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The *in vitro* bioavailability of various drugs formulated as hard gelatin capsules

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A factorially designed experiment has been carried out to study the influence of various additives on the *in vitro* release of drug from hard gelatin capsules. Analysis of variance confirms previous findings that, although the main factors of diluent type, diluent concentration, the absence and presence of both magnesium stearate and sodium lauryl sulphate, were highly significant, the existence of interactions between the factors prevented exact quantitative prediction of the influence of each factor. There appears however, to be a strong indication that the *in vitro* drug release of capsule formulations (y), expressed as the % of the drug content of the capsule which dissolves, can be related to the solubility of the drug (c_s) by the expression $y = 21{\cdot}2 \log c_s + 31.2$.

An attempt to provide guidelines for the formulation of hard gelatin capsules took the form of a factorial designed experiment which studied the influence of various additives on the *in vitro* release of four drugs (Newton & Razzo, 1974). The results provided indications of the way in which the type of drug and diluent and the concentration of diluent, lubricant and wetting agent affect drug release. Treatment of the results by analysis of variance however, confirmed the complexity of the effects showing that the influence of each factor was dependent on the other factors, in statistical terms, interaction effects. A method of overcoming interactions in factorially designed experiments is to increase the number of concentrations of each factor. The influence of the type of drug is an important aspect of formulation and therefore the previous design was extended to include two further drugs, imipramine hydrochloride and phenylbutazone to provide a factorial experiment, with 6 drugs, 3 diluents (at 2 concentrations), the presence (1%) and absence of magnesium stearate and sodium lauryl sulphate (i.e. a $6 \times 3 \times 2 \times 2 \times 2$ design).

MATERIALS AND METHODS

Materials

The additional drugs, imipramine hydrochloride and phenylbutazone were of B.P. specification. The other excipients, lactose, Primojel, starch, magnesium stearate and sodium lauryl sulphate were taken from the same batches employed in the previous experiment (Newton & Razzo, 1974). The mean particle sizes of the drugs and excipients are given in Table 1.

Table 1. *Mean surface area diameter of drugs and additives, determined by Fischer sub-sieve analyser.*

Drugs	Mean surface area diameter, μm
Imipramine	35·8
Nitrofurantoin	42·0
Nitrofurazone	35·9
Oxytetracycline dihydrate	29·7
Phenylbutazone	27·0
Tetracycline hydrochloride	31·3
Additives	
Lactose	38·3
Primojel	41·3
Starch	35·4
Sodium lauryl sulphate	8·0
Magnesium stearate	0·6*

* Determined by nitrogen adsorption.

Methods

The capsule filling and dissolution tests were carried out as described previously (Newton & Razzo, 1974). The drug content of the dissolution fluid (0·1 N hydrochloric acid) was determined spectrophotometrically at the wavelength of maximum absorption, after suitable dilution.

RESULTS AND DISCUSSION

The formulations used in the current work are not intended to represent a particular presentation of the drugs, but to investigate the principles of capsule formulation. The 1% concentration of magnesium stearate and sodium lauryl sulphate represents recognizable use concentrations. The two concentrations of diluent are intended to indicate the maximum concentration of diluent i.e. 20%, used to adjust the

* Correspondence.

volume of capsule fill when the drug has a variable bulk density, and a high concentration of diluent, 80%, that which could be used to incorporate a drug with a low dose. The drugs have approximately the same mean particle diameter but vary in their solubility in the dissolution fluid.

The assessment of the *in vitro* biovailability of the drugs from the various formulations was made by calculating the quantity of drug released into solution, after 5, 10, 20 40 and 80 min, as a percentage of the calculated drug content of the capsule. The release from capsules containing imipramine or tetracycline was such that for many formulations, the total drug content had passed into solution within 40 min. To avoid including the limiting value of 100% in the analysis, formulations were compared at 4, 10 and 20 min. These results were treated by standard analysis of variance procedures (Biomedical Computer programme BMDO8V) as a $6 \times 3 \times 2 \times 2 \times 2$ factorial design indicated significant effects for all the main factors. This contrasts with the previous results (Newton & Razzo, 1974) when the wetting agent did not apparently exert a significant effect. Because of the interactions, the overall mean effect for any one factor is not necessarily a reliable estimate of the effect of that factor. In such circumstances the best way to discover any trends is to examine in detail the factor used at the largest number of concentrations. This is the type of drug, used here at six concentrations. The drug type is, however, a qualitative factor. To give a quantitative measure, drug particle size and drug solubility were tried. Particle size correlation failed, but a relation between drug release after 20 min, y and solubility c_s does exist. It is:

$$y = 21{\cdot}2 \log c_s + 31{\cdot}17 \; (r = 0{\cdot}983) \quad .. \quad (1)$$

which is shown in Fig. 1. Its existence is not unexpected: a relation between intrinsic dissolution rates and solubilities for a wide range of compounds was established by Hamlin, Northain & Wagner (1965).

Formulation factors could well be expected to influence any relation between the dissolution of a drug and its solubility. The relation which exists here cannot be accepted without reservation because of the interaction effects. If however the results are broken down to 2 factor combinations, there are instances in which no interactions between the factors occur. Examination of such results reveals that for each drug, there are certain common combinations of factors which do not interact. Thus for 5 drugs, formulations which do not contain sodium lauryl sulphate provide no interactions

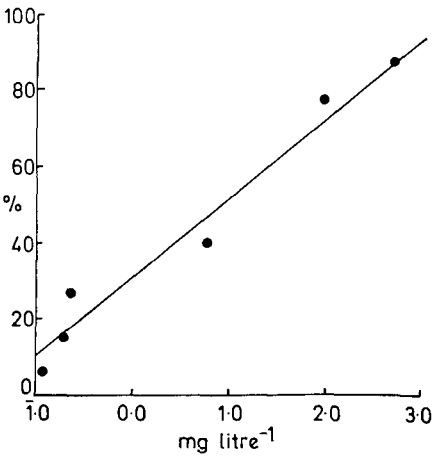

FIG. 1. Influence of drug solubility on the *in vitro* release of drugs from capsules. Ordinate–Overall average percentage of drug content of capsule released solution. Abscissa—log solubility of drug (mg litre^{-1}).

between Primojel at 20 and 80% concentrations and magnesium stearate at 0 and 1% concentration. It is possible, therefore, to build up from the individual results for each drug, a composite picture, Fig. 2A, B. Similarly combinations of lubricant and wetting agent at 80% lactose concentrations do not have interactions for 4 drugs, Fig. 3A, B. The approximation of the points to the general regression line and the similarity of the constants of the least squares regression lines of these figures to those of equation (1) support the validity of the latter expression. With this support for the general increase in drug release with increase in drug solubility, it would appear beneficial to consider the relation between these two factors for each of the combinations of ingredients.

The simplest formulations are those which contain neither lubricant nor wetting agent. At the 20% concentration of diluent, there is the general increase in release with drug solubility but the interesting feature of these results is the reduction in drug release for formulations of the more soluble drugs which contain the larger percentage of starch. There is an obvious decrease in drug release when imipramine formulations containing 80% Primojel. Thus it would appear preferable not to include starch or Primojel in capsule formulations in which it is required to administer a small quantity of highly soluble drugs.

The addition of a wetting agent could be expected to improve release of hydrophobic drugs. At 20% diluent concentrations this is certainly not the case, and there is a marked departure from the linear

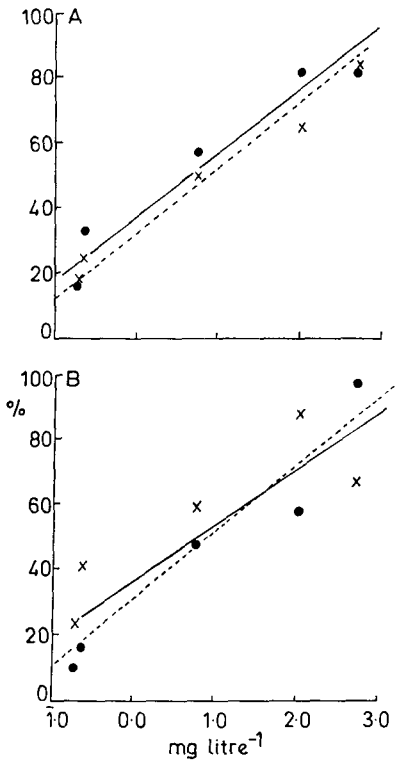

FIG. 2. Average drug release from capsule formulations as a function of drug solubility. These figures are constructed from the results of 2 factor analysis of variance for each drug. The results in these cases have no statistical interactions.

Constant factor	Variable factors	Concentration of factor %	Average effect for factor shown by	
Wetting agent 0%	Lubricant	0	●	
		1	×	(A)
	Primojel	20	●	
		80	×	(B)

Ordinate–Percentage of drug content of capsule released into solution. Abscissa—log solubility of drug (mg litre^{-1}). Regression line calculated from the relation between the overall average drug release and drug solubility, e.g. Equation (1) (– – – –). Regression line calculated from plotted results (——). (A) $y = 18{\cdot}1\,c_s + 36{\cdot}07$ ($r = 0{\cdot}971$); (B) $y = 18{\cdot}1\,c_s + 36{\cdot}1$ ($r = 0{\cdot}83$).

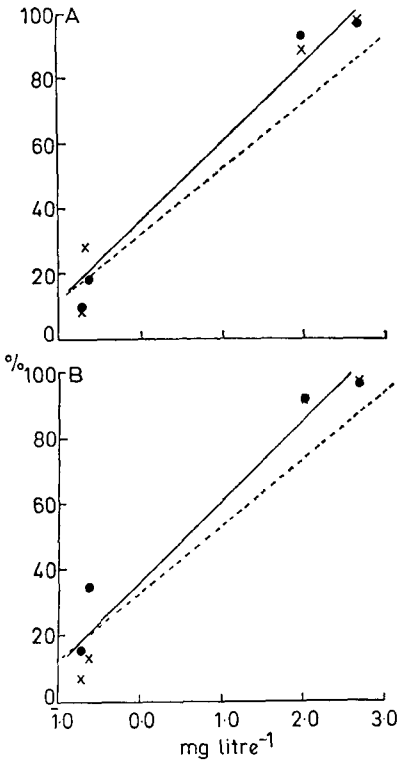

FIG. 3. Average drug release from capsule formulations as a function of drug solubility. These figures are constructed from the results of 2 factor analysis of variance for each drug. The results in these cases have no statistical interactions.

Constant factor	Variable factors	Concentration of factor %	Average effect for factor shown by	
Lactose 80%	Wetting agent	0	●	
		1	×	(A)
	Lubricant	0	●	
		1	×	(B)

Ordinate–Percentage of drug content of capsule released into solution. Abscissa—log solubility of drug (mg litre^{-1}). Regression line calculated from the relation between the overall average drug release and drug solubility, e.g. Equation (1) (– – – –). Regression line calculated from plotted results (——). (A) $y = 25{\cdot}1\,c_s + 35{\cdot}6$ ($r = 0{\cdot}975$); (B) $y = 25{\cdot}4\,c_s + 35{\cdot}1$ ($r = 0{\cdot}987$).

relation. When the diluents are present at an 80% concentration there is some general improvement in drug release, especially with the nitrofurantoin and nitrofurazone, but again there is a decreased release of the more soluble drugs when the diluent is starch.

The addition of hydrophobic magnesium stearate, in the presence of 20% diluents, generally decreases drug release below the overall avarage. In the presence of 80% diluents the presence of 1% magnesium stearate does not always reduce drug release, in fact with formulations containing starch and nitrofurazone, it produces a marked improvement. Formulations containing the more soluble drugs and starch again show below average drug release. The inclusion of both lubricant and wetting

agent, provides very much the same results as those for the addition of lubricant alone, except that this combination appears to improve the formulations containing starch and imipramine.

The general conclusion from these results is that solubility of the drug is a major factor controlling release of drug from capsules. The order of magnitude of the effect is given in equation (1). The departures from this relation are no doubt due to involvement of physical factors such as disintegration and deaggregation of the powder mass within the capsules. For soluble drugs, lactose, rather than starch or Primojel, would be the better diluent if required to be used in large quantities. Little benefit is to be obtained by using a blend containing sodium lauryl sulphate and the presence of the magnesium stearate can retard drug release though not by a predictable amount.

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