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Multifactor Non-linear Modeling for Accelerated Stability Analysis and Prediction

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The right approach can provide a clear, statistically defendable method for determining dissolution and accelerated stability.

Accelerated stability analysis is a strategy used to quickly evaluate alternative formulations, packaging, and processes. Accelerated linear studies are commonly performed and modeled; however, accelerated multiple-factor non-linear modeling has been a gap, and statistical software tools such as SAS/JMP do not directly have any provision to model multiple factor nonlinear responses. This paper outlines an approach to model and predict non-linear multiple factor stability/tablet dissolution data under accelerated and nominal storage conditions.

There are many non-linear stability cases such as dissolution, leachables, and moisture. Being able to model these non-linear processes is crucial to proper drug development. In addition to general non-linear modeling, there are multiple factors that may influence the non-linear curve. The following is a list of factors that may impact the asymptotes, growth rate, and inflection point of a curve:

- Stability storage temperature and humidity
- Particle size
- pH
- Amount of an excipient
- Processing conditions and or set points
- Packaging materials/method

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Study design

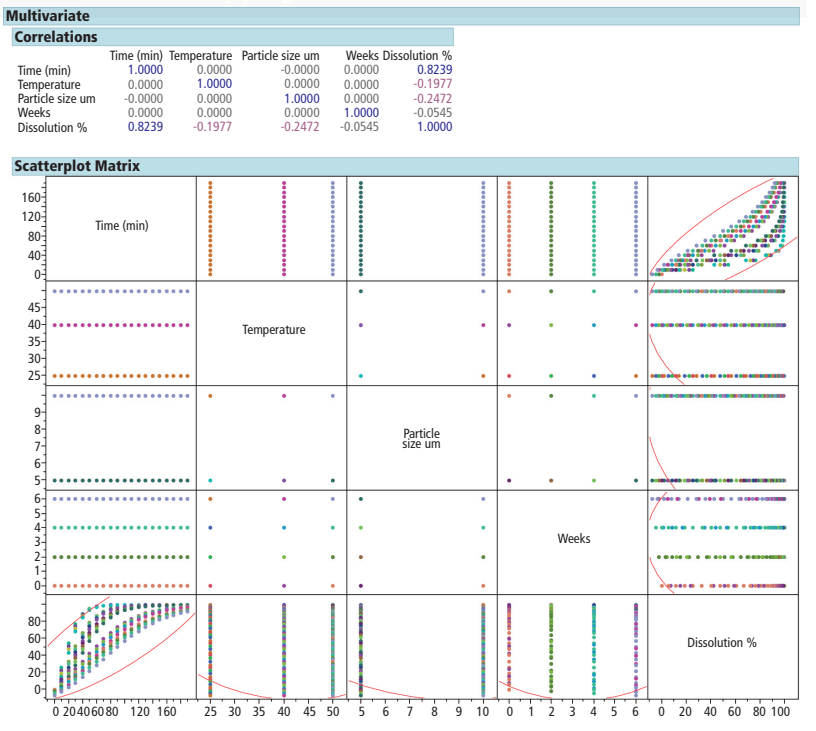
Proper design of experiments for data collection and curve isolation is crucial for building non-linear models. **Figure 1** illustrates the factors that should all be square relative to all other factors and have zero correlation relative to each other. For this tablet dissolution example, multiple time points (minutes), multiple storage conditions (temperature), multiple drug substance particle sizes, and multiple weeks were measured. Percent dissolution was the response of interest.

Analysis method

The following is a step-by-step procedure for non-linear stability modeling and expiry determination.

Step one. Measure the data at multiple time periods, using multiple particle sizes and at multiple temperatures. Generate a plot of the data to visualize the relationship of the curves over time (25-10-0: 25=Temperature, 10=Particle Size, and 0 = days) (see **Figure 2**).

Figure 1: Design of experiment structure and data structure visualization.



Step two. Fit each curve individually. In this example, each dissolution curve was fit using a four- parameter logistics (4PL) curve. The four parameters are: upper asymptote, lower asymptote, inflection point, and slope of the dissolution curve. R-Square should be high (typically above 0.95) and RMSE (DEFINE RMSE) error should be low for each curve. Outliers should be checked using the residuals. Save the parameters of the curve. In this example, there are four parameters, upper asymptote, lower asymptote, growth rate (slope), and inflection point (see **Figure 3**).

Step three. Save the parameters from the curve and the factors that influence them into a table. For this example, the growth rate and inflection point are the coefficients that may change the most based on the factors under consideration. The upper and lower asymptotes are not of concern for this problem as all of the curves have similar lower asymptotes and similar upper asymptotes, but upper and lower asymptotes could be important for other problems, so generally it is best to model all of the curve parameters (see **Figure 4**).

Step four. Fit the curve parameters with a least-squares multivariate regression. Growth rate, the slope of the 4PL fit, and inflection point are the most important as the dissolution starting point and the upper asymptote are essentially the same for all curves. Main effects and interaction models generally work best and p-values and F tests can be used to evaluate each model term (see **Figure 5**).

Step five. Save the equation from the multivariate parameter model. An example of the inflection point model is in **Equation 1**.

Figure 2: Dissolution non-linear curve visualization.

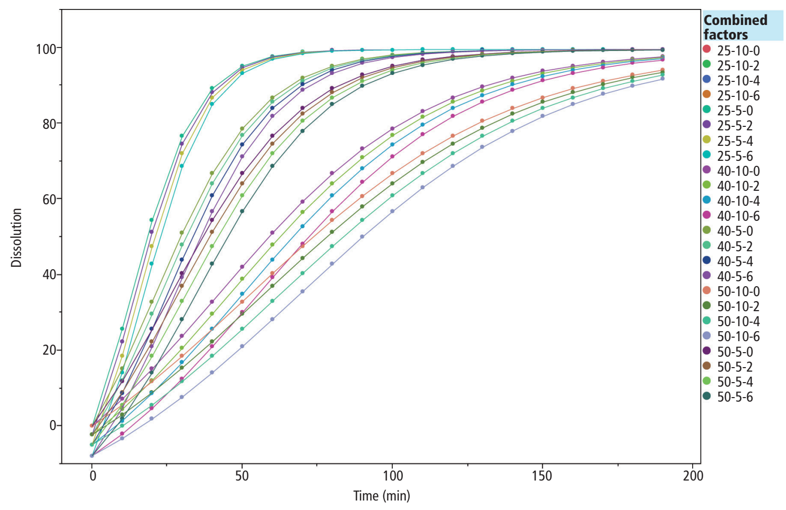
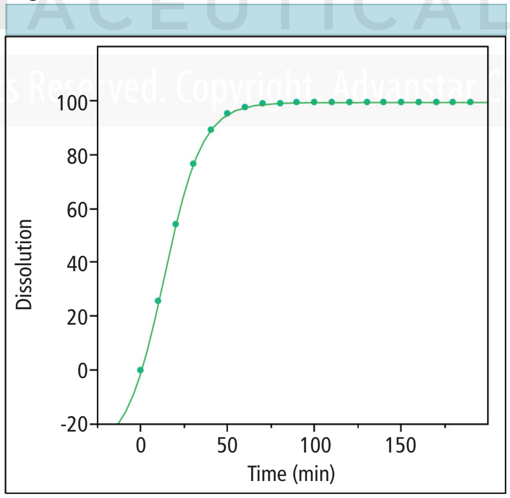


Figure 3: Individual non-linear curve.

Fit curve temperature=25, Particle size um=5, Weeks=0

Model comparison

Model		AICc	BIC	SSE	MSE	RMSE	R-Square
Logistic 4P	—	-90.05487	-89.36192	0.0063508	0.0003969	0.019923	0.9999996



Inflection point=
(-39.2209489504855) + 1.57872813205864 * :Weeks + 4.59873178679376 *:Particle Size um + 0.900151254288678 * :Temperature + (:Weeks - 3) *(:Particle Size um - 7.5) * 0.210156521957134 + (:Weeks - 3) * (:Temperature -38.3333333333333) * 0.0410230542148583 + (:Particle Size um - 7.5) *(:Temperature- 38.3333333333333) * 0.120412939953522

[Eq. 1]

Step six. Substitute the growth rate (slope) and inflection point coefficients from the multivariate model into the nonlinear prediction. The red box in Figure 6 shows the substitution for the inflection point.

Step seven. Check the model to make sure it matches the actual data. Correct any modeling errors by adding or modifying a multivariate model

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Figure 4: Factor and parameter table.

Weeks	Particle size um	Temperature	Growth rate	Infection point
0	5	25	0.0909554588	13.065024341
2	5	25	0.0910094568	14.233400619
4	5	25	0.0910595834	15.597147637
6	5	25	0.0908862161	17.206979311
0	10	25	0.0454271318	26.087752474
2	10	25	0.0454824294	28.424488692
4	10	25	0.0455043466	31.130289669
6	10	25	0.0454248554	34.370306664
0	5	40	0.0568276703	20.912786212
2	5	40	0.056875087	22.756305618
4	5	40	0.0568915501	24.911843234
6	5	40	0.0567602727	27.479985058
0	10	40	0.028387009	41.775242277
2	10	40	0.0284056616	45.429904676
4	10	40	0.028426348	49.794527539
6	10	40	0.0283816079	54.935228092
0	5	50	0.0454271318	26.087752474
2	5	50	0.0454824294	28.424488692
4	5	50	0.0455043466	31.130289669
6	5	50	0.0454248554	34.370306664
0	10	50	0.022749618	52.286382315
2	10	50	0.022749952	56.816249935
4	10	50	0.0227666129	62.312506986
6	10	50	0.0227421152	68.737337419

Figure 6: Generalized non-linear dissolution model.

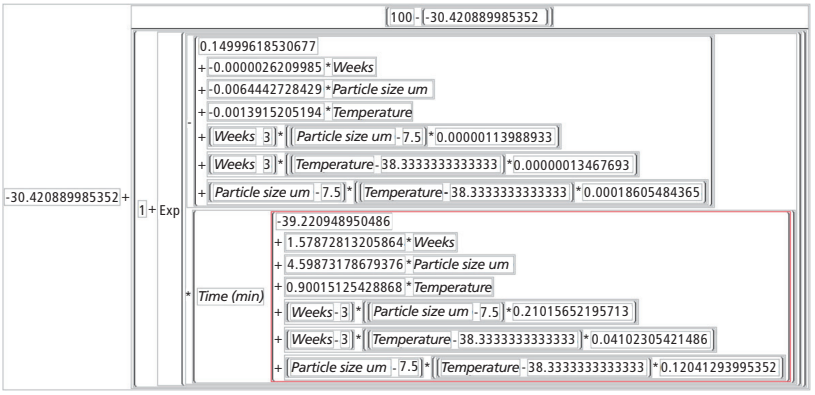


Figure 5: Parameter model quality.

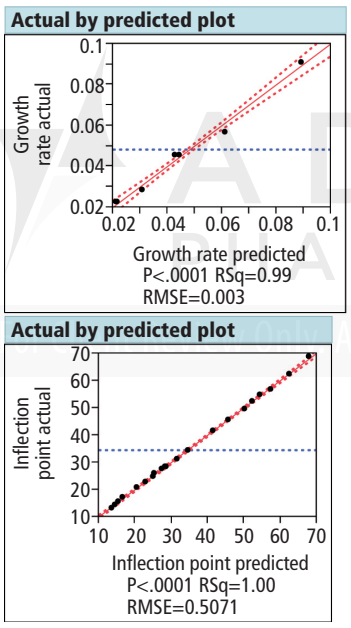
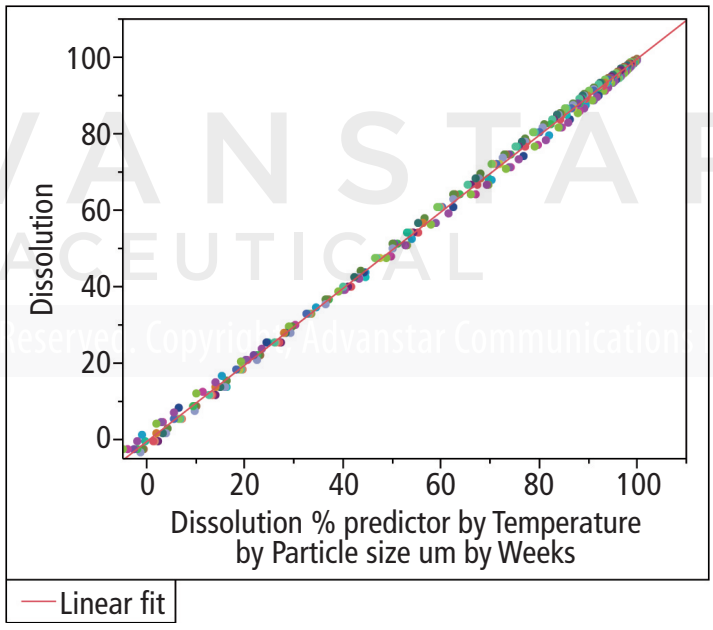


Figure 7: Model versus actual check.



term. A simple YX regression plot of the model versus the measurement will indicate model quality and any systematic errors (see Figure 7).

Step eight. Create a profiler from the equation to predict future dissolution rates. This can be done using a modern statistical package such as SAS/JMP (see **Figure 8**).

Step nine. Predict dissolution at any time, temperature, or particle size combination using the profiler. For this example, particle size was set to 5 µm, temp to 25 and time in weeks to zero. The dissolution time was fixed at 100 min with a specification of not less than 90% (see **Figure 9**).

Step ten. From the profiler at each time point (weeks), make sure the time (min) and particle size (5 um) are fixed, determine dissolution at the nominal temperature (non-accelerated condition). Fit the rate of degradation using either a linear or nonlinear model from the profiler predicted data. In this case, the rate of dissolution is not linear so a non-linear curve is fit to the data and the expiry is determined based on the extrapolated curve (see **Figure 10**).

The same method is used for predicting both the nominal expiry and the 95% CI expiry.

Step eleven. Finally, long-term stability evaluation at nominal storage conditions will be used to confirm the early model prediction and will provide an independent secondary determination of stability and changes in dissolution. Understanding rates of change should factor into shelf life and release specification limits (1).

Figure 8: Generalized multiple factor non-linear profiler.

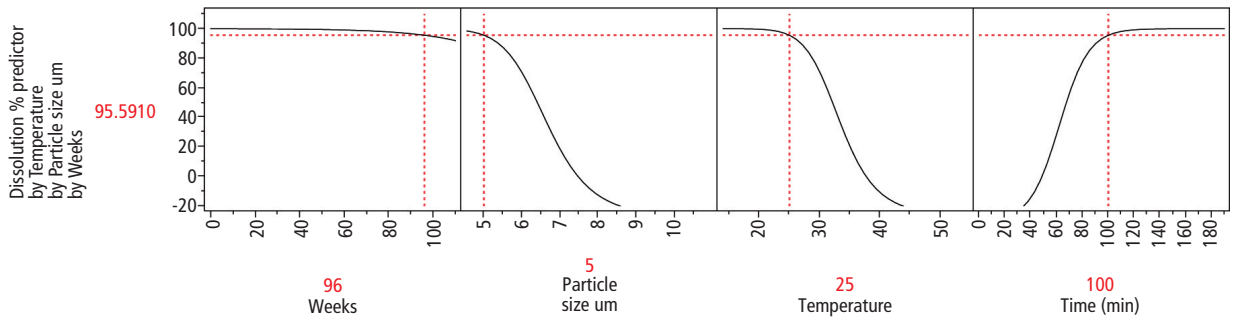
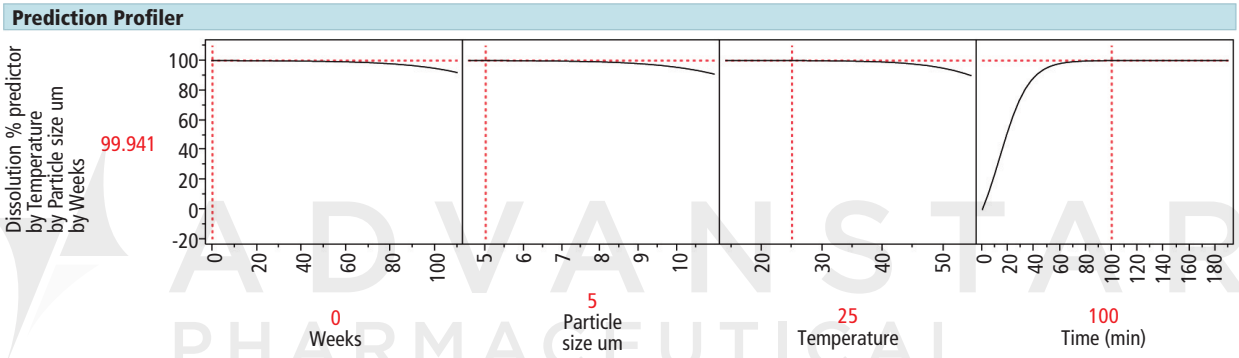


Figure 9: Disslution prediction from the model.



Summary

Non-linear multiple factor analysis has long been a problem in a variety of process and product modeling and prediction. The novel procedure discussed in this paper for the characterization of multiple factor non-linear product performance provides a clear, statistically defendable method for determining dissolution and accelerated stability. Long-term verification of accelerated conditions should always follow early determinations of expiry, acceleration rates, and rates of degradation.

Reference

1. ICH, Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Oct. 6, 1999). **PT**

Figure 10: Expiry determination.