Optimizing Antibacterial Polyherbal Gels with INForm

In traditional medicine, herbal extracts can be used to treat a wide variety of conditions, with many traditional remedies having well-proven antibacterial properties. However, delivering the medicine in a form that can be easily used by patients can be a challenge.

Gel formulations can be useful when intimate prolonged contact is required to a mucous membrane, and in some cases having a system which gels *in situ* can be especially beneficial.

In a study reported in 2007 in *European Journal of Pharmaceutics and Biopharmaceutics*, Chopra and coworkers have described a system in which a gel has been developed for the delivery of a mixture of antibacterials derived from 4 herbal products. This system involved a mixture of a polymer (Carbopol), honey, and Aerosil (which acts as a thickener by absorbing water).

Their study involved 15 experiments, only 13 of which were at unique points. For each experiment, the results of changing the weight/weight percentage of the three variables was investigated, using a three-factor Box Behnken design. The properties measured were the storage modulus, the gel index, and the maximum detachment force (MDF).

Although neural networks do not require designed experiments, because this data set was available we have chosen to investigate it using the **INForm** formulation modeling and optimization program.

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 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 product properties you want, and the optimization process will tell you what ingredients and process conditions are required to obtain them, within the limits of the overall data you have scoped out. This was the process that was adopted in examining the data published by Chopra *et al*.

Preliminary studies using the **FormRules** data mining program (which are the subject of a related application note) showed that excellent models could be developed from the data.

Modelling Polyherbal Gel Properties

As expected, good models could be developed from these data records. In order to avoid biasing the centroid point (which was replicated 3 times in the Box Behnken design) we averaged these 3 values, giving 13 unique points in total. Because of the small number of data points, validation by withholding some of the data was not ideal, but one data record was held back for testing and validation.

Good models, with ANOVA statistics giving R^2 values in excess of 0.93, were found for each of the properties.

Use of **INForm's** Visual Explorer to see the effect of 'hidden variables' showed that the response surface for maximum detachment force vs. polymer concentration and honey concentration showed very little change when the Aerosil concentration was changed.

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The effect on the storage modulus was more noticeable, and Figures 1 and 2 show the response surfaces when the Aerosil concentration was at a minimum and maximum respectively.

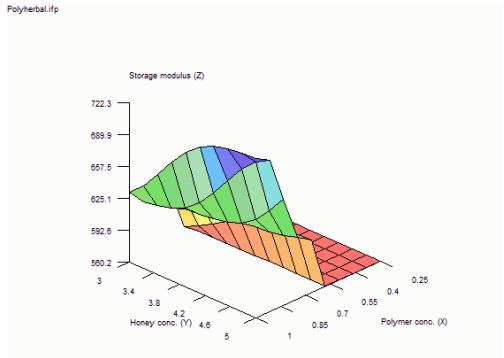

Figure 1. Storage modulus when Aerosil % takes minimum value of 0.5

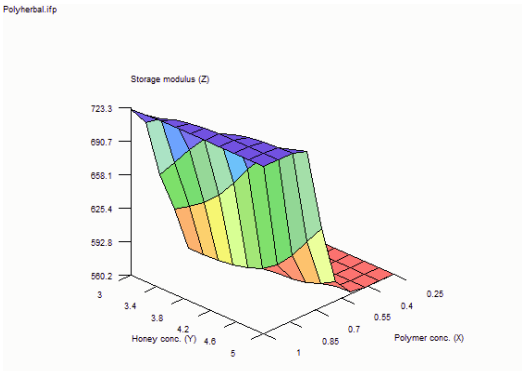

Figure 2. Storage modulus when Aerosil % takes maximum value of 2

The aim of the study undertaken by Chopra *et al* was to optimize the formulation by changing the amounts of the three ingredients. Here, we used INForm's integrated genetic algorithm optimization to perform the same task.

The requirements of the optimization were that

- Storage modulus lie between 500 and 700 Pa
- Gel index lie between 4 and 5
- Maximum detachment force as high as possible.

We used these requirements within **INForm**. **INForm** also allows you to weight the properties according to their relative importance – something that was not possible in the statistical study. We arbitrarily chose the maximum detachment force to have a weight of 10 (i.e. most important property) with gel index weighted at 9, and storage modulus at 8.

The optimum formulation found by **INForm** had a concentration for the polymer of 0.72%. Honey concentration was 4.3%, and Aerosil concentration 1.42%. This compared with the values of 0.76%, 4.5% and 1.32% found by Chopra *et al*. Their study involved a 'comprehensive evaluation of feasibility search and exhaustive grid search' using their response surfaces.

We recall that both our work and that of Chopra et al showed that as long as polymer concentration was greater than about 0.5%, the maximum detachment force was large. This is confirmed both by the optimization studies, and by the contour plot, which shows the behaviour illustrated in Figure 3, when Aerosil is at about 1.5%.

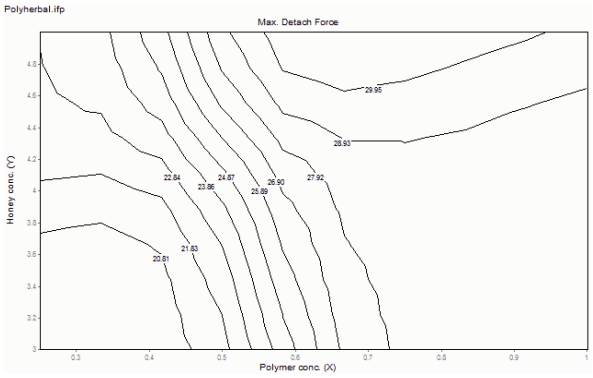

Figure 3. Contour plot shows that MDF is relatively insensitive to polymer concentration at higher concentration values.

Conclusions

The neural network models are of similar quality to those found by statistical modeling, but were considerably easier to develop.

The optimum formulation found by INForm was very similar to that found from statistical response surface methods (RSM), but it was considerably quicker (a few seconds on a PC) quicker to find the optimum than it is using RSM.

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