

# Finding Rules for Analgesic Gels with FormRules

## Background

Transdermal methods attract considerable interest as a route for drug delivery especially in the case (as with the anti-inflammatory analgesic indomethacin, oral delivery has undesirable side effects). However, many drugs have low permeability through the skin, so absorption promoters are added to enhance uptake. This may lead to skin irritation, which is unacceptable, so ways of minimizing such effects are desirable. Understanding how each property is affected by the ingredients is a crucial step in improving formulations while eliminating such undesirable side effects.

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, and is the underpinning technology in the **FormRules** program.

## Gel Ointment Formulation Data

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. The input variables 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. 36 different experiments were undertaken, according to a composite experimental design, with 10 repeats of the centroid point. These data points were imported directly into **FormRules**, and the default parameters were used for training.

## Rules for Indomethacin Ointments

**FormRules** immediately extracted the conclusion that the percutaneous absorption (at 3, 6 and 24 hours) were affected solely by the amount of ethanol and d-limonene in the formulation. For the 3-hour absorption, amounts of ethanol about 35% had little effect, as Figure 1 shows. However, the 24-hour adsorption was sensitive to larger amounts of ethanol.

The rules are presented in simple IF... THEN format. For the 3-hour percutaneous release, the relationship between X4 (amount of ethanol) and Y1 (percutaneous release at 3 hours) is:

IF X4 is LOW THEN Y1 is LOW (1.00)  
IF X4 is MID THEN Y1 is HIGH (0.88)  
IF X4 is HIGH THEN Y1 is HIGH (0.90)

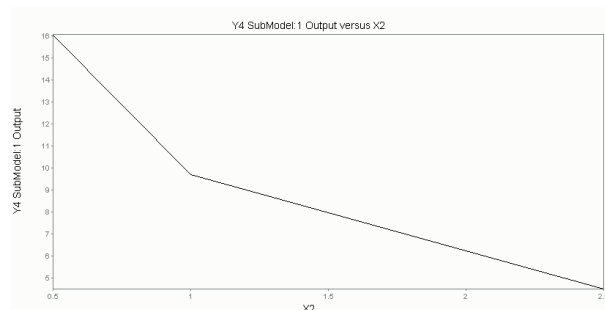
The brackets show the 'confidence levels' in the rules extracted by FormRules for the data. Similarly, rules can be extracted for the effect of X5, d-limonene:

IF X5 is LOW THEN Y1 is LOW (1.00)  
IF X5 is HIGH THEN Y1 is HIGH (1.00)

showing clearly the role of d-limonene as an absorption enhancer, and a linear relationship between the amount of limonene and the update of the drug.

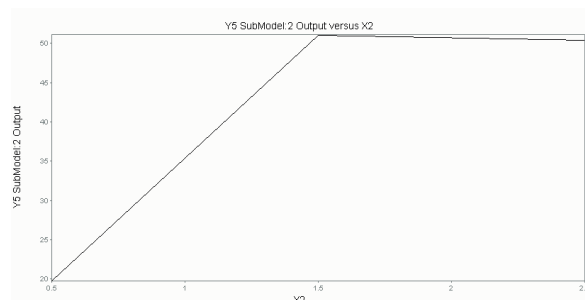
Spreadability is affected by the amount of carboxyvinyl polymer, and the amount of ethanol. Ethanol, perhaps unsurprisingly,

increases spreadability, with a linear relationship. Increasing the amount of carboxyvinyl polymer decreases the spreadability. The relationship is non-linear, as shown in Figure 1 below.



**Figure 1. Spreadability (Y4) decreases with the amount of carboxyvinyl polymer (X3)**

The stability of the IMC in the ointment is affected by the amount of carboxyvinyl polymer, the amount of triethanolamine, and the amount of ethanol. The amount of ethanolamine adversely affects the stability - as the amount of ethanolamine is increased, the stability decreases. Ethanol has the opposite effect, increasing the stability of the drug. As the figure below shows, drug stability (Y5) increases until the amount of carboxyvinyl polymer (X2) reaches approximately 1.5%. Above that, it has little or no effect.



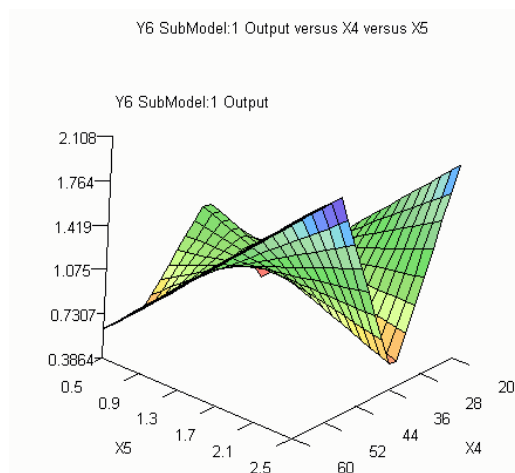
**Figure 2. IMC stability is a nonlinear function of carboxyvinyl polymer concentration**

Skin irritation depends on the amount of ethanol and the amount of d-limonene. The rules are complex, and are encapsulated in table 1 below. Figure 3 shows the inter-relationships between the two variables. At low amounts of d-limonene, ethanol has the opposite effect to that it has when the amount of d-limonene is high. These results may be

surprising, but it is important to note that they have been extracted directly from the data.

Ethanol	Limonene	Irritation	Confidence
Low	Low	Low	1.00
Low	High	High	0.89
Mid	Low	Low	0.77
Mid	High	Low	1.00
High	Low	Low	1.00
High	High	High	1.00

**Table 1. Summary of rules for effect of amounts of d-limonene and ethanol on skin irritability**



**Figure 3. Data mining shows complicated interactions between d-limonene and ethanol, for skin irritability.**

Finally, the appearance of the ointment depends primarily on the amount of ethanol in the formulation.

## Conclusions

Using a relatively small data set, **FormRules** has been able to extract the underlying relationships and rules governing the properties of an indomethacin gel ointment formulation.

With this information, the formulator can see immediately which inputs affect specific properties, thereby developing new formulations that minimize adverse side effects while enhancing product performance.

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

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