

# Optimizing Redispersible Suspensions with INForm

*Suspensions play a valuable role in delivering drugs in both oral and injectable form. However, suspensions can settle over time, and the ease of redispersibility becomes crucial to their acceptability.*

The traditional approach to designing and optimizing new formulations uses statistics, requiring carefully designed experiments for a range of ingredient and processing conditions. Elkheshen, Badawi and Badawi have reported work using a 2<sup>4</sup> full factorial design, using response surfaces to produce an optimum formulation of rifampicin (*Drug Development and Industrial Pharmacy* **22** 623-630, 1996). However, fitting the equations, and obtaining the best solution from the response surfaces, is a complex task.

Now, a powerful alternative, **INForm**, has been developed by Intelligensys. The **INForm** software package integrates neural networks with efficient optimization routines based on Genetic Algorithms. The neural network-based formulation model lets the user bypass many "what if" questions typically required to find an acceptable formulation, and instead, tells the user directly how to achieve certain properties (like stable formulations that are easily adsorbed) with minimum effort.

To use **INForm**, you carry out some initial experiments, and feed these into the neural network directly from your spreadsheet package. Once your model is developed, you can then specify the properties you want, and the optimization process will tell you what ingredients and process conditions are required to obtain them.

## Data for Rifampicin Suspension

Elkheshen *et al* performed 21 experiments with 4 independent variables (formulation ingredients). Five of the experiments were replicates at the centre, to assess the

experimental error. The ingredients and the range over which they were allowed to vary, as percentages of the constituted suspension, were:

- Sucrose (30%, 45% or 60%)
- Avicel (1%, 1.5% or 2%)
- Aerosil (0%, 0.5% or 1%)
- Aerosol (0%, 0.05% or 0.01%)

In addition, there were other ingredients (rifampicin, sodium citrate, citric acid, sodium benzoate and flavour) that were not varied in the experiments.

The properties that were measured were

- bulk density
- flowability of the powder
- viscosity of the suspension after 24 hours
- sedimentation volume as % of initial volume
- percentage ease of redispersability

The experimental data published by Elkheshen *et al* was imported into **INForm**. 10% of the data records (i.e. 2 records) were withheld for model validation, and the rest were used in the training data set. Because there were relatively few data points, a 2-node hidden layer was suggested by **INForm**, and was used in this work. All other "training" parameters were left at their default values.

Good models were developed for all 5 properties, with ANOVA statistics giving values for R<sup>2</sup> in excess of 0.9 in all cases. In fact, for all the properties except bulk density and sedimentation percentage, R<sup>2</sup> exceeded 0.97. The R<sup>2</sup> values were supported by good f-ratio values, indicating that the neural network has produced high quality models.

These models can be used both for 'what if' predictions, and to produce an optimized formulation.

## Predicted Formulations

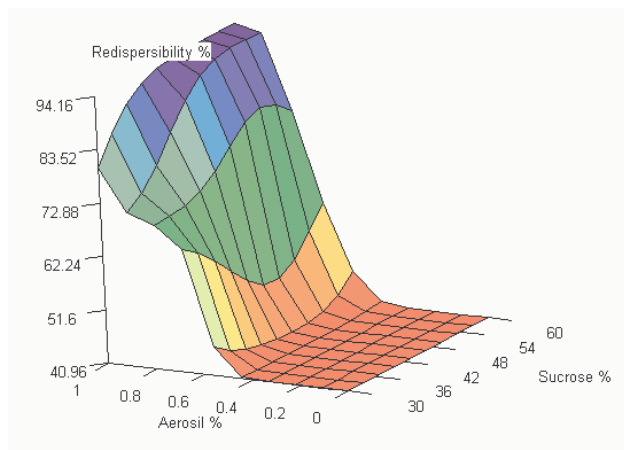
In their paper, Elkheshen *et al* predicted results for 3 novel formulations shown in Table 1. We have investigated the same cases, and the results for Formulation C are presented in Table 2, along with the predicted and experimental values from Elkheshen *et al*.

	Predicted Elkheshen	Experiment	Predicted <b>INForm</b>
Bulk Density	0.814	0.815	0.819
Flowability	12.82	11.33	12.44
Viscosity	18.5	20	18.6
Sedimentation	26.6	30	29.9
Redispersibility	58.69	60	56.02

**Table 2. Results for Formulation C**

The results from **INForm** are generally satisfactory – and took considerably less time to extract - than did the statistical values from the published work.

The models are generally non-linear, as shown in Figure 1, which shows the effect of Aerosil and Sucrose on redispersibility.



**Figure 1. Redispersibility as a function of Aerosil % and Sucrose %**

As Figure 1 illustrates, even a small change to the amount of Aerosil (at amounts greater than 0.5%) can make a significant difference in the redispersibility. This non-linearity is not picked up well in the statistical models. Sucrose has relatively little effect at low Aerosil %.

## Optimized Formulations

Generally, redispersible suspensions have a high sedimentation volume, because a low sedimentation volume usually indicates the presence of caking. High sedimentation volume generally implies that flocculation, rather than caking, occurs. A high viscosity is also frequently associated with a high sedimentation volume. Generally, the aim is to make a formulation in which the powder has high flowability, and the suspension has a high sedimentation volume and a high redispersibility.

Using **INForm**, we tried to make a formulation with a high redispersibility but a low sedimentation volume. This was clearly not possible – although a redispersible suspension (above 90%) could be made, the sedimentation volume was about 50% in each case. Forcing the sedimentation volume to be below 25% meant that the redispersibility percentage could not exceed 67%, in line with the knowledge of experienced formulators.

The trade-offs between flowability and redispersibility were less crucial, and formulations with reasonable flowability and high redispersibility could be found. In all cases, examining these trade-offs was easily accomplished simply by setting the new objectives within **INForm's** Graphical User Interface.

## Conclusions

**INForm's** neural networks have successfully modelled a rifampicin suspension, giving results that are similar to those from statistics. The models were developed quickly, requiring little 'artificial intelligence' expertise from the user.

The 'what if' and optimization facilities in **INForm** allowed a number of possible new formulations to be explored very quickly *in silico*. The optimizer allowed trade-offs between the various properties to be examined more quickly than was feasible with response surface methods.

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