

Finding Rules for Roller Compaction with FormRules

Background

Acetaminophen (paracetamol) has poor flow and compression characteristics, and shows elastic deformation behaviour upon compression. So, it is not easy to manufacture tablets of acetaminophen without a prior agglomeration process. In the present study, an acetaminophen tablet manufacturing process based on neural networks is investigated.

Formulation Data

M Turkoglu and his colleagues have published experimental data on a roller compaction process for acetaminophen in their paper in *European Journal of Pharmaceutics and Biopharmaceutics*, **48** 239-245 (1999). They have varied four different inputs. The binder could be one of three possibilities: hydroxypropyl methyl cellulose (HPMC, trade name Methocel), polyethylene glycol (PEG) or carbomer (Carbopol). The percentage of binder was varied, as was the amount of microcrystalline cellulose (MCC) that was added. In addition to these three ingredients, one process condition (the number of compaction passes) was also changed, taking values of 1 or 2.

The properties that were measured were the crushing strength of the tablets, the friability, ejection force, and disintegration time.

In their paper, Turkoglu *et al* reported 42 different experiments, 30 of which they used to develop their models. For a direct comparison, we used the same 30 experiments in developing our models. These were put into **FormRules** directly from a spreadsheet.

Models for Roller Compaction

Separate models were developed for each property using the Structural Risk Minimization approach to model training, which is most likely to avoid the problem of over-training in which the model 'memorizes' the data. The adjustable parameter C_1 was chosen to have the value 0.85. As Table 1 shows, R^2 values in excess of 95% were developed for all properties except friability. For friability, R^2 was 90%, which indicates that the model still fits the data very well.

Turkoglu *et al* found it difficult to get a good model for ejection force, but this has not been a problem for **FormRules**. All 4 input variables were found to be important for ejection force – this is also the case for the crushing strength.

Property	R^2 (%)
Ejection force	98.3
Crushing strength	94.7
Friability	89.7
Disintegration time	99.1

Table 1. R^2 values for each model

For the disintegration time, both the binder type and binder concentration play an important role as shown in the figure below. The percentage of MCC added also affected this property.

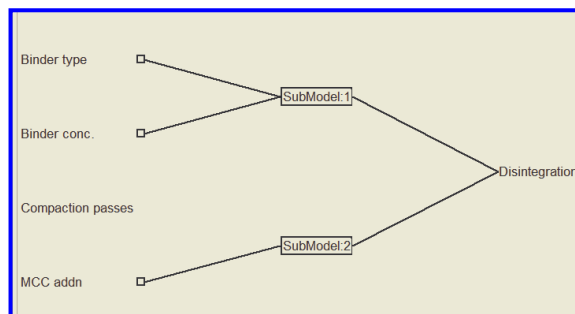


Figure 1. Important inputs for Disintegration Time

Friability depends primarily on the binder type and binder concentration, as shown in Figure 2.

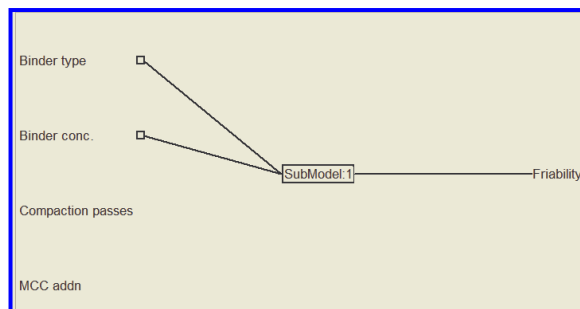


Figure 2. Important inputs for Friability

Rules for Roller Compaction

FormRules can express the information it discovers, in the form of rules. For the ejection force, there are three submodels. The rules from the first submodel are:

- IF Binder type is HPMC AND Binder conc. is LOW THEN Ejection force is LOW (1.00)
- IF Binder type is HPMC AND Binder conc. is HIGH THEN Ejection force is HIGH (1.00)
- IF Binder type is PEG AND Binder conc. is LOW THEN Ejection force is LOW (1.00)
- IF Binder type is PEG AND Binder conc. is HIGH THEN Ejection force is LOW (1.00)
- IF Binder type is Carbopol AND Binder conc. is LOW THEN Ejection force is LOW (1.00)
- IF Binder type is Carbopol AND Binder conc. is HIGH THEN Ejection force is HIGH (0.87)

whereas those from the second model are:

- IF MCC addition is LOW AND Binder type is HPMC THEN Ejection force is LOW (0.79)
- IF MCC addition is LOW AND Binder type is PEG THEN Ejection force is LOW (1.00)
- IF MCC addition is LOW AND Binder type is Carbopol THEN Ejection force is LOW (0.98)
- IF MCC addition is HIGH AND Binder type is HPMC THEN Ejection force is HIGH (0.80)
- IF MCC addition is HIGH AND Binder type is PEG THEN Ejection force is LOW (1.00)
- IF MCC addition is HIGH AND Binder type is Carbopol THEN Ejection force is HIGH (0.63)

The third submodel gives:

- IF Compaction passes are LOW THEN Ejection force is LOW (0.52)
- IF Compaction passes are HIGH THEN Ejection force is HIGH (0.67)

For this final submodel, the values for the confidence levels (given in parentheses following the relevant rule) show that the number of compaction passes does not have a strong effect on the ejection force.

For disintegration time, there are two submodels. The rules from the first are:

- IF Binder type is HPMC AND Binder conc. is LOW THEN Disintegration is LOW (1.00)
- IF Binder type is HPMC AND Binder conc. is MID THEN Disintegration is LOW (1.00)
- IF Binder type is HPMC AND Binder conc. is HIGH THEN Disintegration is LOW (1.00)
- IF Binder type is PEG AND Binder conc. is LOW THEN Disintegration is LOW (1.00)
- IF Binder type is PEG AND Binder conc. is MID THEN Disintegration is LOW (1.00)
- IF Binder type is PEG AND Binder conc. is HIGH THEN Disintegration is LOW (0.91)
- IF Binder type is Carbopol AND Binder conc. is LOW THEN Disintegration is LOW (0.59)
- IF Binder type is Carbopol AND Binder conc. is MID THEN Disintegration is HIGH (0.52)
- IF Binder type is Carbopol AND Binder conc. is HIGH THEN Disintegration is HIGH (1.00)

Clearly the disintegration time is low, except when the binder is Carbopol, added at fairly

high concentrations. The second submodel gives the rules:

- IF MCC addn is LOW THEN Disintegration is HIGH (0.50)
- IF MCC addn is HIGH THEN Disintegration is LOW (0.56)

which shows clearly that the MCC addition has only a minor effect on disintegration time.

Crushing strength also has three submodels. Again, two of them have a relatively small effect. The most important rules are:

- IF Binder conc. is LOW AND Binder type is HPMC THEN Crushing strength is LOW (1.00)
- IF Binder conc. is LOW AND Binder type is PEG THEN Crushing strength is LOW (1.00)
- IF Binder conc. is LOW AND Binder type is Carbopol THEN Crushing strength is LOW (1.00)
- IF Binder conc. is HIGH AND Binder type is HPMC THEN Crushing strength is HIGH (1.00)
- IF Binder conc. is HIGH AND Binder type is PEG THEN Crushing strength is HIGH (1.00)
- IF Binder conc. is HIGH AND Binder type is Carbopol THEN Crushing strength is LOW (0.86)

The crushing strength is low when binder concentration is low, regardless of binder type. If the binder concentration is high, though, the crushing strength is high unless the binder type is Carbopol.

Finally, friability has only one submodel, involving binder type and binder concentration. The rules are:

- IF Binder type is HPMC AND Binder conc. is LOW THEN Friability is HIGH (0.80)
- IF Binder type is HPMC AND Binder conc. is MID THEN Friability is LOW (1.00)
- IF Binder type is HPMC AND Binder conc. is HIGH THEN Friability is LOW (1.00)
- IF Binder type is PEG AND Binder conc. is LOW THEN Friability is HIGH (0.74)
- IF Binder type is PEG AND Binder conc. is MID THEN Friability is LOW (1.00)
- IF Binder type is PEG AND Binder conc. is HIGH THEN Friability is LOW (1.00)
- IF Binder type is Carbopol AND Binder conc. is LOW THEN Friability is HIGH (1.00)
- IF Binder type is Carbopol AND Binder conc. is MID THEN Friability is HIGH (0.95)
- IF Binder type is Carbopol AND Binder conc. is HIGH THEN Friability is LOW (0.87)

Conclusions

FormRules has been able to discover useful models and rules for the roller compaction process, even for the properties where the published work had problems in finding a good model. One of the advantages of **FormRules** is that it does not 'fuzzify' the binder type, which must fall into a discrete class.

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