Setting Process Conditions to Optimize Yield and Roundness for Spheronized Pellets

Introduction

In a published paper entitled "Studies of parameters important in the spheronisation process", Baert, Vermeersch, Remon, Smeyers-Verbeke and Massart[1] have investigated a binary mixture of Avicel PH 101 and water, looking at the effect of changing the Avicel/water ratio, the spheronization time and the spheronization speed on the yield and roundness of the spheronized particles. They used a design-of-experiments approach, with 3 spheronizer speeds, 5 spheronization times, and 3 different water/Avicel ratios. This led to 45 unique combinations of formulation and process conditions. In addition, they performed 16 'replicate' experiments.

Their data were used in **INForm** to derive a model that could be used to investigate optimized process conditions that would give a high yield of spherical particles. The 45 'designed' records were used as training data, with the 16 replicates used to test the model's predictivity.

Network Architecture and Model Validity

The default network parameters were used to develop the models; for this case **INForm's** inbuilt rules suggested that a single 3-node hidden layer network architecture should be used. An asymmetric sigmoid transfer function was used on the hidden layer, and a linear transfer function was used for the output. (These are the defaults.) The default backpropagation algorithm, RPROP, was used for the training. This requires no user-specified parameters. The results from Analysis of Variance (ANOVA) statistics are summarized in Table 1. It is clear that excellent models have been developed for both properties. In addition, the models are reliably predictive, shown by the good values for the Test R^2.

Model	Training R^2	Test R^2
Yield	0.971	0.969
Roundness	0.957	0.982

Table 1. ANOVA statistics for the neural network models when all 3 variables contribute

All 3 input variables (Avicel%, spheronization speed and spheronization time) were allowed to contribute to the model. However, the related **FormRules** study showed that although for Roundness, all three variables were important, only Avicel % and spheronization speed played a large role for the Yield. Consequently, an alternative model was developed, in which the connection between spheronization time and Yield was broken. This gave a Training R^2 value of 0.926, and a Test R^2 of 0.947, a slight decrease from the values in Table 1. However, the values are still very high, confirming the **FormRules** result that spheronization time is relatively unimportant. Of course, the model for Roundness was not affected by this change, since all connections were assumed in developing this model.

Actual vs predicted plots have been produced, to show how well the models fit the training data. These are shown in Figures 1 and 2 respectively.

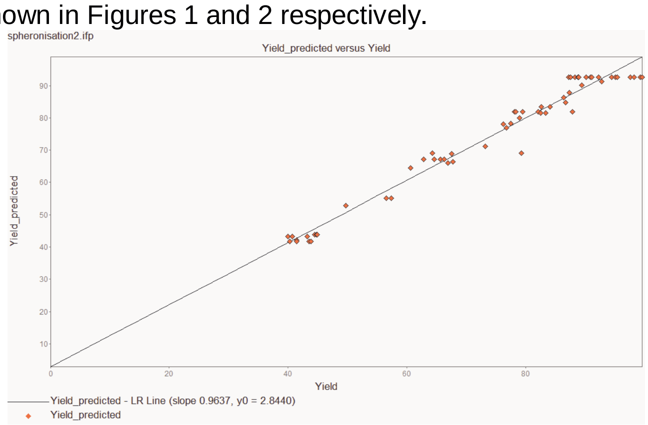

Figure 1. Actual vs. predicted values for Yield

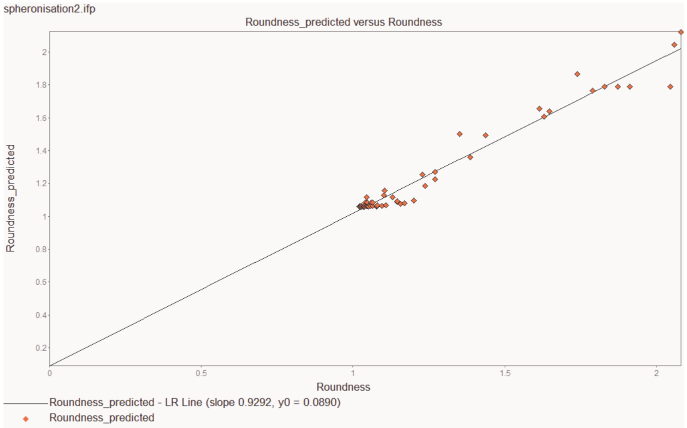

Figure 2. Actual vs predicted values for Roundness

If a perfect fit had been found to the data, this curve would be a straight line with intercept 0 and slope 1, which passed through all the data points. The degree of scatter shows the discrepancy between actual and predicted values. In both cases the scatter is relatively small. (This is another way of expressing the information captured in the ANOVA statistics.)

Discussion

The aim of the spheronization process is to produce a high yield of particles that have a Roundness value close to 1. Supplementary to this is the inbuilt assumption that if spheronization time could be decreased, then processing could be speeded up. This study looks at aspects of prediction and optimization to find which values should be used for the process parameters.

It is possible to use the neural network models to make predictions of how the properties will change when the formulation or process conditions are changed. Experimentally, three different Avicel/water ratios were used, with Avicel % of 42.5, 47.5 and 52.5. The models allow investigation of other formulations, and Table 2 gives some representative results when some other values of the Avicel % were investigated. In Table 2, the statistical prediction was calculated using the expression taken from Baert *et al*, Y=114.1881-0.000377*proportion Avicel*speed + 0.12595*speed. It is, of course, also possible to make predictions for different values of the process variables, for example a spheronization time of 2 minutes (which was not examined experimentally) or a speed of 800 cps.

Avicel %	Speed	Time	Predicted value	Statistical Prediction
50	500	10	81.9	82.9
50	500	20	77.4	82.9
50	800	10	72.4	64.1
50	1000	10	42.3	51.6
50	1000	5	45.8	51.6
50	1000	2	50.4	51.6
45	500	10	92.6	92.3
45	500	2	92.6	92.3
45	800	5	92.5	79.2
45	1000	5	69.4	70.5

Table 2. Predictions of Yield from neural network and statistical models for various formulations and process conditions

Although Table 2 is by no means comprehensive, it shows that there is generally good agreement between the statistical and neural network models. However, the neural network model has been able to take account of spheronization time on the Yield, so gives a better model. It can be seen that the greatest discrepancies between the two models happens at values (like speed of 800) which were not part of the training data. This probably occurs because the statistical model is forced to be linear with respect to changes in the number of parameters, while the neural network model is allowed to take a non-linear form that best fits the data. This can be illustrated in Figure 3, which shows how Avicel % and spheronization speed affect the yield, at a fixed spheronization time of 10. Similar non-linear behaviour is seen at different spheronization times.

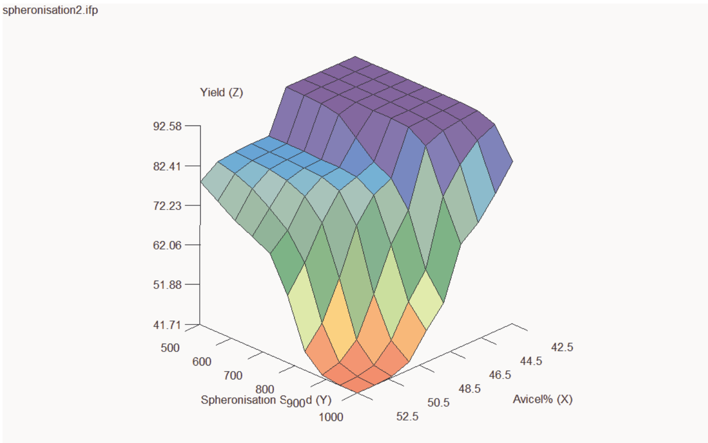

Figure 3. Effect of Avicel % and Spheronization Speed upon Yield, at fixed spheronization time = 10

The results from the statistical model of Baert *et al*[1] are plotted in Figure 4. Because this graph does not use a model internal to **INForm**, it has not been possible to produce a graph of similar quality to that shown Figure 3; however, it can be seen that the predicted yield behaves very smoothly and linearly, as expected from the nature of the model.

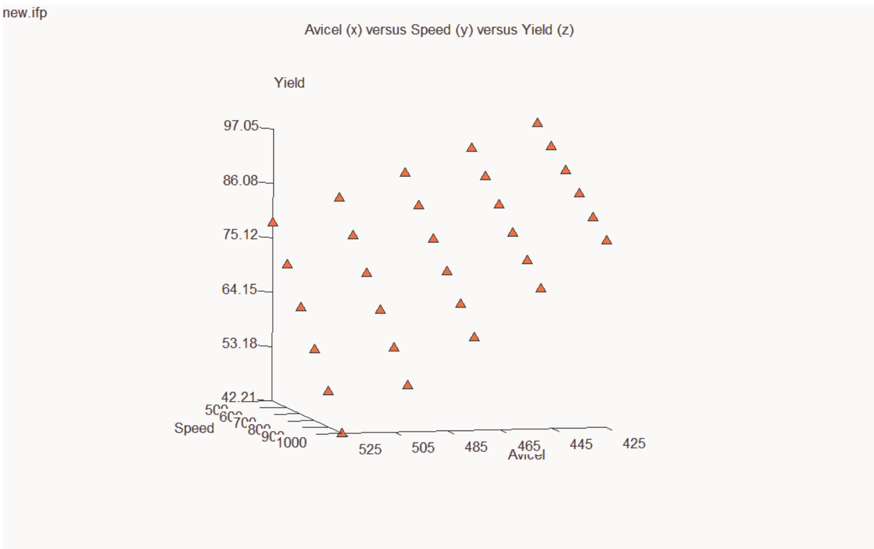

Figure 4. Predictions from the statistical model

In addition to these ‘what if’ investigations, optimizations can also be performed. Within **INForm**, each property can be ranked according to its importance, and desired values and ranges can be specified. In the present study, the aim was to have a yield of acceptable particles in excess of 90%, with roundness less than 1.05.

The screenshot in Figure 5, taken from **INForm**, shows that in our study Yield has been assigned a ranking of 9, but that Roundness has been ranked more highly, at 10. Yields of less than 70% have been set to be unacceptable (desirability is 0), while yields above 90% are completely acceptable. Values less than 1.05 for Roundness are completely acceptable (shown by the ‘Downhill’ desirability function).

Genetic algorithms were used to find an optimum solution using the default parameters with 50% replacement of 'genetic material' from one iteration to the next, and a maximum of 100 iterations (generations). These are the default optimization parameters within **INForm**.

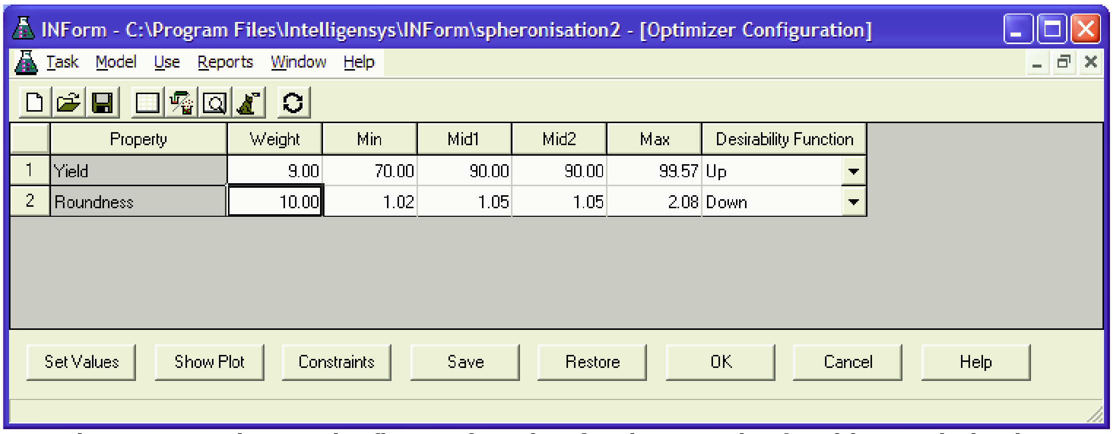

Figure 5. Setting up the fitness function for the genetic algorithm optimization

The optimization objectives discussed above were substantially achieved with a formulation containing 42.5% Avicel, at a spheronization speed of 950 cps and time of 30 minutes. The model in this case predicted that Roundness would take a value of 1.06, while Yield was 90.02%.

Changing the criteria so that Yield was required to be in excess of 95% gave a different formulation, with Avicel % still 42.5%, but with a spheronization speed of 640 cps and time 26.5 minutes.

Both of these – in common with the optimized formulations of Baert *et al* – involved relatively long spheronization times. In our third optimization, the spheronization was fixed at 5 minutes with the challenge being to find a formulation that met our criteria while obeying this time constraint. A formulation of 42.5% Avicel, with spheronization speed 870 cps, gave a yield of 92% and roundness of 1.08. Therefore, yield and roundness did not need to be sacrificed significantly when the spheronization time is reduced. Lowering the spheronization speed to 800 cps led to a slightly higher roundness of 1.1, which could still be acceptable for some applications. (For example, simulations of capsule filling indicate that as long as roundness is less than 1.2, reproducibility of fill can generally be achieved.)

In common with the results of Baert *et al*, our study found that all the optimized formulations had an Avicel % of 42.5 (i.e. a high water content). This suggests that reducing Avicel % still further (in effect increasing the water content) might lead to better properties – although of course there might be different processing problems encountered with this softer formulation.

Conclusions

The statistical study in general had to focus on one formulation at a time, simply varying the process conditions. Trying to combine all of the formulations into one model did not give good results; the ANOVA statistics were poor. This was not a problem with the neural networks models, where all the data could be treated in the same dataset without difficulty. This can be attributed in large measure by the ability of the neural network to generate non-linear models easily.

The neural network models were of better quality (as assessed by ANOVA statistics) than those from the statistical treatment reported in the literature[1], and the model for yield also displayed significant non-linearity particularly with respect to Avicel%. The process of validation (i.e. withholding some of the data to assess the model's ability to predict) showed that the models were reliable, although it would have been useful to have additional points other than the 'designed' ones to probe the non-linearity fully.

A number of optimum formulations were explored, given the aim of achieving high yield and low roundness (i.e. spherical particles). In common with the statistical study, the optimum formulations were all found to have low percentages of Avicel (and hence high water content).

References

(1) L Baert, H Vermeersch, J P Remon, J Smeyers-Vereke and D L Massart, International Journal of Pharmaceutics 96 (1993) 225-229