

Finding Rules for Immediate Release Tablets with FormRules

Background

Amongst the various formulation types for pharmaceutical preparations, the tablet is by far the most popular. Tablet formulations typically consist of a drug which is mixed with a filler (diluent) to aid compaction, a disintegrant to assist the break-up of the ingested tablet, a binder to facilitate formation of granules that have correct flow properties, and a lubricant to help with ejection of the tablet from the die. Properties of interest usually include tablet friability, hardness, disintegration time and dissolution rate.

Despite the fact that tablets have been in use for more than a century, the relationship connecting the ingredients and process conditions with the final properties of the tablets are known only anecdotally and are rarely quantified.

One new technology that can be applied is neurofuzzy logic - a technique that combines the learning and adaptive capability of neural networks with the ability of fuzzy logic to express conclusions based on vague, ambiguous, incomplete and imprecise information. This technique is rapidly gaining acceptance in data mining applications - including formulation data sets.

Tablet Formulation Data

FormRules uses neurofuzzy logic to discover the rules hidden within formulation data. Neurofuzzy logic has been evaluated for tablet formulation by Elizabeth Colbourn of Intelligensys and Ray Rowe of AstraZeneca. This study, published in *Pharmaceutical Technology Europe* in January 2000, 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 dry or in solution.

There were 32 data points in this work; variables included the amount of lubricant (PVP) and diluent (either lactose or dicalcium phosphate dihydrate), whether the binder was added in solution or dry, and the type of granulation equipment (fluidized bed or high shear mixing).

The tablet properties that were measured included hardness, friability, and disintegration time.

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

Tablet Formulation Rules

In this study, the work of Rowe and Colbourn has been repeated using **FormRules**, which is based on neurofuzzy logic. Three of the inputs (Diluent, Granulation Equipment and Binder Addition) fall into 'crisp' sets; they are not numerical values. PVP% and Diluent% are continuous numerical values. Neurofuzzy logic was used to train and validate the neural network and to generate the fuzzy rules. The rules were all expressed in the form *IF (condition 1) AND (condition 2) AND (condition 3), THEN (conclusion 1 with confidence factor)*. The number of conditions in each rule is determined automatically by the neurofuzzy system.

The fuzzy rules for hardness and friability are given in Table 1. (Note that high hardness is associated with low friability, and vice versa - and **FormRules** has discovered this for itself.)

GRANULATION EQUIPMENT	DILUENT	BINDER ADDITION	PVP%	HARDNESS	FRIABILITY
Fluidized Bed	Lactose	Dry	Low	Low (0.83)	High (0.81)
Fluidized Bed	Lactose	Dry	High	Low (0.97)	High (0.63)
Fluidized Bed	Lactose	Wet	Low	Low (1.00)	High (1.00)
Fluidized Bed	Lactose	Wet	High	High (0.52)	Low (1.00)
Fluidized Bed	Ditab	Dry	Low	Low (0.63)	High (0.99)
Fluidized Bed	Ditab	Dry	High	Low (0.74)	High (0.78)
Fluidized Bed	Ditab	Wet	Low	High (0.54)	Low (0.92)
Fluidized Bed	Ditab	Wet	High	Low (0.60)	Low (0.89)
High Shear Mixer	Lactose	Dry	Low	High (0.66)	Low (0.98)
High Shear Mixer	Lactose	Dry	High	High (0.73)	Low (1.00)
High Shear Mixer	Lactose	Wet	Low	Low (0.65)	Low (0.77)
High Shear Mixer	Lactose	Wet	High	Low (0.67)	Low (0.93)
High Shear Mixer	Ditab	Dry	Low	High (0.69)	Low (0.94)
High Shear Mixer	Ditab	Dry	High	High (1.00)	Low (0.99)
High Shear Mixer	Ditab	Wet	Low	High (0.88)	Low (0.93)
High Shear Mixer	Ditab	Wet	High	High (0.76)	Low (0.98)

Table 1: Fuzzy rules with confidence levels for Hardness and Friability

Tables 2 and 3 give the fuzzy rules, with confidence factors, for disintegration time of the tablet.

The rules for hardness and friability are complicated, with interactions between all the variables. The rules (Table 2) for disintegration time are less complicated, with interactions between the PVP concentration, the type of granulation equipment, and whether the binder was added wet or dry.

GRAN. EQUIPMENT	BINDER ADDITION	DISINTEGRATION TIME
Fluidized Bed	Dry	High (0.86)
Fluidized Bed	Wet	High (0.96)
High Shear Mix	Dry	High (0.89)
High Shear Mix	Wet	High (0.68)

Table 2. First submodel for disintegration time

DILUENT	DILUENT %	DISINTEGRATION TIME
Lactose	Low	Low (0.97)
Lactose	Medium	Low (0.82)
Lactose	High	Low (0.73)
Ditab	Low	Low (0.66)
Ditab	Medium	High (0.68)
Ditab	High	High (0.67)

Table 3. Second submodel - disintegration time

Clearly from Table 3, Ditab produces tablets that disintegrate more slowly than those containing lactose.

These specific, actionable, rules can be used to guide future experiments.

Conclusions

The rules generated are those which would be expected by experienced formulators, showing that the technique can be used confidently by relatively inexperienced formulators, and for new problems where experience is lacking.

The existence of non-numerical inputs was no bar to developing useful rules that can guide future experimentation.

For further information on FormRules, and applying neurofuzzy logic to your problems, contact us at the address below.

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