

Finding Rules for Nanoemulsion Particle Sizes with FormRules

Background

Nanoemulsions are good options for delivering drugs with poor aqueous solubility. Ease of preparation and scale-up, stability and increased bioavailability are features of such formulations. For delivery, though, minimizing the concentration of any surfactants is important, to reduce possible toxic effects. This in turn can reduce the options for controlling particle size, making understanding the processing variables especially important.

Classical statistical techniques often prove inadequate for modelling these systems, because the relationships between the components and/or processing conditions are non-linear. However, neural computing techniques have been applied successfully.

This note reports on how data mining techniques – notably neurofuzzy logic – can be used to identify quickly the important parameters – in addition to surfactant and internal phase content – that control particle size.

Nanoparticle Data

The data used in this study have been published by A Amani, P York, H Chrystyn, B J Clark and D Q Do, in *European Journal of Pharmaceutical Sciences* (2008) doi: 10.1016/j.ejps.2008.06.002. Their system used a mixture of medium chain triglyceride, polysorbate 80, ethanol and normal saline loaded with budesonide, and particles were created by varying rates and the amount of energy used in particle preparation.

Amani *et al* performed 60 experiments in total, then used multi-layer perceptron (MLP) neural networks to model the data, with 41 records used for training their model, 4 for testing, and a further 15 for validation. However, although MLP neural networks provide valuable models, they can be 'black box' in nature. Consequently, in the present study, the 45 records (training and test set) from their data were used for the 'grey box' models developed by **FormRules**. A second model, using all 60 inputs, was also considered.

For the models, the input variables were:

- w/w% ethanol
- amount of drug (budesonide) in mg
- total energy (J)
- saline (N)
- rate of applied energy (J/s)

Just one output, particle size, was monitored. Particle sizes ranged from 10 to 24 nm.

In both cases, when 45 and 60 data records were used, reasonable models were developed with R^2 values approaching 0.7. The same results were found whether the model selection criterion was Structural Risk Minimization or Minimum Descriptor Length.

Controlling Nanoparticle Size

When the original 45 data records were used, the results shown below were found.

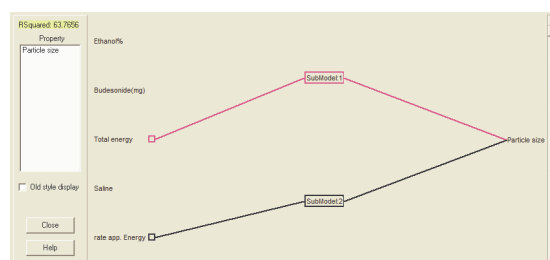


Figure 1. Graphical representation of model developed using 45 data records, with Structural Risk Minimization as model selection criterion.

As this figure shows, the main parameter (shown by the purple line) that affects particle size is the Total Energy, while the Rate of Applied Energy is also significant.

The rules are also given by FormRules. These are

IF Total energy is LOW THEN Particle size is HIGH (1.00)
IF Total energy is HIGH THEN Particle size is LOW (1.00)

and

IF rate app. Energy is LOW THEN Particle size is LOW (0.50)
IF rate app. Energy is MID THEN Particle size is LOW (1.00)
IF rate app. Energy is HIGH THEN Particle size is LOW (0.61)

The values in brackets are 'confidence levels', and the second set of roles shows that only if the rate of applied energy is in the middle of the range can the particle size be said to be LOW with confidence. If the rate of applied energy is either low, or high, then the particle size lies towards the middle of the range.

Adding the 15 records from the validation set, and using all 60 records in the model, gives a somewhat more accurate model, and the results are shown below.

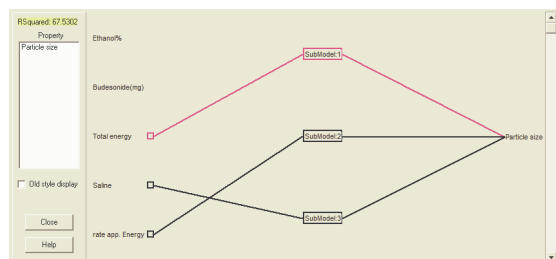


Figure 2. Graphical representation of model developed using 60 data records, with Structural Risk Minimization as model selection criterion.

Although the Total energy remains the most important factor, and the rate of applied energy remains significant, the saline is also shown to be important. The w/w% percentage of ethanol and the budesonide play no important role in determining the particle size.

The rules for this second model are:

For the most important sub-model:

IF Total energy is LOW THEN Particle size is HIGH (1.00)
IF Total energy is HIGH THEN Particle size is LOW (1.00)

For the second sub-model:

IF rate app. Energy is LOW THEN Particle size is HIGH (0.56)
IF rate app. Energy is MID THEN Particle size is LOW (1.00)
IF rate app. Energy is HIGH THEN Particle size is LOW (0.61)

and for the final sub-model:

IF Saline is LOW THEN Particle size is HIGH (0.69)
IF Saline is HIGH THEN Particle size is LOW (1.00)

As discussed above, the R^2 values for the models were relatively low, and to try to develop a model that fitted better to the data, the other model selection criteria built into **FormRules** were tried.

Using Leave One Out Cross Validation as the model selection criterion, a model with R^2 of 0.73 was developed.

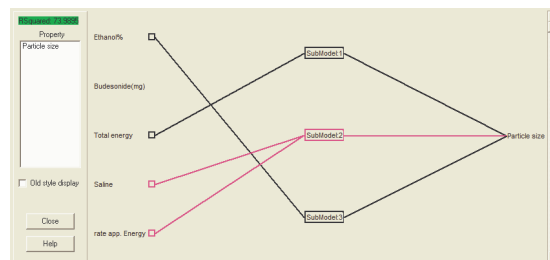


Figure 3. Graphical representation of model developed using 60 data records, using Leave One Out Cross Validation

Here, the rate of applied energy, interacting with the amount of saline, makes the most important contribution, with rules

IF rate app. Energy is LOW AND Saline is LOW THEN Particle size is HIGH (0.94)
IF rate app. Energy is LOW AND Saline is HIGH THEN Particle size is LOW (1.00)
IF rate app. Energy is MID AND Saline is LOW THEN Particle size is LOW (1.00)
IF rate app. Energy is MID AND Saline is HIGH THEN Particle size is LOW (1.00)
IF rate app. Energy is HIGH AND Saline is LOW THEN Particle size is LOW (1.00)
IF rate app. Energy is HIGH AND Saline is HIGH THEN Particle size is HIGH (1.00)

The total energy and the w/w% ethanol also contribute. Interestingly, though, in this case the total energy is not involved in the most important sub-model.

F Total energy is LOW THEN Particle size is HIGH (1.00)
IF Total energy is HIGH THEN Particle size is LOW (1.00)

IF Ethanol% is LOW THEN Particle size is LOW (0.93)
IF Ethanol% is MID THEN Particle size is HIGH (0.58)
IF Ethanol% is HIGH THEN Particle size is LOW (0.69)

The fact that in no case (whether 45 or 60 data records were used) could a model with a very high value of R^2 developed indicates that there may be other variables, not measured in this study, which are affecting particle size. However, the important effects have been identified and captured by the models.

Conclusions

The rules obtained from **FormRules** (neurofuzzy logic) are consistent with those from the more complicated published studies, *but they were significantly easier to obtain*. The analysis reported here took only a couple of minutes on a PC, showing that once good data are available, models and rules can be extracted quickly.

For further information on FormRules and on applying neurofuzzy logic to your problems, contact us at the address below.

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