Optimizing Nanoparticle Size with INForm

Nanoemulsions are good options for delivering drugs with poor aqueous solubility. Ease of preparation and scale-up, stability and increased bioavailability are all features of such formulations.

Control of particle size can be important in determining particle stability and for ensuring the desired delivery characteristics.

Because these systems frequently show non-linear relationships, modelling by traditional techniques (like statistics) can be difficult. Now, however, neural networks can be used to develop good models quickly.

This study reports the use of **INForm**, a software package based on neural networks and genetic algorithms, to model and optimize nanoparticle properties.

Nanoparticle emulsions

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 total amount of energy used in particle preparation.

Amani and his coworkers performed 60 experiments in total. Only one property, particle size, was measured, and this ranged between 10.84 and 24.81 nm.

Their data has also been used in a separate study using **FormRules** to 'data mine' to find the key rules controlling particle size, and this is given in a separate application note.

Developing Neural Network Models

Of the 60 experiments carried out, 41 were used for training the neural network model, while 4 were withheld for 'testing' to ensure that the model remained predictive, and did not fit to 'noise' in the data. 15 data records were withheld for validation; these played absolutely no role in the training process, so are a genuine test of the predictivity of the model.

The best models were trained using standard batch backpropagation. The hidden layer had 5 nodes, and tanh transfer functions were used for both the hidden and output layers. These gave R^2 values (ANOVA statistics) of 97.8% for the training set, 92.7% for the test set, and 91.2% for the validation set respectively.

Figure 1 shows the actual vs predicted values for the validation data set.

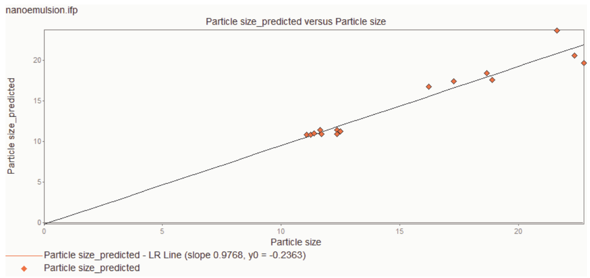

Figure 1. Predicted vs actual particle sizes for validation data set

This shows a very good fit, particularly at the smaller particle sizes. The model can therefore be used with confidence for optimization of particle size.

Minimizing particle size

Amani *et al* used response surfaces to try to understand the detailed behaviour of their nanoparticles. Here, we have adopted a different approach, by using genetic algorithms (as implemented in **INForm**) to try to find the best formulation and processing conditions to give stable small particles.

Since there is only one property, **INForm's** ability to examine trade-offs in conflicting properties is not tested by this study. However, this work does illustrate the ability to set constraints on the ingredients and process conditions and consequent effects on the optimization.

In the first optimization, we searched for conditions that gave the smallest possible particle size (10.84 nm, the minimum in the experimental data) subject to the constraint that the total energy had to be less than 1000 J. **INForm** determined that conditions given in Table 1 would be suitable.

Ethanol %	2.43
Budesonide (mg)	0.20
Total energy (J)	650
Saline	1.75
Rate Applied Energy	629

Table 1. Conditions to produce smallest nanoparticles, with requirement that total energy <1000 J

However, this formulation contains no budesonide. If we require that the amount of budesonide is greater than 25 mg, while maintaining the constraint that the total energy has to be less than 1000 J, we find that it is not so easy to achieve the smallest particle sizes. The best conditions, as suggested by **INForm**, would be those given in Table 2, but the minimum particle size that could be achieved was 11.8 nm.

Ethanol %	2.74
Budesonide (mg)	25.0
Total energy (J)	650
Saline	1.75
Rate Applied Energy	661

Table 2. Conditions to produce smallest nanoparticles, with requirement that total energy <1000 J and budesonide > 25mg.

Should we desire more than 30 mg of budesonide, then maintaining the constraint that the total energy < 1000 J gives the conditions shown in table 3. The predicted particle size from these conditions is 12.2 nm.

Ethanol %	2.32
Budesonide (mg)	30.0
Total energy (J)	650
Saline	1.75
Rate Applied Energy	1771

Table 3. Conditions to produce smallest nanoparticles, with requirement that total energy <1000 J and budesonide > 30 mg.

You will note that in all of these cases, the amount of saline remains at 1.75. This is the maximum value in the data set, and indicates that perhaps increasing this value might lead to a decrease in particle size.

The rate of applied energy must be increased substantially when the amount of budesonide is increased, in order to maintain a reasonably small particle size.

Ethanol percentage does not affect particle size significantly. This is consistent with the results found by Amani *et al* using response surfaces. Amani *et al* found that the total amount of energy was the main factor affecting particle size, but that below a critical value (4000 J) then other factors came into play.

Using **INForm's** 'graphical Explorer' shows that particle size is actually near a maximum when the total energy lies towards the middle of the range (at about 2600 J). Smaller particles are obtained at both higher and lower total energy inputs. The plot of particle size as a function of the amount of budesonide and the rate of applied energy is shown in Figure 2.

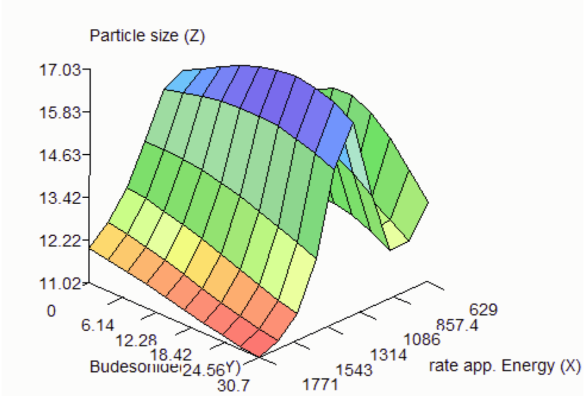

Figure 2. Particle size as a function of budesonide concentration and rate of applied energy. Hidden variables have values total energy 2600 J, saline 1.75 and ethanol 2.32%

Conclusions

Neural networks gave very good models for determining the cause-and-effect relationships between the formulation and processing conditions used in producing nanoparticles, and the resulting particle size.

The work of Amani et al showed that response surfaces could be used to understand which variables had a significant role, and (to a limited extent) to optimize the properties.

The work described in this note shows that genetic algorithms can be used, in conjunction with the neural network models, to produce optimum particle size. Constraints can be put on the variables (for example, the amount of encapsulated drug) when these required to achieve specific formulation process limitations, and the 'fitness function' in the optimization will take account of these.

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