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The influence of additives on the presentation of a drug in hard gelatin capsules

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The influence of the concentration of lactose, magnesium stearate and sodium lauryl sulphate on the *in vitro* dissolution and the drug content of hard gelatin capsules filled under conditions which result in a maximum tapped bulk density, has been evaluated by a factorially-designed experiment. The 3 factors have a significant effect on both drug release and capsule filling. Interactions between the 3 factors, however, limit the exact quantification of the magnitude of their influence by a simple linear model. A quadratic relation, when only 2 factors are considered, can be used to provide a prediction of the influence of these factors. The relations between 2 factors are demonstrated as contours of equal *in vitro* drug release and equal drug content of capsule, at constant concentrations of the third factor. The contours show the important influence of lactose concentration on drug release and capsule filling, and the large changes in response which can occur by the addition of a third factor. They also provide a clear guide to the formulation of hard gelatin capsules.

The two important requirements for presentation of drugs in hard gelatin capsules are that the correct dose must be contained within the volume of the capsule shell, and that the drug must be released from the capsule, at the required rate, when administered to the patient. A formulation therefore can consist of a drug, to which a diluent can be added to ensure complete filling of the shell; a lubricant to ensure reproducible filling by a suitable machine and a wetting agent, added to promote fluid penetration of a hydrophobic powdered drug or a formulation containing a hydrophobic lubricant. The complex influence of three additives on *in vitro* drug release has been reported previously (Newton, Rowley & Törnblom, 1971a, b; Newton & Razzo, 1974). To provide a further insight into the problem and a more informed guide to formulation, an experimental design which involves 3 factors; a diluent (at 5 concentrations); a lubricant (at 4 concentrations) and a wetting agent (at 5 concentrations), giving a $5 \times 4 \times 5$ factorial experiment has been undertaken. The influence of the factors on the quantity of drug which can be filled into a size 0 capsule, under conditions which provide a maximum tapped bulk density within the capsule and the quantity of drug which is released *in vitro* have been assessed.

MATERIALS AND METHODS

Materials. Nitrofurazone, B. Vet. C. (SKF) used to represent a hydrophobic drug of low water solubility, had mean surface area diameter 35·9 μm†. Lactose B.P. (Whey Products Regular grade) had mean surface area diameter 38·3 μm†. Magnesium stearate B.P. superfine (Bush Boake and Allen Ltd) had mean surface area diameter 0·6 μm‡. The sodium lauryl sulphate (Evans Medical Ltd.) had mean surface area diameter 8·0 μm†.

Methods

The capsule filling and dissolution tests were as described previously (Newton & Razzo, 1974). The method of capsule filling (i.e. tapping until no further powder can be filled into the shell), provides a measure of the maximum tapped bulk density of the powder blend. This value will depend upon the composition of the blend and cannot be predicted theoretically. The drug content of the capsule can be calculated from the capsule fill weight and the proportion of drug within the formulation. The value for the drug content of the capsule does not give a measure of the reproducibility of capsule fill weight. The controlled filling system provided capsules whose weight variation was well within $\pm 5\%$ of the mean capsule fill weight. The results for the drug content of the capsule and *in vitro* drug release, at known times were evaluated by analysis of variance (Biomedical Statistics Computer program BMD08V).

RESULTS AND DISCUSSION

The analysis of variance calculations for the drug content of the capsule and the *in vitro* drug release clearly established that the 3 factors had a highly

* Correspondence.

† Determined by Fisher sub-sieve analyser.

‡ Determined by low-temperature nitrogen adsorption.

significant effect on these measured properties. In all cases however, there were highly significant second and third order interactions. Thus the magnitude of the effects of the diluent, lubricant and wetting agent cannot be predicted by the simple model

$$Y = A_0 + A_1 X_1 + A_2 X_2 + A_3 X_3 \quad .. \quad .. \quad (1)$$

where Y is the measured response, i.e. drug content of capsule or % of drug capsule content released *in vitro*, X_1, X_2 and X_3 represent the concentrations of diluent, lubricant and wetting agent respectively and A_0, A_1, A_2 and A_3 are partial regression coefficients. When the analysis of variance was broken down into two-factor systems, there were several instances which did not result in 2 factor interactions. Thus as a first approximation an alternative predictive model need not necessarily be of much greater complexity than equation (1). A quadratic model which would allow non-linearity and interactions is:

$$Y = A_0 + A_1 X_1 + A_2 X_2 + A_3 X_3 + A_{11} X_1^2 + A_{12} X_1 X_2 + A_{22} X_2^2 + A_{13} X_1 X_3 + A_{23} X_2 X_3 + A_{33} X_3^2 \quad .. \quad (2)$$

where the various sub-scripted values of A are again partial regression coefficients. Such a model however would not allow for a three factor interaction. A computer program was written to calculate the values of the partial regression coefficients by a least squares method (the program can calculate from 2 to 10 values of X), estimate the standard error of the fit, determine the maximum value of the response indicated by equation (2), and the concentrations of the factors which give the maximum value of the response. Thus if the values for the % of drug released after 80 min are taken, considering all the concentrations of the 3 factors, the model indicates that the maximum value for drug release would be given by a formulation with 80% lactose, 0·00002% magnesium stearate and 0·00003% sodium lauryl sulphate—an indication of the limitations of such a simple model. For practical purposes this supports the experimental results that the lubricant and wetting agent should be excluded. This could provide the basis of a formulation but no assistance in terms of what happens if a lubricant is necessary for filling or if the amount of lactose precludes getting the dose of drug into the capsules. The results would be more useful if the analysis resulted in a more detailed indication of the way in which the additives influence drug release and drug content of the capsules. To illustrate the influence of additives, and to avoid the complexity of a third factor, 2 factors were consid-

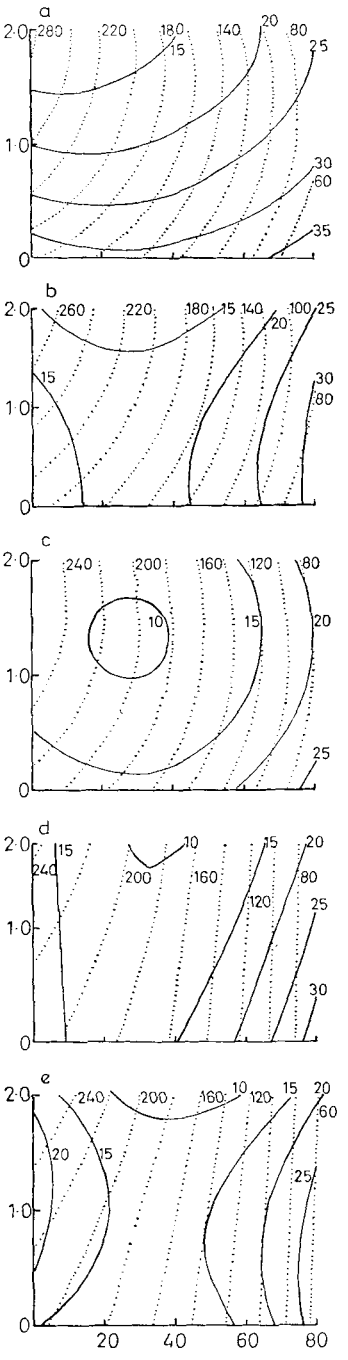

FIG. 1. Contours of equal *in vitro* drug release (% of the drug of the capsule content appearing in solution after 80 min) ——, and equal drug content of capsule mg · · · ·, as a function of concentration of lactose and magnesium stearate at (a) 0, (b) 0·5, (c) 1·0, (d) 2·0 and (e) 4·0% sodium lauryl sulphate. Ordinate–Magnesium stearate content of formulation (%). Abscissa—Lactose content of formulation (%).

ered, the third being retained constant, using the model

$$Y = A_0 + A_1 X_1 + A_2 X_2 + A_{11} X_1 + A_{12} X_1 X_2 + A_{22} X_2^2 \quad (3)$$

where Y, X_1, X_2 and the subscripted values of A have the same meanings as previously. The standard errors of each fit are given in Table 1. From the

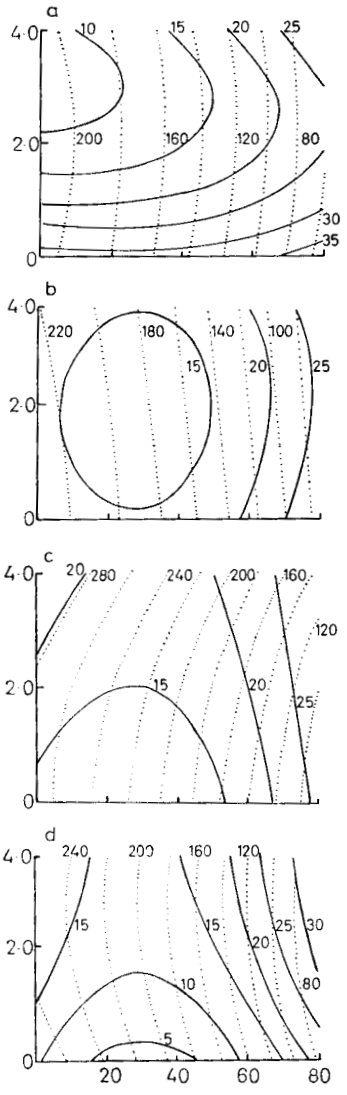

FIG. 2. Contours of equal *in vitro* drug release (% of the drug content of the capsule content appearing in solution after 80 min) ——, and equal drug content of capsule mg · · · ·, as a function of concentration of lactose and sodium lauryl sulphate at (a) 0, (b) 0·5, (c) 1·0 and (d) 2·0% magnesium stearate. Ordinate—Sodium lauryl sulphate content of formulation (%). Abscissa– Lactose content of formulation (%).

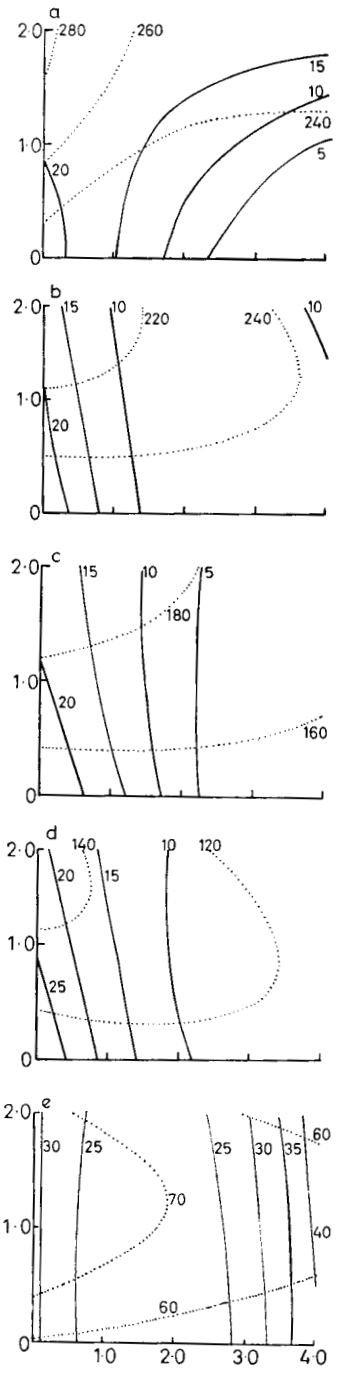

FIG. 3. Contours of equal *in vitro* drug release (% of the drug content of the capsule appearing in solution after 80 min) ——, and equal drug content of capsule mg · · · ·, as a function of concentration of magnesium stearate and sodium lauryl sulphate at (a) 0, (b) 20, (c) 40, (d) 60 and (e) 80% lactose. Ordinate—Magnesium stearate content of formulation (%). Abscissa—Sodium lauryl sulphate content (%).

computer fitted equations, it is possible to calculate contours of equal *in vitro* drug release and drug content of capsule, as a function of 2 additives. The results in Figs 1 to 3 each represent a section of the 3 dimensional model of the whole system.

Table 1. *Standard error for the fit of the quadratic model (Eqn 3) to the experimental values of drug release from, and drug content of, the capsule.*

Constant factor	Concn %	Variable Factors 1	2	Standard Error of fit Drug release	Drug content
Wetting agent	0	Diluent	Lubricant	3·16	5·16
	0·5			4·08	4·04
	1			4·59	3·80
	2·0			3·77	2·86
	4			5·12	6·71
Lubricant	0	Diluent	Wetting agent	4·76	3·97
	0·5			5·54	4·37
	1·0			5·80	6·00
	2·0			3·85	6·33
Diluent	0	Lubricant	Wetting agent	6·14	6·57
	20			5·14	5·91
	40			5·01	5·66
	60			5·22	2·77
	80			5·51	2·67

The various types of contours clearly indicate the variation in response caused by the combination of additives. The changes which occur by addition of a third factor appear to represent discontinuities in the total design. The computer program does not attempt to make the sections continuous, fitting the curve to one section only. The magnitude of the changes from section to section are greater than the error in curve fitting and hence are real effects, perhaps slightly exaggerated by the limited model. The changes are usually of greater complexity for drug release than for drug content of the capsule, for constant lubricant of wetting agent but vice versa for constant diluent concentration cf. Figs 1 and 2 with 3. This shows that the quantity of diluent is the major factor controlling the drug content of the capsule over the wide range of concentrations represented in this work. Nevertheless, the incorporation of a lubricant into the formulation does have an important effect on the drug content, cf. Figs 2a and c which indicates as much as 40 mg difference in drug content for the same diluent concentration. As the drug and diluent are of approximately the same particle size, differences in surface characteristics between nitrofurazone and lactose in the presence of magnesium stearate would appear to be an important factor in the packing of the particles. There is an optimum concentration of lubricant, to give maximum drug content, that varies with the quantity of lactose (Fig. 3b to d). The presence of sodium lauryl sulphate reduces the influence of magnesium stearate on filling, in that less drug can be filled into the capsule, cf. Fig. 2a c, and that the optimum is more pronounced at low lactose levels, cf. Fig. 2d e.

In addition to capsule drug content, the *in vitro* drug release also seems to be predominantly controlled by the quantity of lactose present. The hydrophilic nature of lactose appears to promote greater dissolution of the drug than the wetting effect of sodium lauryl sulphate. Reference to Fig. 3 demonstrates that from zero to about 40% of lactose, sodium lauryl sulphate is detrimental to drug release. It would appear therefore that factors other than wetting are involved. The improved drug release of high lactose content formulations obviously opposes the incorporation of a high drug content into the capsule. In cases where such a high diluent content is prohibitive, other additives should be considered, although granulation would appear to provide a more useful alternative to the release problems of insoluble drugs (Newton & Rowley, 1970).

Obtaining the contours of drug release and drug capsule content as presented here does represent an extensive experimental effort which may not always appear justifiable in the development of a capsule formulation. It does, however, provide a clear picture of what is often only hinted at in the more unusual random formulation program. Hence obtaining such information for a range of systems could provide improved generalizations to assist formulation problems. The application of a quadratic, as opposed to a linear, model for two additive combinations, appears useful, until such time as the physicochemical factors controlling capsule filling and drug release from capsules can be used to construct an exact mathematical model. Without some kind of model it is not possible to apply the extremely valuable constrained optimization techniques discussed by Fonner, Buch & Banker (1970) to specific capsule formulation problems.

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