

Using the various inputs for dissolution of the drug product, the exposure to acalabrutinib was predicted using a previously published PBBM developed with GastroPlus,[15] and compared to observed clinical data. The AFE and AAFE previously described were calculated between predicted and measured C_{max} and AUC for all the different dissolution integration techniques. In addition, the average absolute prediction error (AAPE%) was calculated according to two equations. AAPE1 (%) and AAPE2 (%) are defined by the following equations:

$$AAPE_1(\%) = Geomean\left(\left|\frac{Pred_i - Obs_i}{Obs_i}\right|\right) \times 100$$

$$AAPE_2(\%) = Average\left(\left|\frac{Pred_i - Obs_i}{Obs_i}\right|\right) \times 100$$

These equations differ in the average which is geometric for AAPE1 and arithmetic for AAPE2. AAPE is measurement of prediction error scaled to percentage units, which makes it easier to understand. It is very close quantitatively to (AAFE-1) *100. A model is considered satisfactory when the AAPE is less than 20%, passable if AAPE is comprised between 20%-40% and poor is AAPE ≥ 40%.

2.1 BATCH L0505009

On batch L0505009, the fitting of pH 6.8 data was utilized for Z-factor, DDDPlus®, and Excel P-PSD prior to prediction of pH 1 and pH 3 data. For DS-PSD a bottom-up prediction is shown at all pHs (Figure 1). The prediction performance is shown in Table 1.

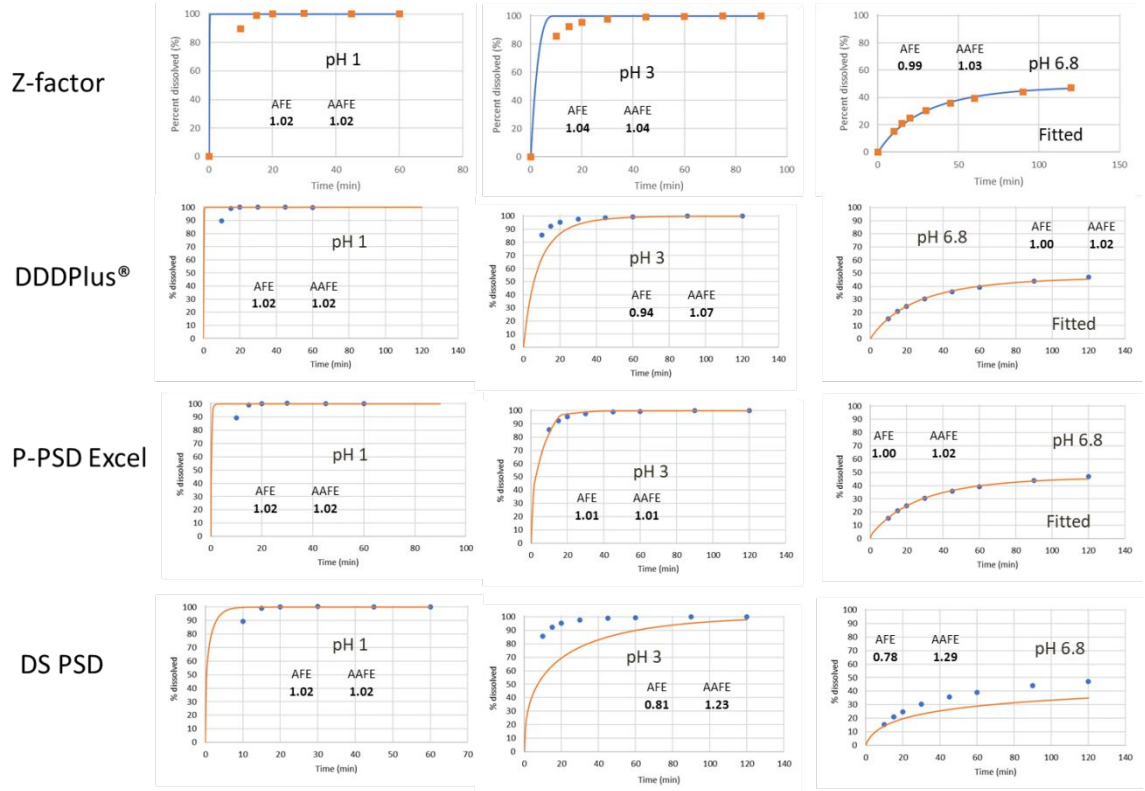


Figure 1 – Comparison of Z-factor, DDDPlus®, P-PSD Excel and DS-PSD to predict dissolution of 100 mg acalabrutinib capsule batch L0505009. Dissolution data from Pepin et al.[8]

Table 1 – Dissolution modeling performance on acalabrutinib batch L0505009

Performance indicator	P-PSD Pepin (fit pH6.8)	Z-factor (fit pH6.8)	P-PSD DDD+ (fit pH6.8)	DS-PSD (Laser)
AFE pH 6.8	1.00	0.99	1.00	0.78
AAFE pH 6.8	1.02	1.03	1.02	1.29
AFE pH 1	1.02	1.02	1.02	1.02
AAFE pH 1	1.02	1.02	1.02	1.02
AFE pH 3	1.00	1.04	0.94	0.81
AAFE pH 3	1.02	1.04	1.07	1.23

There are no major differences between the fitting methods. However, the bottom-up approach using DS-PSD tends to under-predict the observed dissolution by 20%. The sizes obtained with the various fitting methods for batch L0505009 are compared in Figure 2. For Z-factor, it is easy to transform the measured Z-factor for 100 mg acalabrutinib batch L0505009 (5.62E-03

mL/mg/s) in the radius of 15.92 µm using the equation defining Z-factor ($z = \frac{3D}{\rho h r_0}$). The sizes obtained from DP dissolution using Z-factor, Excel P-PSD or DDDPlus compare well to one another and are centered around 15-20 µm (Figure 2). For the DS, the population of particles is multimodal with larger particles around 200 µm. This mode is attributed to aggregated primary drug particles and explains why the dissolution of the drug product predicted from DS PSD is under-estimated at all discriminant pH values (Figure 1).

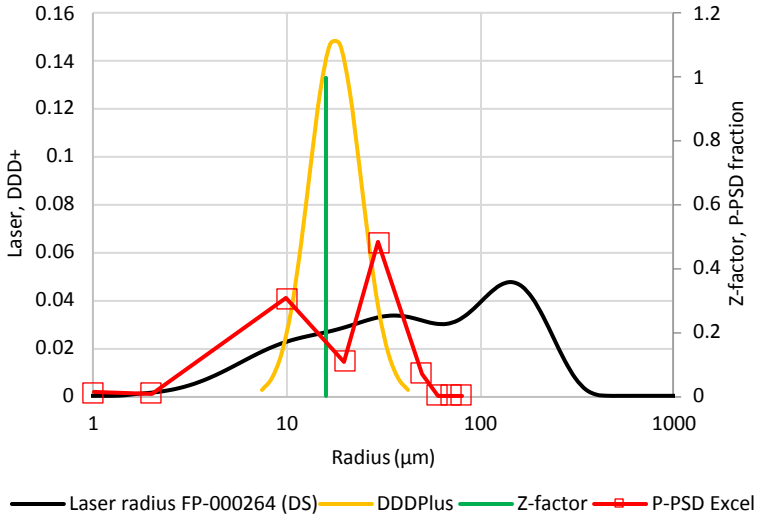
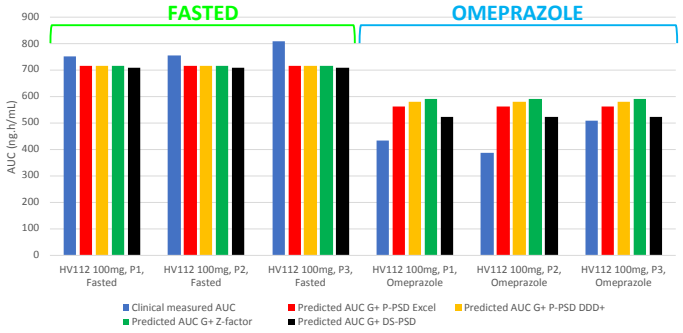


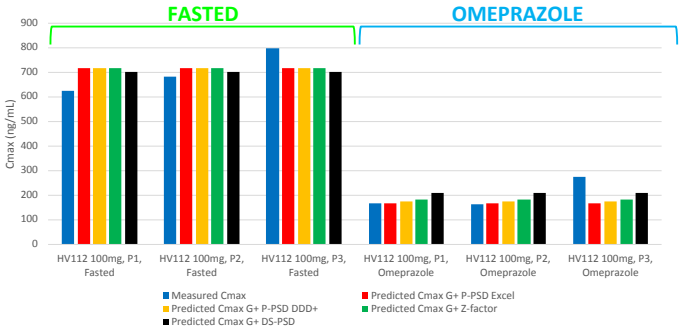
Figure 2 – Comparison of sizes obtained by various DP dissolution fitting methods and the DS PSD for batch L0505009. Batch FP-000264 is the DS batch number in DP batch L0505009.

The exposure to acalabrutinib was predicted with the various inputs shown in Figure 2. Results of C_{max} and AUC prediction in the fasted state and following omeprazole for the four dissolution introduction techniques are shown in Figure 3 together with model prediction performance.



Clinical data (AUC)	GastroPlus P-PSD Excel (fit pH6.8)	GastroPlus P-PSD DDD+ (fit pH6.8)	GastroPlus Z-factor (fit pH6.8)	GastroPlus DS-PSD (Laser)
$AAPE_1$	12.3	13.4	14	9.8
AFE	1.09	1.11	1.12	1.05
AAFE	1.17	1.19	1.20	1.14
$AAPE_2$	17.7	19.8	20.9	14

1: geometric mean, 2: arithmetic mean



Clinical data (C_{max})	GastroPlus P-PSD Excel (fit pH6.8)	GastroPlus P-PSD DDD+ (fit pH6.8)	GastroPlus Z-factor (fit pH6.8)	GastroPlus DS-PSD (Laser)
$AAPE_1$	3.3	10.3	12.5	14.5
AFE	0.93	0.96	0.99	1.04
AAFE	1.15	1.16	1.17	1.19
$AAPE_2$	11.9	13.2	14.6	17.9

1: geometric mean, 2: arithmetic mean

Figure 3 – Comparison of measured and predicted C_{max} and AUC following administration of 100 mg acalabrutinib capsule batch L0505009 in healthy volunteers in the fasted state or following PPI treatment in study ACE-HV-112. Predictions obtained with DP dissolution fitting methods and the DS PSD for batch L0505009.

Overall, predictions of exposure using a previously published PBBM for 100 mg acalabrutinib batch L0505009 in the fasted state or following omeprazole treatment are similar regardless of the method chosen. Based on the proposed model performance indicators and criteria defined above, all methods are acceptable. There is a notable difference between AAPE1 and AAPE2 methods. This is related to the geometric mean calculation which will lead to a lower error when one prediction is very close to a measurement, i.e., close to zero. In this case, since the geometric mean relies on the product of the prediction errors, the mean is underestimated compared to summing the errors in the arithmetic mean. This should be considered when setting acceptance criteria for AAPE.

2.2 BATCH NVTF

Batch NVTF was a phase 1 batch for which only pH 1 dissolution data existed. This data was used to fit the Z-factor, P-PSD with DDDPlus® or with Excel, to the drug product dissolution. In addition, a bottom-up prediction of drug product dissolution using measured DS PSD was done. Results are shown in Figure 4.

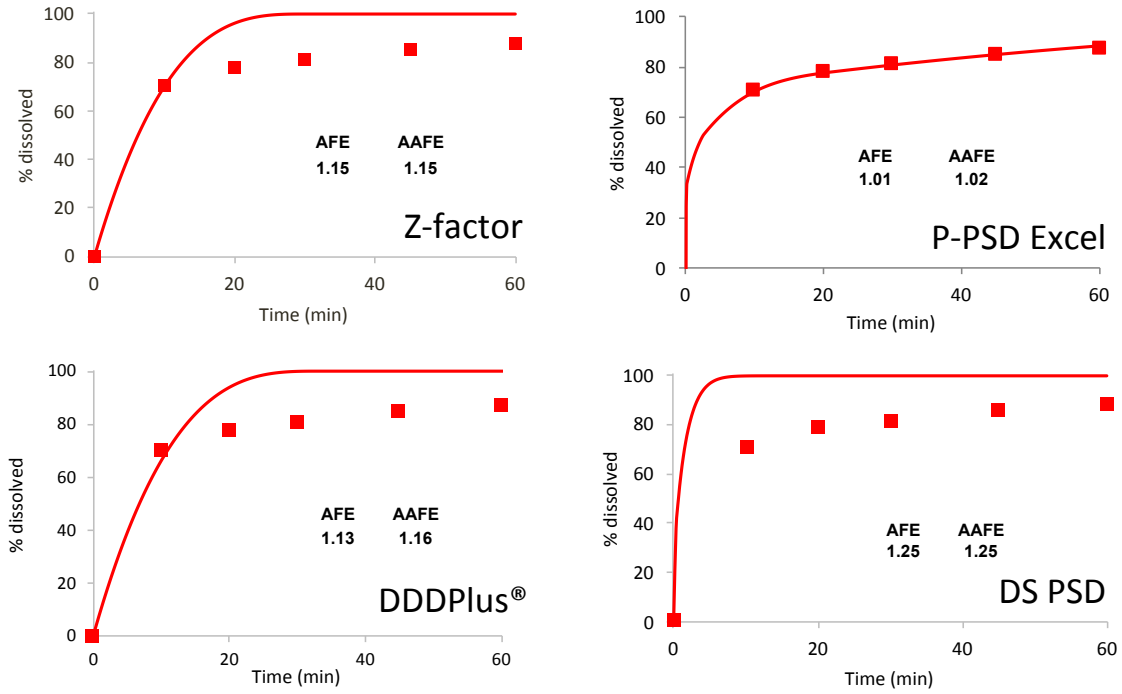


Figure 4 – Comparison of Z-factor, DDDPlus®, P-PSD Excel and DS-PSD to predict dissolution of 100 mg acalabrutinib capsule batch NVTF in 0.1N HCl. Dissolution data from Pepin et al.[8]

Figure 4 clearly shows that the use of DS PSD as input to predict 100 mg acalabrutinib capsule batch NVTF dissolution leads to an over-estimation of the drug dissolution rate. For this binary blend in capsule, the drug wettability becomes limiting, and the dissolution rate clearly proceeds in two steps: A rapid dissolution step followed by prolonged dissolution. Note that for this drug product, 103% dissolved is observed after 75 min and infinity spin from 60 min (where 90% of the drug is dissolved). No acceleration of the dissolution is observed during infinity spin. It was concluded that the drug dissolution after the initial rapid step is limited by the wettability of the drug. Comparison of the sizes obtained from the different fitting methods is shown in Figure 5. The Z-factor was equivalent to a size of 521 µm radius, whilst DDDPlus® provided an estimated centered to a 730 µm mean radius. The P-PSD using the Excel tools provided fines of less than 100 µm and a mode of 32% w/w at a radius of 3000 µm. Although all fits are satisfactory as per the criteria defined above, the Excel P-PSD provided the AFE and AAFE closest to 1. The fit with Z-factor and DDDPlus® captured the first dissolution measurement at 10 min but failed to capture both the rapid initial dissolution phase of the drug product and the second phase of the release. Because these fitting methods are producing monomodal particle size distributions, they will not be able to fit bi-phasic dissolution rates as shown by acalabrutinib capsule batch NVTF.

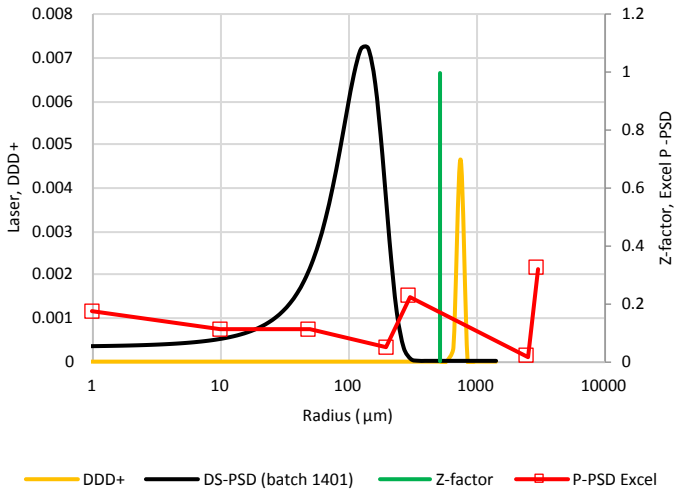
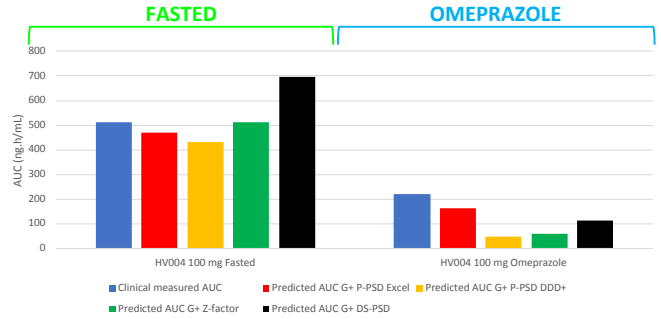


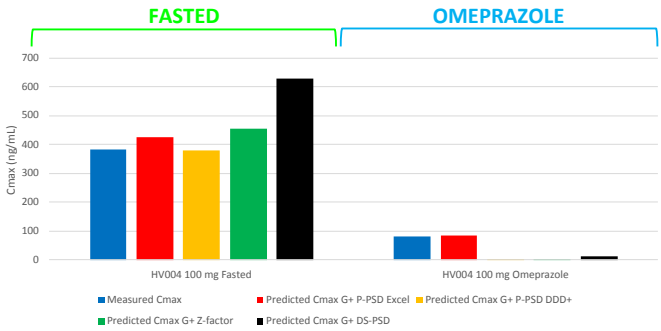
Figure 5 – Comparison of sizes obtained by various DP dissolution fitting methods and the DS PSD for batch NVTF. Batch 1401 is the DS batch number used in DP batch NVTF.

The predicted and observed C_{max} and AUC following administration of 100 mg acalabrutinib capsule batch NVTF to healthy volunteers in the fasted state and following omeprazole treatment is shown in Figure 6.



Clinical data (AUC)	GastroPlus P-PSD Excel (fit pH6.8)	GastroPlus P-PSD DDD+ (fit pH6.8)	GastroPlus Z-factor (fit pH6.8)	GastroPlus DS-PSD (Laser)
$AAPE_1$	15.3	34.9	3	41.6
AFE	0.82	0.42	0.51	0.84
AAFE	1.23	2.37	1.95	1.62
$AAPE_2$	17.9	47.2	36.8	42.1

1: geometric mean, 2: arithmetic mean



Clinical data (C_{max})	GastroPlus P-PSD Excel (fit pH6.8)	GastroPlus P-PSD DDD+ (fit pH6.8)	GastroPlus Z-factor (fit pH6.8)	GastroPlus DS-PSD (Laser)
$AAPE_1$	6	7.3	41.9	74.5
AFE	1.07	0.18	0.26	0.48
AAFE	1.07	5.44	4.60	3.43
$AAPE_2$	7.1	48.6	56.5	75.3

1: geometric mean, 2: arithmetic mean

Figure 6 – Comparison of measured and predicted C_{max} and AUC following administration of 100 mg acalabrutinib capsule batch NVTF in healthy volunteers in the fasted state or following PPI treatment in study ACE-HV-004. Predictions obtained with DP dissolution fitting methods and the DS PSD for batch NVTF.

The use of the DS-PSD led to an over-estimation of the drug exposure in the fasted state since the wettability cannot be predicted with laser diffraction. In addition, because of the general under-prediction of the true surface area available for dissolution for acalabrutinib batches due to the shape of primary drug substance particles and the presence of aggregates in the drug substance,[15] the DS-PSD failed to predict the extent of dissolution in vivo when volunteers received PPI treatment. It is apparent from the comparison of Excel P-PSD and DS-PSD in Figure 5, that there are not enough fines measured by the laser diffraction which could dissolve when the solubility is less favorable.

Regarding the prediction obtained with DDDPlus® and Z-factor, the fasted state C_{max} and AUC are correctly predicted whilst they are largely under-estimated when the stomach shows a higher pH following PPI treatment. As mentioned above, these monomodal fits capture a slow dissolution initially and therefore can predict fasted state relatively well, but there are not enough fine particles to predict dissolution in the stomach when the solubility becomes more limiting.

The P-PSD fitted with multiple modes or bins with the Excel tool allowed a good prediction of exposure in the fasted state and following PPI administration. This P-PSD shows fines which can dissolve in conditions where the solubility is less favorable together with larger particles which attest for the wettability limitation of the drug substance which limits the dissolution in fasted state conditions.

2.3 HOW MANY BINS OR MODES TO SELECT?

Since the Excel P-PSD can use from 1-10 bins, the tool was utilized in a degraded way to illustrate the minimum number of bins which can be utilized to provide an adequate fit of the dissolution and observed PK data. Batch NVTF which shows bi-phasic dissolution in vitro was used for this exercise. The fit of batch NVTF dissolution obtained with 7 bins, 2 modes,[15] 1 bin or 2 bins is shown in Figure 7.

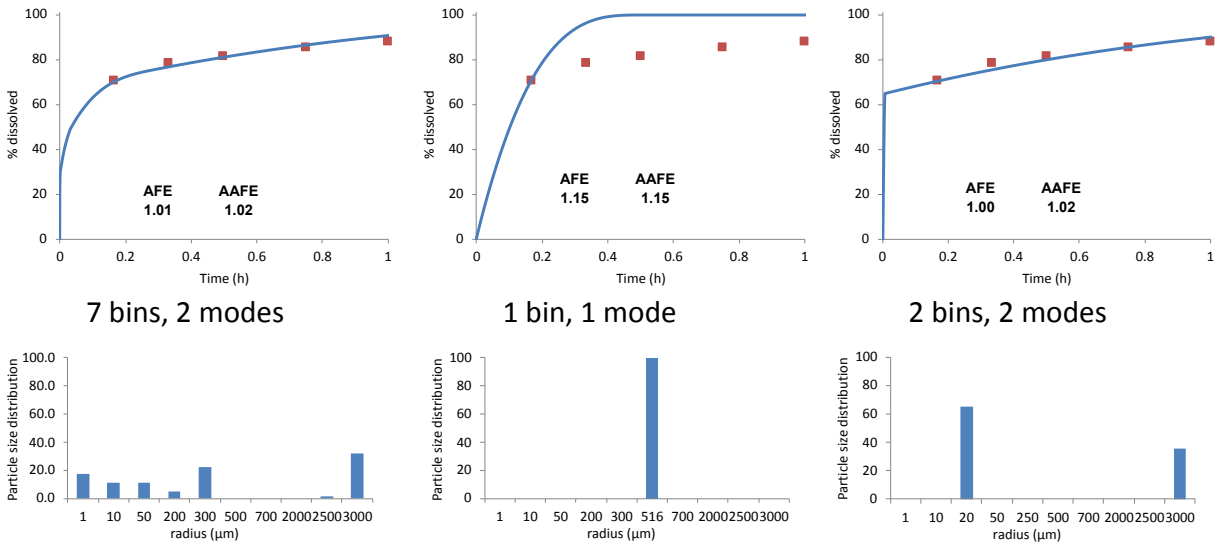
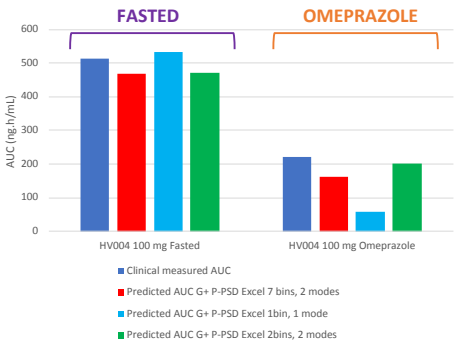
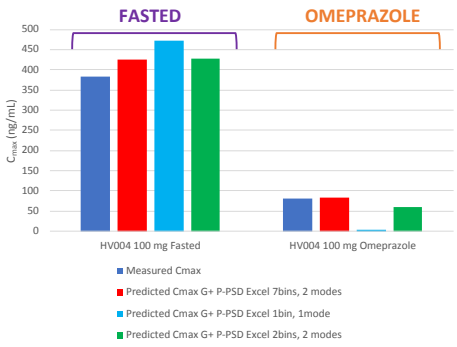


Figure 7 – Comparison of P-PSD Excel with 7bins, 1 bin or 2 bins to predict dissolution of 100 mg acalabrutinib capsule batch NVTF in 0.1N HCl. Dissolution data from [8]

Unsurprisingly, when only one bin is used with the Excel P-PSD tool, the predicted profile and errors are very close to those observed for the Z-factor or DDDPlus® approach. Interestingly, the radius obtained with one bin is of 516 µm, which is essentially the same as that obtained with the Z-factor (521 µm). When two bins are selected, the fit is adequate with 65% w/w fines around 20 µm radius and 35% large particles around 3000 µm. Using 2 bins only, the initial fast dissolution of the drug product followed by the prolonged release phase is well captured with AFE and AAFE values close to those observed with the reference 7-bin P-PSD. Prediction of exposures with the PBBM using degraded P-PSD models are shown in Figure 8. The one bin P-PSD reproduces the issue observed with monomodal distribution or the Z-factor, in that the fasted state exposure is well predicted but the AUC and C_{max} when a PPI is administered are underpredicted. The single bin fails to capture the initial rapid dissolution phase of the product. With 2 bins, this issue is removed and although the prediction performance on C_{max} is slightly decreased compared to the 7-bin P-PSD, similar or better prediction performance is achieved for the AUC with the 2-bin P-PSD.





Clinical data (AUC)	GastroPlus P-PSD Excel (7 bins-2modes)	GastroPlus P-PSD Excel (1bin-1mode)	GastroPlus P-PSD Excel (2bins-2modes)
$AAPE_1$	15.3	16.9	8.4
AFE	0.82	0.52	0.92
AAFE	1.23	2.01	1.09
$AAPE_2$	17.9	39.1	8.4

Clinical data (C_{max})	GastroPlus P-PSD Excel (7 bins-2modes)	GastroPlus P-PSD Excel (1bin-1mode)	GastroPlus P-PSD Excel (2bins-2modes)
$AAPE_1$	6	47.2	17.5
AFE	1.07	0.24	0.91
AAFE	1.07	5.19	1.23
$AAPE_2$	7.1	59.4	18.7

1: geometric mean, 2: arithmetic mean

Figure 8 – Comparison of measured and predicted C_{max} and AUC following administration of 100 mg acalabrutinib capsule batch NVTF in healthy volunteers in the fasted state or following PPI treatment in study ACE-HV-004. Predictions obtained with Excel P-PSD fitting using 7 bins, 1 bin or 2 bins.

2.4 TAKE HOME MESSAGES

Different methods exist to mechanistically fit in vitro dissolution data. When dissolution proceeds with a first order mechanism/shape, the use of the Excel P-PSD, Z-factor or DDDPlus® lead to equivalent fitting performance and in vivo prediction performance. If the drug product dissolution is biphasic, there is a minimum of two modes needed to fit the dissolution data. In practice, three modes would be a good starting point to fit all types of dissolution profiles. Currently, only the Excel P-PSD permits the fitting of multiple modes to in vitro dissolution data.

The Z-factor can be expressed as an equivalent radius which is handy when comparing different methods.

It is recommended to test dissolution fitting methods in conditions where the solubility is limiting and validate them with in vivo in conditions where solubility is limiting, i.e., where differences in particle size will have most impact and importance on the in vivo dissolution. As was demonstrated for acalabrutinib, the use of fasted state for a weak base alone cannot differentiate dissolution models in a PBBM, whilst more discrimination can be achieved if the subjects are pre-treated with PPI.

Altogether, the use of model prediction performance indicators is recommended when comparing in vitro dissolution fitting methods, however more examples are needed to define acceptable thresholds.

The use of DS as direct input to predict in vivo dissolution of solid oral dosage forms should be exercised with caution as the chance of reliability will be limited.

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