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The influence of additives on the *in vitro* release of drugs from hard gelatin capsules

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A factorially designed experiment has been used to assess the total percentage of drug released from hard gelatin capsules *in vitro* as a function of (a) the drug—the drugs being nitrofurantoin, nitrofurazone, oxytetracycline dihydrate and tetracycline hydrochloride; (b) the diluent—the diluents being lactose, Primojel and Dry-Flow starch; (c) the quantity of diluent, either 20 or 80%; (d) the presence (at a 1% level) and absence of magnesium stearate and (e) the presence (at a 1% level) and absence of sodium lauryl sulphate. Treatment of the results by analysis of variance, in 5, 4, 3 and 2 factor combinations, indicates that the influence of a given factor is often dependent on the other factors. These interdependencies take the form of either a variation in the extent of an effect or the reversal of an effect. The influence of drug and level of diluent show interdependencies of the former kind. Hence, whilst the overall average for drug release indicates that the drugs can be ranked in the ascending order: nitrofurantoin < nitrofurazone < oxytetracycline < tetracycline, the interactions predict that the quantitative ratios of 1 : 1·8 : 2·7 : 5·1 for the drugs above will vary when an additive is present and according to the additive. The rank order will, however, remain unchanged. Similarly, the higher level of diluent will usually increase drug release but not by a constant ratio between drugs. A reversal of an effect is shown by the addition of magnesium stearate, which in some instances increases rather than decreases drug release (its more usual effect). The addition of 1% sodium lauryl sulphate does not provide a major enhancement of drug release, and in certain cases can be detrimental. There is no consistent order of effectiveness of the three diluents, and thus a universal capsule diluent, which will always improve drug release, does not appear to be a possibility.

The factors which control the release of drugs from hard gelatin capsules have not yet been fully elucidated. One approach towards a better understanding is the study of numerous systems and examination of the results for regular patterns of behaviour as has been done by Newton, Rowley & Törnblom (1971a, b). The factorial design used includes four drugs and three diluents at two levels, with and without lubricant and a wetting agent. Such a design can be analysed by analysis of variance techniques, using a standard computer program, and can be readily modified to incorporate other factors.

MATERIALS AND METHODS

Materials

The drugs were supplied by Thomas Kerfoot Limited and Smith Kline and French Ltd. and complied with the necessary official standards, i.e. nitrofurantoin B.P., nitrofurazone B.P.C. 1968, oxytetracycline dihydrate E.P. II, 1971 and tetracycline hydrochloride B.P. The lactose was B.P. quality (Whey Products Limited regular

grade). Dry-Flow starch was supplied by Laing-National Limited, and Primojel by Kingsley and Keith Limited. The magnesium stearate B.P. was the superfine grade of Bush Boake, Allen Limited. The sodium lauryl sulphate B.P. was obtained from Evans Medical Limited.

Capsule filling

The powder blends were prepared in accordance with the systems chosen, quantities being: 20 or 80% of diluent, 0 or 1% of lubricant and 0 or 1% of wetting agent. The blends were filled into size 0 opaque hard gelatin capsules (LOK-CAP, Eli Lilly & Co.) by placing excess powder over the capsule bodies held in a Perspex block, which was displaced 2·5 cm vertically at a rate of 40 taps min^{-1}, until tamping provided no further incorporation of powder within the shell. The uniformity of weight was well within $\pm 5\%$ of the mean weight.

Dissolution testing

This was carried out by a four station multistirrer beaker method, similar to that described by Newton & Rowley (1970), except that 2 litre beakers were used and the capsules were held in a wire spiral, suspended across the beaker from supports which centralized the stirrer (speed 45 rev min^{-1}) within the beaker. (It was shown by analysis of variance that the variation between stirrers was not significantly different from that within stirrers.) The dissolution medium was 2 litres of hydrochloric acid (0·1 N), which was maintained at $37 \pm 0{\cdot}1°$. Samples were removed at known times through a filter by means of a peristaltic pump. The solutions were analysed colorimetrically with a Unicam S.P. 600 spectrophotometer after suitable dilution. Four capsules from each blend were tested.

RESULTS AND DISCUSSION

The possibility that a general pattern of behaviour existed was investigated by treating the whole five factor design by a standard analysis of variance procedure. For tetracycline hydrochloride, because of the rapid release from the capsules, this could only be done for the 5, 10 and 20 min samples. A typical variance analysis is shown for the 20 min sample time in Table 1; this is similar to analyses for the 5 and 10 min sample times. All the main factors other then the wetting agent have a significant effect on drug release, but it will be observed that 1st, 2nd and 3rd order interactions are also significant. This means that the influence of each factor is dependent on the presence of the other factors; it is not possible to give an absolute answer to the question of how each factor influences drug release. Examination of the average value of drug release for each factor (Table 2) suggests the following general conclusions:

(*a*) The extent of drug release increases with the type of drug, in the ascending order: nitrofurantoin < nitrofurazone < oxytetracycline < tetracycline.

(*b*) The effectiveness of the diluent is in the order: Primojel < lactose < starch.

(*c*) An 80% diluent level is more effective than a 20% level.

(*d*) The addition of 1% magnesium stearate reduces drug release.

(*e*) The presence of 1% sodium lauryl sulphate does not influence drug release.

Table 1. *Statistical significance of results for drug release from capsules.*

Source of error	Code	Mean square	Degrees of freedom	F ratio
Medicament	M	69756	3	2277·2 *
Diluent	A	1182	2	38·6 *
Level of diluent	D	15877	1	518·3 *
Lubricant	L	1592	1	52·0 *
Wetting agent	W	28	1	0·9
Interaction terms	MA	3896	6	127·2 *
	MD	1454	3	47·5 *
	AD	1334	2	43·6 *
	ML	381	3	12·5 *
	AL	806	2	26·3 *
	DL	477	1	15·6 *
	MW	731	3	23·9 *
	AW	142	2	4·6 **
	DW	11	1	0·4
	LW	313	1	10·2 *
	MAD	2674	6	87·3 *
	MAL	236	6	7·7 *
	MDL	346	3	11·3 *
	ADL	312	2	10·2 *
	MAW	168	6	5·5 *
	MDW	85	3	2·8 **
	ADW	23	2	0·8
	MLW	182	3	6·0 *
	ALW	370	2	12·1 *
	DLW	17	1	0·5
	MADL	137	6	4·5 *
	MADW	116	6	3·8 *
	MALW	72	6	2·4 **
	MDLW	54	3	1·8
	ADLW	23	2	0·7
	MADLW	21	6	0·7
Residual	R(MADLW)	31	288	

* F values significant at the 1% level.

** F values significant at the 5% level.

Values of F less than 1 indicate that this source of variation is less than the residual error.

Table 2. *The influence of the 5 factors on drug release, as indicated by the overall average of the % of drug released from the capsules after 20 min.*

Factor	Level of factor	% Drug released
Medicament	Nitrofurantoin	15·1
	Nitrofurazone	27·4
	Oxytetracycline dihydrate	40·6
	Tetracycline hydrochloride	77·4
Diluent	Lactose	39·8
	Primojel	43·3
	Starch	37·3
% Diluent	20	33·7
	80	46·6
% Lubricant	0	42·2
	1	38·1
% Wetting agent	0	40·4
	1	39·6

Each of these general conclusions has an exception, hence the interactions. The results were separated and treated as 4, 3 and, finally, 2 factor analyses of variance. Interactions are present in all 4 and 3 factor analyses. There are cases of no interactions with 2 factor analyses, but even here it is impossible to treat 2 factors at all levels of the other factors without interactions occurring. To illustrate the findings and to establish the nature of these interactions the results are presented as histograms for each time of sampling.

Before discussing the results in detail, it is important to point out that an interaction, in terms of this type of analysis, means that the effect of one variable on another is not simply additive (Snedecor & Cochran, 1967). Hence it is possible to have an interaction in which one factor gives an increase in effect at one level of another factor and a decrease at another level; or there may be an increase or decrease in both cases, but this cannot be predicted by simple addition of the individual effects. Both these types of interaction are observable in the present results. For example, in assessing the order of release associated with different drugs, all the formulations of tetracycline have higher drug release than oxytetracycline, but in varying amounts. Again the formulation of oxytetracycline containing 80% starch and 1% magnesium stearate has a lower drug release than the equivalent formulation of nitrofurazone. The converse is true for all the other formulations of these two drugs.

Comparison of the formulations of different drugs shows that, in most cases, the relation between drug type and the release of drug is that given in the first general conclusion (*a*). (Departures from this relation are mainly due to non-additive effects.)

This ranking of drugs in terms of release coincides with the relative water solubilities of these drugs. One can therefore conclude that the less soluble drugs will present greater formulation problems.

The order of effectiveness of the different types of diluents is influenced by the drug, the presence of both lubricant and a wetting agent, and by the level of diluent used. For nitrofurantoin and nitrofurazone, Primojel or starch, especially at the high level, appear better diluents, whereas for oxytetracycline and tetracycline, lactose is generally better. It is, however, impossible to provide a consistent generalization for all the drugs, even when the lubricant and wetting agent are absent. Thus the interactions here provide a definite warning that it is not possible to predict which of the diluents will provide the best drug release. The overall generalization that the higher the level of diluent, the greater is the drug release, is essentially correct for the two highly insoluble drugs nitrofurazone and nitrofurantoin, even when lubricant and/or wetting agents are present (Figs 1 and 2). The extent of the increases is inconsistent, so that interaction should be indicated in the analysis of variance. With oxytetracycline, the higher level of diluent generally produces increased drug release, but there is usually little difference between the two levels of Primojel. Tetracycline formulations containing lactose can show a decrease at higher levels of the diluent, whereas the starch and Primojel formulations all follow the generalization indicated by the overall averages (Table 3). The reduction of the release of chloramphenicol from capsules, by increasing the lactose content, has been reported by Withey & Mainville (1969); hence the present findings with tetracycline are not completely unexpected.

The addition of magnesium stearate, which is hydrophobic, would be expected to reduce drug release. Such expectation is confirmed by the results of Samyn & Jung (1970), and the general conclusions of Newton & others (1971). Closer examination

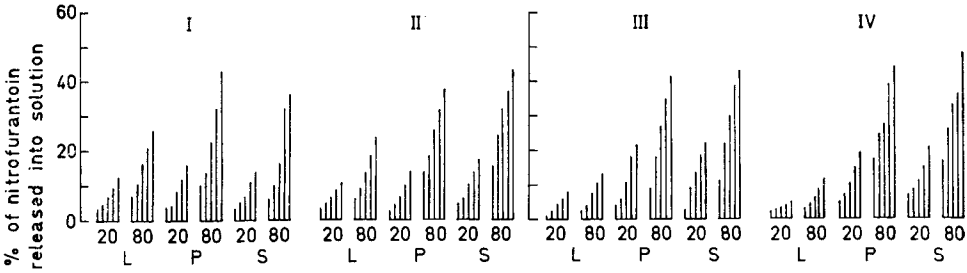

FIG. 1. The percentage of nitrofurantoin released into solution at known time intervals as a function of concentration. For each combination of ingredients the bars indicate the % of drug released into solution after 5, 10, 20, 40 and 80 min.

Group	% Magnesium stearate	% Sodium lauryl sulphate
I	0	0
II	0	1
III	1	0
IV	1	1

L = lactose, P = Primojel, S = starch. The % of diluent is indicated below each formulation.

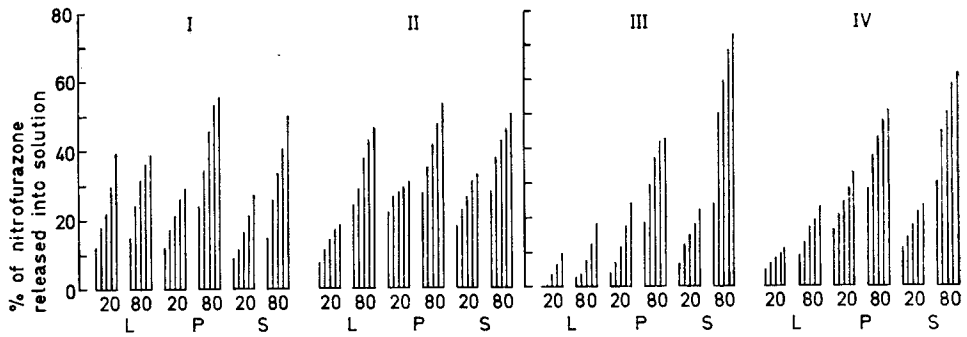

FIG. 2. The percentage of nitrofurazone released into solution at known time intervals as a function of formulation. Other details as in Fig. 1.

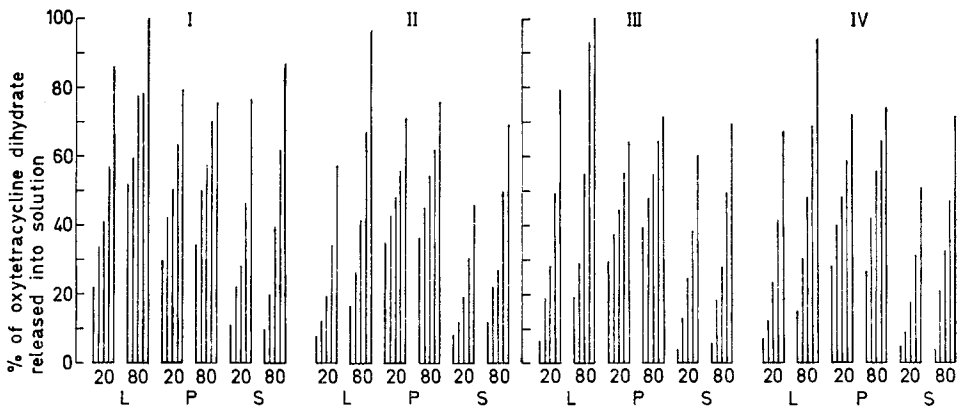

FIG. 3. The percentage of oxytetracycline dihydrate released into solution at known time intervals as a function of formulation. Other details as in Fig. 1.

of Table 2 from the latter paper shows that there are cases where the magnesium stearate actually increases drug release, which may well give rise to the interaction obtained in the analysis of variance.

Comparison of the sections I and II of Figs 1 to 4 shows the influence of the addition of 1% magnesium stearate. Clearly its presence usually does cause a reduction in drug release, but this is not the case for formulations of nitrofurantoin and nitrofurazone containing starch. In fact the presence of magnesium stearate enhances the release from the latter formulation. This behaviour is not only associated with starch: formulations of tetracycline and lactose show a similar effect.

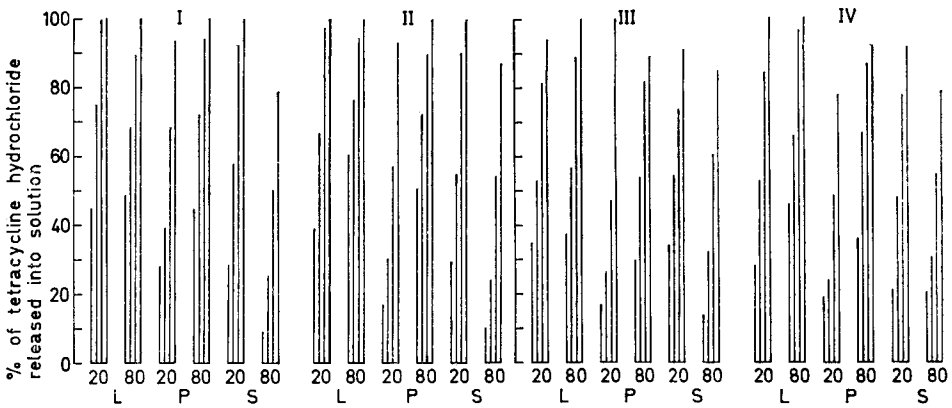

FIG. 4. The percentage of tetracycline hydrochloride released into solution at known time intervals (up to 40 min) as a function of formulation. Other details as in Fig. 1.

These results suggest that wetting is not the controlling feature of the release of drugs from capsules, a concept first suggested by Rowley & Newton (1970). This idea is further supported by the lack of significant effect produced by the addition of sodium lauryl sulphate (Tables 1 and 2). In fact comparison of sections I and III of Figs 1 to 4 show that there are instances where the addition of sodium lauryl sulphate actually reduces drug release, especially with oxytetracycline and tetracycline formulations. It could be argued that the addition of a wetting agent would be unnecessary with these water-soluble drugs, but this trend of a reduction still persists when the hydrophobic lubricant is present. The increases in drug release which the wetting agent does produce with the poorly soluble nitrofurantoin and nitrofurazone, are hardly dramatic. The apparent lack of a significant effect of the wetting agent and the presence of interactions are in fact a warning that sodium lauryl sulphate at this particular level is not a useful addition to make to capsule formulations.

The present approach does show the emergence of some general patterns of behaviour, but perhaps a more important finding is the confirmation of previous research (Newton & others, 1971 a,b) that the response of drug release to additives cannot always be anticipated. It is essential therefore to provide more information, using a wider range of materials, and to investigate the process of drug release in greater detail. In the case of highly water-insoluble drugs, there appears to be a need for methods of formulation other than the simple admixture of conventional additives, if dissolution is a controlling feature of the drug's biological activity.

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