Finding Rules for Reconstitutable Suspensions with FormRules

Background

Pharmaceutical drugs are sometimes delivered as suspensions of powders in a liquid medium. The aim is to develop a suspension that can easily be redispersed, should sedimentation occur. In order to do this, an understanding of the effect that each ingredient has on various properties is required.

One new technology that can be applied is neurofuzzy logic - a technique that combines the learning and adaptive capability of neural networks with the ability of fuzzy logic to express conclusions based on vague, ambiguous, incomplete and imprecise information. This technique is rapidly gaining acceptance in data mining applications - including formulation data sets, and is the underpinning technology in the **FormRules** program. Here, we have used **FormRules** to extract knowledge directly from a formulation data set.

Rifampicin Suspension Formulation Data

Elkheshen, Badawi and Badawi have published a study on reconstitutable suspensions of rifampicin, in *Drug Development and Industrial Pharmacy* **22**, 623-630 (1996). They carried out a 2^4 factorial design, with 5 additional repeats of the centroid point to assess experimental scatter, and have analyzed the results using response surface methods.

In the work of Elkheshen *et al*, 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

We have imported the published data directly into **FormRules**, and have used the neurofuzzy technique to examine the data. The default parameters were chosen throughout, generating the simplest models that reproduce the data adequately.

Rules for Rifampicin Suspensions

Bulk density was shown by **FormRules** to depend on Sucrose % and Aerosil %. This is consistent with the results of Elkheshen et al from their statistical study. In addition, **FormRules** produced 'rules' of the form

IF Sucrose % is LOW AND Aerosil % is LOW THEN Bulk density is HIGH (0.81)

IF Sucrose % is LOW AND Aerosil % is HIGH THEN Bulk density is LOW (0.72)

IF Sucrose % is HIGH AND Aerosil % is LOW THEN Bulk density is HIGH (0.78)

IF Sucrose % is HIGH AND Aerosil % is HIGH THEN Bulk density is HIGH (0.89)

Numbers in parentheses show the 'confidence level' of the rule. At low levels of Sucrose, Aerosil has a marked effect. This is not the case when the Sucrose % is at the high end of the range. In that case, Aerosil has only a small effect. Only the confidence level is affected; the conclusion is that Bulk density will be high if Sucrose % is high. The inter-relationship between Sucrose % and Aerosil % on the bulk density is shown in Figure 1.

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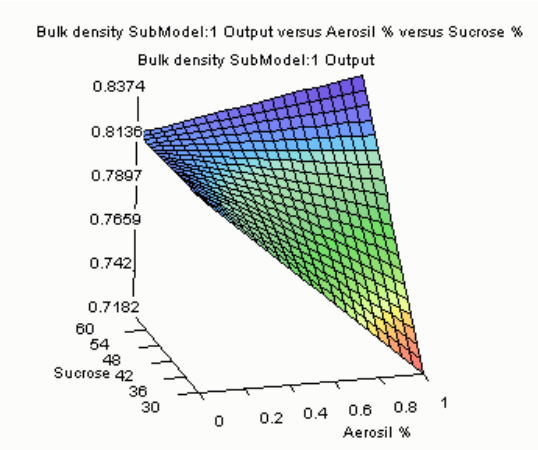

Figure 1. Effect of Aerosil and Sucrose on Bulk Density

For Flowability, **FormRules** showed that only Aerosil% was important. This is consistent with the statistical study – although the statistical work also suggested that sucrose might play a role. Figure 2 shows the relationship between Aerosil % and flowability – above about 0.5%, adding more aerosil does not significantly increase flowability.

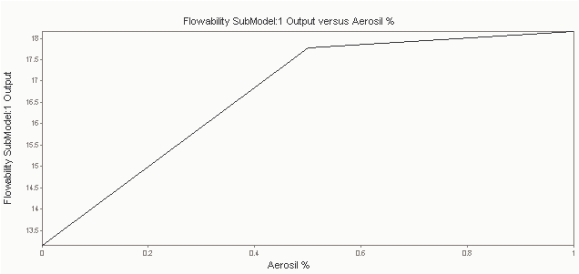

Figure 2. Effect of of Aerosil % on Flowability

Viscosity was more complex, depending on Sucrose, Avicel % and Aerosil %. Adding sucrose increased the viscosity in a linear fashion, as did adding Avicel. The Aerosil had a complex effect, decreasing viscosity at low concentrations, but increasing it at higher ones, as Figure 3 shows.

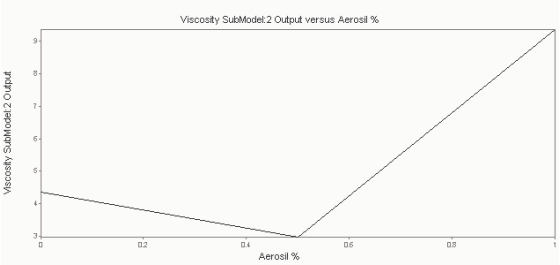

Figure 3. Effect of Aerosil % on viscosity

Sedimentation volume was affected primarily by Aerosil %, giving the simple rules:

IF Aerosil % is LOW THEN Sedimentation % is LOW (0.91)

IF Aerosil % is HIGH THEN Sedimentation % is HIGH (0.64)

The statistical study showed some effect from the other parameters as well, but these were insufficiently important for **FormRules** to highlight them when Structural Risk Minimization was used as the model selection criterion. Changing the model selection criterion so that more complex models were developed showed that all 4 inputs played some role, in line with findings of Elkheshen *et al*. However, the rules, in the form IF…AND…AND…AND…THEN… were quite complicated to interpret.

Redispersibility % was also affected mainly by Aerosil, with a linear relationship between the amount of Aerosil and the redispersibility. Again, changing the model selection criterion showed that the other ingredients played a lesser role in redispersibility. This is consistent with the statistical results of Elkheshen *et al*.

Conclusions

FormRules discovered which variables affected each property, and these were consistent with the findings from the published statistical study. Using the default model selection criterion, Structural Risk Minimization (SRM), gave simple models and rules. Using other model selection criteria like Minimum Descriptor Length or Bayesian Information Criterion gave more complicated rules.

Importantly, these results were discovered in minutes, and immediately displayed to the formulator – a considerable saving of time over the statistical methods.

ANOVA statistics on the models developed with SRM showed that the models captured most of the variation in the data, with R^2 values in excess of 0.8 in nearly all cases.

FormRules had the added advantage, though, that it produced simple linguistic rules in the form IF (inputs) THEN (properties). These can be used by the formulator to guide their next batch of experiments.

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

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