

# Optimizing Controlled Release Beads with INForm

Multiparticulate dosage forms are especially suitable for drug combinations when incompatibilities exist, to release the drugs at different rates. They can also cut the likelihood of dose dumping. One popular form is membrane-controlled drug loaded beads. Coating the beads can be achieved by organic or aqueous based systems; increasingly the drive is to use aqueous systems on environmental grounds. The aim is to produce coated beads with a specified release profile.

The traditional approach uses statistics, requiring carefully designed experiments for a range of ingredient and processing conditions. Siva Vaithiyalingam and Mansoor Khan, reporting in the *International Journal of Pharmaceutics* **234** 179-193 (2002), present experimental results analyzed with statistical and neural network methods. They predicted optimum formulations, made these, and tested them.

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. **INForm** 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 release profile you want, and the optimization process will tell you what conditions are required to obtain them. In the example given here, the optimization was carried out in minutes, with full assessment of the trade-offs in achieving the best fit to the release profile at different times.

## Multi-particulate Beads

Vaithiyalingam and Khan performed a 3-level central composite face-centred experimental design, with 3 inputs and 5 outputs, detailed in the text-box. In their paper, they recognize that time should be included as a variable because it plays a crucial role in the interaction between coating weight gain and the amount of plasticizer. However, their statistical treatment restricted them to three input variables, in order

to be able to get useful results from the Response Surface Method - this is not a restriction that would have been required with neural networks.

Vaithiyalingam and Khan also used CAD/Chem (an early formulation design program based on neural networks, which is no longer available) with a 2-node 2-hidden layer network, to develop a set of models.  $R^2$  values for the statistical and CAD/Chem models were generally similar and generally in excess of 90%.

### Inputs

- Coating weight gain
- Duration of coating
- Plasticizer level

### Outputs

Amount of drug released at

- 2 hours
- 4 hours
- 6 hours
- 9 hours
- 12 hours

### Optimization Aim

- produce a specific release profile

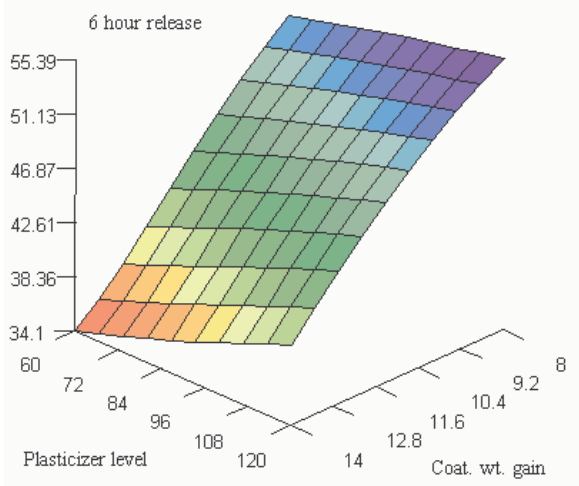
The data published by Vaithiyalingam and Khan were taken directly into **INForm** by copying from a spreadsheet. Just 16 experimental records were available. One was selected at random to be withheld for model validation. (Typically, **INForm** keeps back 10% of the data for validation.)

## Results

As expected, **INForm** generated excellent models with  $R^2$  values exceeding 94%. These were with a single hidden layer, with 2 nodes, and the default backpropagation training parameters. **INForm's** neural network has developed better models than those reported by Vaithiyalingam and Khan from CAD/Chem - in the latter case, with a simpler network and hence fewer adjustable parameters.

In carrying out the optimization, we noticed that the best fits at long times (12 hours) were obtained by selecting high values of plasticizer. However, these gave poorer values for the 4 and 6 hour release. 4 and 6 hour release were best

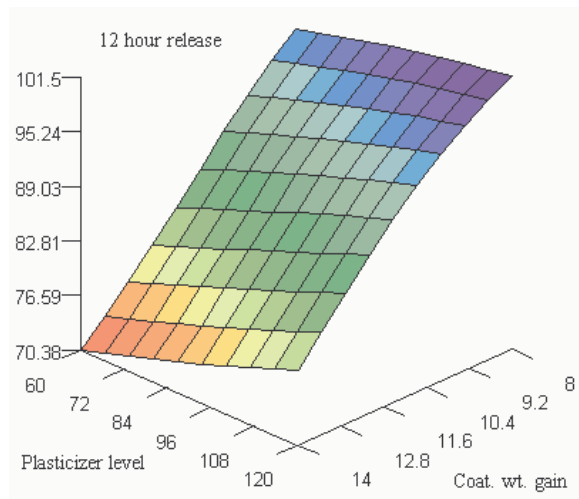
when the amount of plasticizer was low. Both 'high' and 'low' values in the two optimized formulations were near the limits used in the experimental design, suggesting that the design space should be increased in order to determine a better optimum. Although these results were obtained directly from the genetic algorithm optimization, Figures 1 and 2 illustrate what is



happening.

**Figure 1. Desirable value of 33.3% for 6 hour release lies at minimum plasticizer level and minimum coating weight gain**

We also noticed that none of the experimental values used to develop the model had achieved a 2-hour release as high as the desired 16.6%. Only 2 formulations in the 'training set' had values for the 4-hour and 6-hour release that were higher than the desired 33.3% and 50% respectively. This means that the optimization is a particularly challenging task.



**Figure 2. Desirable value of 100% for 12 hour release lies at high plasticizer level and minimum coating weight gain.**

The optimum formulations found by RSM and by CAD/Chem had a plasticizer level of approximately 120% - as discussed above, this gave the best fits at longer time scales. As expected, **INForm** also found an optimum at this point. However, we noted that **INForm** also developed an alternative optimum, in which the Plasticizer level was at a minimum. This arises because of the effect of changing the amount of plasticizer, discussed above, and gave a better fit at shorter time scales.

## Conclusions

The neural network implemented in **INForm**, with default parameters for the network training, gave results comparable to the statistical results given by Vaithiyalingam and Khan, and better than they reported with the neural network in CAD/Chem.

For the optimization, **INForm** highlighted that there are two possible optimum regions, depending on exactly which part of the release profile is emphasized in the optimization. This information was not reported for the RSM or CAD/Chem studies.

The benefits of using **INForm** compared to RSM were:

- These results were considerably easier to find using **INForm** than using Response Surface Methods. This meant that time and money could be saved with **INForm**.
- Unlike Response Surface Methods used in the published paper, **INForm** could have coped with other important variables, like time, in a multi-dimensional model and optimization. Therefore, with **INForm** it would not be necessary to limit the investigation in order to fit the software's capabilities - a substantial advantage over RSM.
- **INForm** was able to find an optimum formulation quickly. Because the data set was 'skewed', it was necessary to weight some of the properties (especially the release at 12 hours) as being more important, in order that the optimization objectives be achieved.

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