

Optimizing In Vitro Release Profiles with INForm

Controlling drug release from tablets is a challenging task. Over half the medicines used in the UK are in the form of compressed tablets - tablets are stable, simple to prepare, and easy to package, with established patient compliance.

The development of controlled release forms with desired *in vitro* dissolution and *in vivo* bioavailability is challenging, because complex nonlinear relationships can exist between the formulation variables and the drug release rate. Models exist to link the *in vitro* dissolution to the bioavailability profile. Therefore, producing the desired *in vitro* release becomes especially important.

The traditional approach involves statistical formulation models, with considerable experimentation and trial batching to determine how a change in formulation will change the *in vitro* release. This can become very complex when the task has nonlinear relationships and many 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. 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 the desired release profile) 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 ingredients and process conditions are required to obtain it.

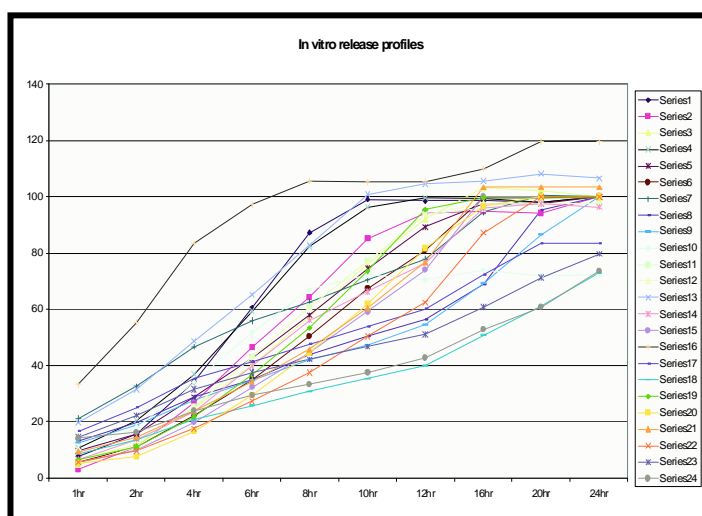
Modelling In Vitro Controlled Release

Neural networks have been used by Yixin Chen and colleagues (*Journal of Controlled Release* **59** 33-41 (1999)) to develop models for a controlled release formulation. In this particular study, there were ten possible formulation variables:

- ✂ Amount of Polymer A in each tablet
- ✂ Amount of Polymer B
- ✂ Amount of Dextrose
- ✂ Amount of Lubricant
- ✂ Tablet Weight
- ✂ Drug/(Polymer+Drug) ratio
- ✂ Polymer A/Polymer B ratio
- ✂ Tablet hardness
- ✂ Particle size
- ✂ % Moisture

Some of these are combinations of other variables – for example, the two ratios – and are used to constrain the possible formulations.

The output variables were the percentage release at various times: 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 16 hrs, 20 hrs, and 24 hrs.



Chen and coworkers prepared 24 tablet formulations. Here, we have used their

data with **INForm**, to develop a model that related the *in vitro* release to the formulation variables. We considered two cases - one when all ten inputs were used, and the other with the drug/polymer ratio, the tablet weight, and the polymer A/polymer B ratio set as Not Used, leaving 7 input variables. Chen and coworkers had found that tablet hardness, particle size and percentage of moisture were important variables - a finding which we confirmed with **INForm**.

Because there are relatively few experiments for the number of variables, **INForm** selected a simple neural net architecture, with a single hidden layer with two nodes. Separate models were developed for each of the properties - in this case, for each time period.

Model validation is important, so we used **INForm's Smart Select** option to withhold 10% of the data records, to see how well the model predicted. We also used the **SmartStop** option, to ensure that the neural net did not 'overtrain'. These features of **INForm** make it very useful for users who are formulation, not neural network, specialists.

INForm's real strength for this problem, though, is that a target release profile can be specified, and the model, used with an inbuilt genetic algorithm optimizer, produces the formulation that gives this profile. The user can specify any constraints on the formulation. For example, in our first case (10 input variables) we specified that the amounts of Polymer A and Polymer B had to satisfy the PolymerA/PolymerB ratio. We also constrained the Drug/Polymer ratio to ensure a constant amount of drug (9.6 mg per tablet), and set a constraint that the total tablet weight equalled the sum of the ingredients. The input variables were further constrained to the 'known' formulation space; we did not allow **INForm** to explore beyond this range.

We compared the performance of **INForm** with that of CAD/Chem, the program used by Chen et al, and found that similar models

were generated. In fact, **INForm** gave *better* models for the shorter time periods, up to about 8 hours.

To establish whether the predictions were useful, Chen and colleagues generated two target *in vitro* profiles which differed from (but were within the bounds of) the known formulations. They used evolutionary algorithms to predict the formulations which should be made, and then manufactured these formulations. They then compared the target dissolution profiles with the actual ones for the new formulations. **They found very good agreement between the target and observed profiles**, although there was a modest deviation for one of the formulations in the release between 10 and 20 hours.

Conclusions

- ✕ **INForm** was able to discover the cause and effect models within the formulation data with a high level of accuracy, comparing favourably with the neural network used by Chen et al.
- ✕ It is possible to specify the target profile, and to use **INForm's** optimization capability to predict the formulation that would give this profile. This is in agreement with the published results.
- ✕ Chen and colleagues state that there is 'the potential for an artificial neural network, along with pharmacokinetic simulations, to assist in the development of complex dosage forms. The method can be obtained to achieve a desired *in vitro* dissolution profile.'
- ✕ We conclude that **INForm's** integration of neural networks and genetic algorithms gives a powerful support tool in design of new controlled release tablets.

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