

Finding Rules for Tablet Film Coatings with FormRules

Background

During film coating, a material consisting of a polymer, plasticizer, colorant and opacifier is deposited onto the surface of a granule or tablet. Other materials may also be included. Coatings can be used to improve appearance, protect the drug from light, or help to control its release into the body. The aim is to generate coatings that are sufficiently opaque to light, yet strong enough to avoid cracking leading to dose dumping.

During the past 25 years, coating technology has made dramatic advances. Consequently, a large data base is now available, but it must be structured in a form that can be used to solve problems.

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 Film Coating Data

The work described here was carried out by Ray Rowe of AstraZeneca, working with Chris Woolgar of Neusciences, and was published in *Pharmaceutical Science & Technology Today*, December 1999. The film formulation consisted of:

- hydroxypropyl methylcellulose (molecular weight 35,000 to 150,000)
- an opacifier (anatase or rutile TiO₂) in varying amounts from 1-30% v/v with mean particle size in the range 0.2 to 1 µm, and a particle size distribution 0-2, expressed as a fractional standard deviation of the mean.

For each formulation, a computer simulation was used to obtain the crack velocity; opacity was determined by calculating the contrast ratio using a specially designed algorithm. These models have both been shown to reproduce observed behaviour accurately, and enabled 102 examples to be generated quickly.

Tablet Film Coating Rules

FormRules, based on neurofuzzy logic, was used to repeat the Rowe and Woolgar work, to discover the fuzzy rules governing tablet film coatings. 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.

Crack velocity was affected only by polymer molecular weight, pigment size, standard deviation and concentration. This is expected, since film thickness and pigment type were not inputs into the simulation program that was used to generate the crack velocities. It is reassuring to see that the software has discovered this for itself! The rules for crack velocity are shown in Tables 1 and 2; the most important are shown as a flow diagram in Figure 1.

POLYMER MOLECULAR WEIGHT	CRACK VELOCITY
Low	Slow (0.88)
Medium	Slow (0.93)
High	Slow (0.94)

Table 1. Fuzzy Rule: Effect of Polymer Molecular Weight on Crack Velocity

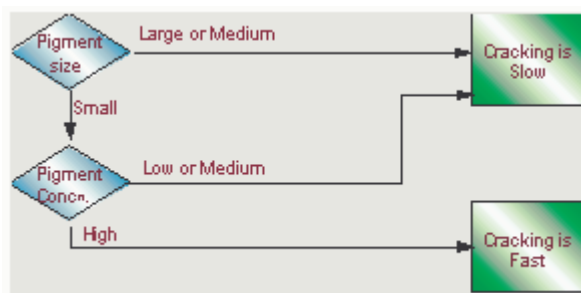


Figure 1. Flow diagram for most important rules for Pigment Size and Concentration

PIGMENT SIZE	STD. DEVIATION	PIGMENT CONC.	CRACK VELOCITY
Small	Small	Low	Slow (1.00)
Medium	Small	Low	Slow (1.00)
Large	Small	Low	Slow (0.98)
Small	Large	Low	Slow (0.85)
Medium	Large	Low	Slow (1.00)
Large	Large	Low	Slow (0.96)
Small	Small	Medium	Slow (0.90)
Medium	Small	Medium	Slow (0.93)
Large	Small	Medium	Slow (0.94)
Small	Large	Medium	Fast (0.98)
Medium	Large	Medium	Slow (0.92)
Large	Large	Medium	Slow (0.97)
Small	Small	High	Fast (0.58)
Medium	Small	High	Slow (0.91)
Large	Small	High	Slow (0.98)
Small	Large	High	Fast (0.55)
Medium	Large	High	Fast (0.51)
Large	Large	High	Slow (0.83)

Table 2. Fuzzy Rules, with confidence levels, for Crack Velocity

PIGMENT SIZE	PIGMENT CONCENTRATION	OPACITY
Small	Low	High (0.60)
Large	Low	Low (1.00)
Small	Medium	High (0.99)
Large	Medium	High (0.72)
Small	High	High(0.98)
Large	High	High (0.80)

Table 3. Fuzzy Rules, with confidence levels, for Opacity (Submodel 1)

PIGMENT SIZE	FILM THICKNESS	OPACITY
Small	Low	High (0.69)
Large	Low	Low (0.97)
Small	Medium	High (0.99)
Large	Medium	High (0.72)
Small	High	High(0.99)
Large	High	High (0.89)

Table 4. Fuzzy Rules, with confidence levels, for Opacity (Submodel 2)

Opacity was affected by pigment size, concentration and film thickness, as illustrated in Tables 3 and 4. Again, this is consistent with the algorithm used to generate the data. Note that pigment size interacts with both film thickness and with pigment concentration.

The rules can of course be expressed verbally: for example, from Table 3, *IF (Pigment Size is Small) AND (Pigment Concentration is High) THEN (Opacity is High)*, with a Confidence Factor of 98%.

Crack velocity is slow, except when there is a high concentration of small particles.

Conclusions

The data points used here were generated from simulation models that assumed specific interactions. The neurofuzzy network, with no prior knowledge of these interactions, managed to discover these relationships for itself. The rules generated are those expected by experienced formulators, showing that **FormRules** can be used confidently by relatively inexperienced formulators, and for new problems where experience is lacking.

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

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