

Optimizing Tablet Formulations with INForm

Formulating pharmaceutical tablets is a challenging design task. Over half the medicines used in the UK are in the form of compressed tablets - they are stable, simple to prepare, and easy to package, with established patient compliance. Important properties include release behaviour (fast for pain release, modified release for longer-term control of symptoms).

In addition to the active ingredient, tablets contain other inert compounds ('excipients') which are added to impart good processing characteristics and properties.

Most tablet formulations have to meet complex and often conflicting performance criteria - e.g. high strength but rapid disintegration. Rarely can the relationships between ingredient levels, processing and product performance be quantified precisely. Formulating tablets is therefore a challenging design task.

The traditional approach involves statistical formulation models, with considerable experimentation and trial batching to determine how changes in formulation will change the tablet properties.

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 disintegration time and hardness) 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.

Components of Tablet Formulation

- ▶ **Filler/Diluent** to increase bulk and aid compaction
- ▶ **Disintegrant**: to facilitate rapid break-up in the body
- ▶ **Binder** to facilitate the production of granules:
- ▶ **Lubricant** to facilitate tablet ejection from the die

A Tablet Formulation Application

Here, we have used literature data from Kesavan and Peck (*Proc. 14th Pharm Tech Conference, Barcelona, 1995*) on a tablet formulation consisting of:

- ▶ anhydrous caffeine (40% w/w) as a model active
- ▶ dicalcium phosphate dihydrate (Ditab) or lactose (44.5-47.5% w/w) as a filler
- ▶ polyvinylpyrrolidone (PVP) (2.0 -5.0% w/w) as a binder
- ▶ corn starch (10% w/w) as a disintegrant
- ▶ magnesium stearate (0.5% w/w) as a lubricant.

Two types of granulation equipment - fluidized bed and high shear mixing - were

used, and the binder was added either wet or dry. 32 different experiments (data records within **INForm**) were available.

Data were imported directly into **INForm** from a spreadsheet file. **INForm** allows the user to specify whether a particular variable is an input (Ingredient or Processing Condition), a Property or whether it is Not Used. Thus, all the different models could be developed from a single data file by specifying these different options. This greatly facilitated exploring all possible cases quickly.

Because the amount of caffeine, corn starch and magnesium stearate was held fixed in the experimental measurements, no information on the effect of varying their amounts could be obtained. It was possible to see whether lactose or Ditas was the preferred diluent, since a numerical 'switch' to distinguish between the two could be used.

In this application, the goal was to look at the trade-offs between hardness and other properties (disintegration time, friability and thickness). Various possibilities were investigated - with five different models studied. The most important are listed in the box above.

Run	Hardness	Friability	Thickness	Disinteg. time
1	9	9	5	10
2	9	5	5	10
3	5	2	2	5
4	10	2	2	5

Table 1: Relative Weights of different properties in Optimization runs

The neural network was trained using a 4-node hidden layer in each case.

*With **INForm**, a good model could be developed to relate the input formulation and process conditions directly to the tablet properties, without needing to know about the intermediate granule properties.*

With this model, various optimizations were carried out. These varied the relative importance of the hardness and the disintegration time, as shown in Table 1.

Each optimized formulation depends on the relative weights, and this feature means that different formulations can be developed if a different range of properties is required for different end-use applications.

In all cases, lactose was the preferred diluent for this formulation. The PVP% was in the lower half of the design range, which is consistent with increasing friability and decreasing disintegration time. Little change was seen in the tablet hardness. The only way a high value of hardness could be achieved is at the expense of all the other variables, especially the disintegration time. And the only way that a low disintegration time could be achieved was if we were prepared to sacrifice some of the hardness.

Conclusions

- ✕ Constraints and preferences can be accommodated easily, allowing a range of optimized formulations to be developed.
- ✕ **INForm** let us develop a number of models quickly and easily - and showed that a model which related input formulation and process conditions directly to tablet properties was viable, thereby saving considerable future experimentation.
- ✕ For the case studied, tablet hardness could be achieved only at the expense of all other properties, including friability, thickness, and disintegration time. Low disintegration time could only be achieved when hardness was sacrificed.

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