

Optimizing Roller Compaction Processes with INForm

Roller compaction can be used in the production of acetaminophen (paracetamol) tablets. Acetaminophen has poor compression and flow characteristics, and deforms elastically upon compression, so an agglomeration process is useful. The choice of binder type and amount impacts on the final properties of the finished tablets, making this a complicated process to understand and optimize.

Modelling a process like this can be complex undertaking, especially since there can be interactions between the ingredients and between ingredients and processing conditions. Neural networks can provide a good approach especially when the nature of the interactions is not clear at the outset.

Roller Compaction for Acetaminophen Tablets

The data used in this study are taken from published work by M Turkoglu *et al*, reporting in the *European Journal of Pharmaceutics and Biopharmaceutics* **48**, 239-245 (1999). There were four variables (three ingredients and one process condition). These were

- Type of binder, chosen as one of hydroxypropyl methyl cellulose (HPMC), polyethylene glycol (PEG) or Carbopol
- Amount of binder, as a percentage
- Amount of microcrystalline cellulose, MCC, as a percentage
- Number of passes through the roller compactor (1 or 2)

Using these, Turkoglu *et al* created 42 different formulations. Four different properties were measured – the ejection force, the crushing strength of the tablets, the friability and the disintegration time. Turkoglu and his coworkers then used 30 of these experiments to develop a model of

the roller compaction process, saving 12 of the experiments to validate the model.

We used the same approach, taking the same 30 experiments as Turkoglu *et al* used when we developed our models. Like Turkoglu *et al*, we used the remaining 12 data records for validation and testing of the model.

Models for Roller Compaction

INForm was used with default parameters throughout, to develop a separate model for each of the properties. Using INForm's SmartStop facility, training was halted when the predictions for the Test Set indicated that the model might start to lose its predictive capabilities. ANOVA statistics were performed, and the R² values for both training and test sets are given in Table 1.

Property	Training R ²	Test R ²
Ejection force	98.9	88.0
Crushing strength	98.6	96.3
Friability	95.2	64.1
Disintegration time	99.0	81.4

Table 1. ANOVA statistics for INForm's neural network models

INForm suggested that 4 nodes should be used in the hidden layer. This is considerably fewer than the 16 to 24 hidden neurons used in Turkoglu's paper – their large number of neurons could introduce too many degrees of freedom into the model. We were therefore especially gratified that the R² values indicated that INForm has developed good models for all the properties, since Turkoglu *et al* reported difficulties in getting a good model for the ejection force.

INForm's predictions for the ejection force, for the test set, are shown in Figure 1.

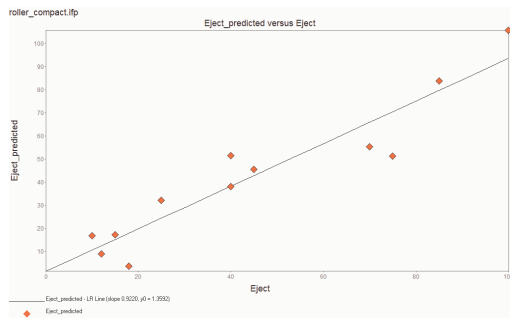


Figure 1. Actual vs Predicted values for ejection force, for the test data set

This shows about the same scatter as is seen in the training set (Figure 2). When the model is trained, the aim is to have the predicted value equal to the actual value, without over-training or ‘memorizing’ the data.

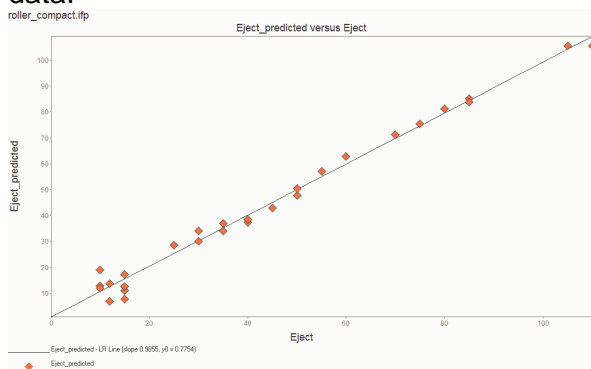


Figure 2. Actual vs Predicted values of ejection force, for the training data set

If a perfect model was developed, then Figure 2 would show an exact straight line. However, given that there is some experimental error, this would undoubtedly mean that the model had actually learned the noise, as well as the underlying relationships.

Optimization

If we are looking for tablets that have a high crushing force (greater than 10 kp) and a disintegration time of lower than 15 minutes, we can set these up in **INForm** and use the **INForm**’s genetic algorithm optimization to find a suitable formulation.

Turkoglu *et al* have also looked at some limited optimizations, assuming that tablet crushing strength is the most important property. However, they were forced to

carry out their optimization by examining response surfaces. This makes it difficult for them to balance conflicting requirements for the formulation.

In our optimization, looking for conflicting objectives was not a problem. It was also simple for us to constrain the optimization, so that the MCC addition (which was 0 or 1, a simple ‘yes’ or ‘no’), and the number of passes, were restricted to integral values. (A non-integral value would not be meaningful for these inputs.) Similarly, the binder had to be one of the three specific choices used.

The optimum formulation was found to be:

- HPMC, at 19.7%
- 1 compaction pass
- without extragranular MCC addition

Turkoglu *et al* also found that HPMC was the most promising binder, with a rapid increase in crushing strength when HPMC was added at concentrations above 12%. Figure 3 shows the corresponding response surface from **INForm**.

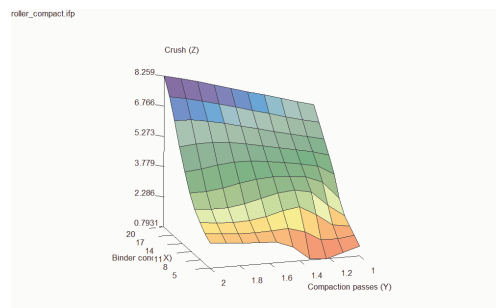


Figure 3. Crushing strength as a function of binder addition and compaction passes

Conclusions

INForm developed better models, judged by ANOVA statistics, than were reported in the paper by Turkoglu *et al* (who used the NeuroShell Easy Predictor toolkit).

The optimization results are in line with those found by Turkoglu *et al*. However, it was considerably easier to use **INForm**’s genetic algorithms for optimization, rather than examine response surfaces as done in the published paper.

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