

Optimizing Analgesic Gel Ointments with INForm

Transdermal drug delivery has been attracting considerable interest, and adsorption promoters are added to improve the permeability of drugs through the skin. However, depending on the materials added, side effects like skin irritation can be observed. The aim is to produce a formulation in which the drug is stable, uptake of the drug is optimized, and no skin irritation is observed.

The traditional approach uses statistics, requiring carefully designed experiments for a range of ingredient and processing conditions. Takayama *et al* (*International Journal of Pharmaceutics* **61**, 225-234, 1990) have investigated an indomethacin gel ointment that contains d-limonene as an absorption promoter. They have used the Adaptive Least Squares method, together with investigation of the response surfaces in order to produce an optimum formulation. However, producing an optimum can be challenging especially when there are several formulation variables.

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 properties you want, and the optimization process will tell you what ingredients and process 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 different properties, compared with the longer time required to optimize using the response surfaces from the ALS method used by Takayama *et al*.

Indomethacin Gel Formulations

Takayama and coworkers carried out a composite design for five factors, consisting of 36 experiments in all. Central experimental points were repeated ten times, for evaluating experimental error. The 5 inputs were

- Amount of indomethacin (IMC)
- Amount of carboxyvinyl polymer
- Amount of triethanolamine
- Amount of ethanol
- Amount of d-limonene

while the output properties measured were

- plasma concentration of IMC at 3, 6 and 24 hours
- spreadability of ointment
- stability of IMC in ointment
- skin irritation by ointment
- appearance of ointment

The last two properties did not take numerical values, but had to satisfy a 'pass or fail' criterion. Particularly in the case of skin irritation, the degree of irritation was judged purely visually.

The 10 centroid 'repeat' points show a considerable degree of scatter especially for the percutaneous release. Takayama *et al* found that a log scale was required for the data for the plasma, in order to model it properly. We consequently used the same transformation in our work.

The data points published by Takayama *et al* were taken directly from a spreadsheet into **INForm**, and the inputs and outputs were specified. 10% of the data records were selected for 'model validation', and the other 33 data records were used to train the

neural network. We found that a network architecture with a single hidden layer, with 4 nodes, gave good models (as assessed by ANOVA statistics, as well as predictivity of the validation data set).

Results

As Figure 1 shows, the value for spreadability increases as X2 (the amount of carboxyvinyl polymer) decreases. X5 (the amount of d-limonene) has no significant effect on the spreadability.

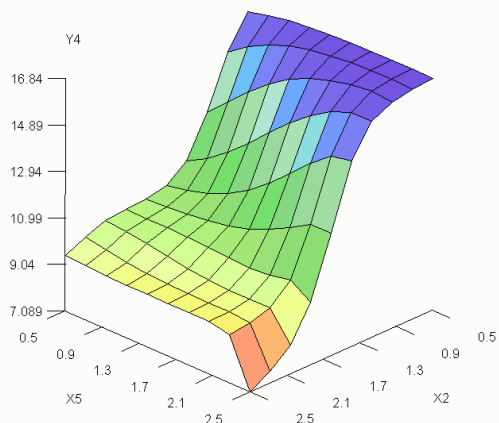


Figure 1. Spreadability as a function of carboxyvinyl polymer (X2) and d-limonene (X5)

Figure 2 shows that Y1, the log of the percutaneous absorption after 3 hours, depends among other things on X2, the amount of carboxyvinyl polymer, and X3, the amount of triethanolamine. However, at higher concentrations of carboxyvinyl polymer, the ethanolamine has no significant effect.

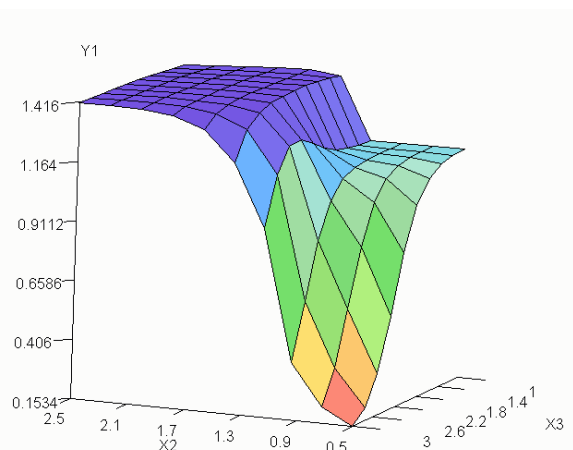


Figure 2. Percutaneous absorption after 3 hours, as a function of the amount of carboxyvinyl polymer (X2) and ethanolamine (X3)

Optimizing Formulations

For optimization, we set the explicit targets that spreadability should lie between 8 to 12 cm², that stability should exceed 90%, that the formulation should be non-irritant, and that it should be colourless. In addition, we maximized the percutaneous absorption parameters. This last is in line with work done by Phil Plumb in his M Phil Thesis on *Evaluation of Artificial Intelligence in the Modelling and Optimization of Pharmaceutical Formulations* (University of Bradford, 2000), who studied this same data using the CAD/Chem program (a forerunner of INForm).

INForm's ability to specify optimization goals flexibly meant that optimization was more straightforward with INForm than with CAD/Chem. In addition, INForm did not require reliance on interpreting complex response surface graphs to give the global optimum formulation. As the table below shows, INForm has found a formulation very close to the experimental optimum from the paper by Takayama *et al.*

Property	Experimental (Takayama)	Predicted (Takayama)	Predicted (INForm)
Log Y1	1.41	1.66	1.42
Log Y2	1.69	1.81	1.73
Log Y3	1.93	1.96	2.42
Spreadability	11.8	12.0	12.0
Stability	86.2	90	91.3
Irritancy	1	1	1
Appearance	1	1	1

Table 1. Optimized Ointment Formulation from INForm, compared with results from Takayama *et al* and with experiment

Conclusions

INForm has been used to model successfully an indomethacin ointment gel. Good models were obtained for all of the measured properties, with ANOVA statistics giving R² values in excess of 0.95 in each case. The models from INForm (using default parameters) were better than those from CAD/Chem.

Optimization of the formulation was more easily achieved with INForm than with the response surfaces of Takayama *et al*, or with CAD/Chem (according to the study by Plumb). In addition there was a considerable time saving compared with the ALS method used by Takayama *et al*.

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