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Further studies on the effect of additives on the release of drug from hard gelatin capsules

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An experiment based on a 3^3 design has been undertaken to establish the effect on drug release from capsules produced by adding lactose (0, 10 and 50%), magnesium stearate (0, 1 and 5%), and sodium lauryl sulphate (0, 1 and 10%) to a 76–105μm particle size fraction of ethinamate filled into capsules at a high and low packing density. Statistical analysis of the results indicated the presence of 2nd order interaction at all time intervals and for both sets of capsule fill weights. This signifies that the effect produced by each additive is dependent on the presence and the level of the other two additives. The interaction limits the conclusions that can be drawn about the main factors of diluent, lubricant and wetting agent, but the indications are that (a) 10% diluent reduces drug release, whereas 50% produces enhanced release; (b) the presence of 1% sodium lauryl sulphate is sufficient to enhance drug release; (c) the additive effects are independent of the capsule packing density.

As a result of a preliminary experiment of restricted design (Newton, Rowley & Törnblom, 1971), a full three way analysis of variance of the factors diluent, lubricant and wetting agent has been made, to elucidate their influence on drug release from capsules. In the light of experience, the number of replicates was reduced from 8 to 4 and the time intervals were reduced from 5 to 3. The levels of the three additives were those used previously and thus the design can be represented by the scheme shown in Table 1.

MATERIALS AND METHODS

Materials

A single batch of ethinamate (1-ethynylcyclohexyl carbamate) U.S.N.F. was sieved to give a 76–105 μm size fraction. The lactose, magnesium stearate and sodium lauryl sulphate were of B.P. quality. All other chemicals were of BDH reagent grade.

Capsule filling

The way in which the different levels of the three additives were combined is set out in Table 1. The powder blends were filled into size 0 clear gelatin capsules as described by Newton & Rowley (1970) to give a series of capsules of low fill weight (95% of the theoretical value predicted from the maximum bulk density), and a high fill weight (that produced with a load of 45 kg on the loading plate). Twenty capsules were prepared from each blend and only those capsules within $\pm 5\%$ of the mean filling weight were tested further. By replicate assay on random sets of capsules, the mixing was found to provide capsules which contained within $\pm 5\%$ of the predicted mean drug content.

Table 1. *Scheme for testing the variables of diluent, lubricant and wetting agent.* D represents diluent, L, lubricant and W, wetting agent. The subscript represents the % of additive present.

Lubricant %	Wetting agent (%) 0			1			10		
	Diluent %								
	0	10	50	0	10	50	0	10	50
0	$D_0L_0W_0$	$D_{10}L_0W_0$	$D_{50}L_0W_0$	$D_0L_0W_1$	$D_{10}L_0W_1$	$D_{50}L_0W_1$	$D_0L_0W_{10}$	$D_{10}L_0W_{10}$	$D_{50}L_0W_{10}$
1	$D_0L_1W_0$	$D_{10}L_1W_0$	$D_{50}L_1W_0$	$D_0L_1W_1$	$D_{10}L_1W_1$	$D_{50}L_1W_1$	$D_0L_1W_{10}$	$D_{10}L_1W_{10}$	$D_{50}L_1W_{10}$
5	$D_0L_5W_0$	$D_{10}L_5W_0$	$D_{50}L_5W_0$	$D_0L_5W_1$	$D_{10}L_5W_1$	$D_{50}L_5W_1$	$D_0L_5W_{10}$	$D_{10}L_5W_{10}$	$D_{50}L_5W_{10}$

Dissolution testing

This was made according to Newton & Rowley (1970) with a multistirrer system driven by an electric motor fitted with a Kop Variator, to give a stirrer speed of 45 rev/min. After known time intervals 2 ml samples were removed through a filter by means of a syringe. The ethinamate in solution was hydrolysed with sulphuric acid at 90° and the ammonium salt formed with sodium phenate and sodium hypochlorite solution estimated, the whole process being carried out using a Technicon Autoanalyser. Statistical analysis of the multistirrer system proved the interchangeability of results between beakers. Four capsules from each batch were tested.

RESULTS AND DISCUSSION

The percentage of drug content of the capsules which appears in solution 5, 20 and 40 min after commencing the dissolution test is shown in Table 2. The analysis of variance of the results is summarized in Table 3 where the complexity of the effects reported by Newton & others (1971) is confirmed. An important feature of the results is the presence of 2nd order interactions (Table 3), which signifies that the effect produced by each additive is dependent on the presence and the level of the other two. It is thus not possible to predict from a knowledge of the levels of the individual factors how combinations of the three additives will influence drug release. This is illustrated by Fig. 1a, b and c Here the effect of lubricant concentration on the drug release is shown for each level of diluent, at each level of wetting agent for high capsule fill weight after 40 min. If there were no interactions, for each diluent level each curve for the 3 wetting agent levels would have the same general shape, and these would be repeated at each diluent level. The complexity of shapes, within and between diluent levels illustrates the presence of 2nd order interactions.

The nature of the interactions is a matter for speculation. The % of the drug which dissolves during the test is a complex function of numerous factors, such as rate of solution of the gelatin shell, rate of penetration of water into the powder mass, the rate of de-aggregation of the powder mass and the characteristics of the powder mass after break up. The analysis of variance has confirmed the complexity of these events.

In spite of the presence of 2nd order interactions, the analysis of variance (Table 3), shows that diluent and wetting agent have a statistically significant effect on drug release. Assessment of the magnitude of the effects of each additive is made by averaging the results for a given level of a factor, irrespective of the other factors.

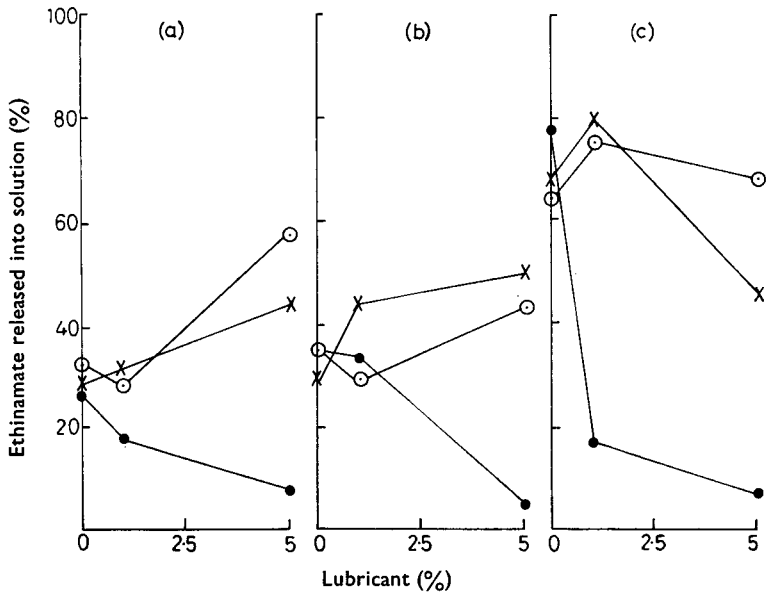

FIG. 1. The effect of lubricant content on the release of ethinamate from high fill weight capsules after 40 min at zero wetting agent (●), low wetting agent (×) and high wetting agent (○) content for (a) zero diluent, (b) low diluent, (c) high diluent.

For example, the effect of a 10% diluent level is obtained by averaging the results for the nine experiments in which 10% diluent was present, i.e. the results for all the systems D_{10} of Table 1. When treated in this way the results for the three levels of each additive for the low capsule fill weights are depicted in Fig. 2. These results

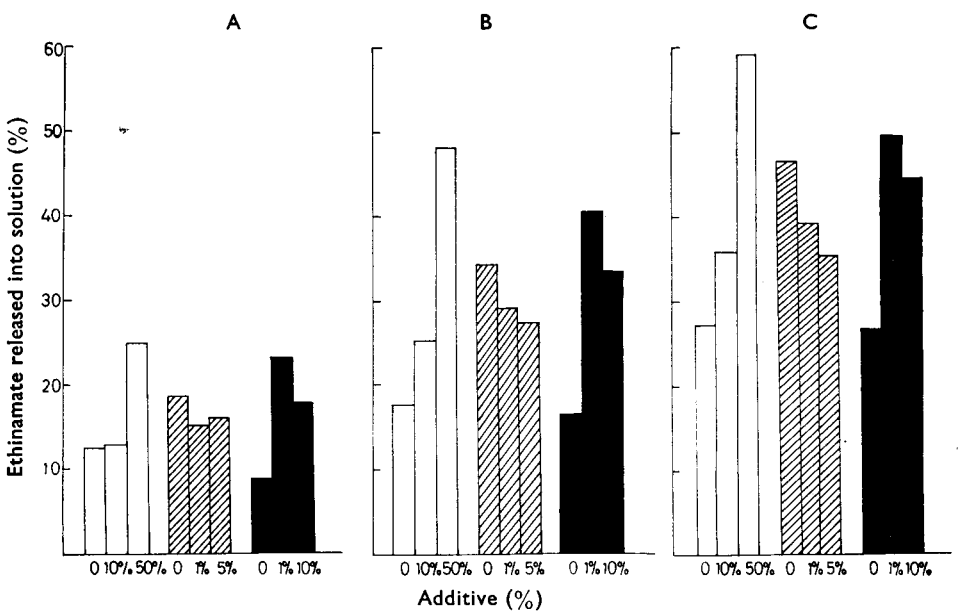

FIG. 2. The averaged effect of diluent (lactose) open columns, lubricant (magnesium stearate) hatched columns and wetting agent (sodium lauryl sulphate) solid columns on the release of ethinamate from capsules after (A) 5, (B) 20, (C) 40 min.

show that the significant effect of diluent is to produce an increase in drug release, especially at the 50% level. Lactose, being water soluble, will produce this effect by changing the powder bed from one which is hydrophobic to one which is more hydrophilic. A change in the hydrophobic character of the bed will also be produced by the wetting agent, hence the increase in drug release, Fig. 2. The effect, however, appears somewhat less at the high wetting agent concentration (10%), which implies that wetting is not the only factor involved in drug release and agrees with our previous findings using liquid penetration as an assessment of drug release from capsules (Rowley & Newton, 1970).

The finding that the presence of magnesium stearate does not significantly affect drug release is somewhat surprising in view of earlier results (Rowley & Newton, 1970). In the present experiments, when magnesium stearate is the only additive, drug release is clearly reduced (Table 2, Fig. 1a). In the absence of wetting agent

Table 2. *Mean percentage of drug released from capsules in dissolution tests.* Each block of figures represents the design of Table 1 and each entry is the mean of four determinations.

Time (min)									
				High capsule fill weight					
5	15·75	12·45	37·18	10·88	21·18	33·05	11·45	11·75	30·38
	4·25	3·48	4·75	8·85	18·75	42·80	7·30	9·73	34·05
	2·70	1·78	5·40	11·13	14·33	17·00	14·63	14·60	21·43
20	17·78	23·08	16·53	17·45	22·68	59·30	20·05	22·48	54·85
	11·38	13·93	7·65	24·55	35·90	72·60	16·18	19·80	65·93
	3·90	2·40	5·58	28·83	41·40	36·95	20·90	32·70	57·05
40	26·35	34·73	79·15	28·03	29·13	68·33	32·03	34·38	64·18
	17·58	28·08	17·13	31·20	43·93	79·50	27·98	29·00	75·18
	7·60	4·93	7·03	43·78	50·03	46·05	57·03	43·20	68·03
				Low capsule fill weight					
5	6·93	12·65	34·75	11·30	12·05	38·73	8·78	13·95	27·05
	3·95	2·55	4·73	16·15	20·58	31·58	7·38	14·78	33·40
	3·40	2·15	6·23	39·50	22·60	14·38	11·95	10·73	31·40
20	14·08	25·03	65·35	15·18	20·78	69·85	16·65	27·08	55·95
	8·90	12·73	6·60	24·68	42·52	72·40	20·03	17·83	55·98
	5·40	3·73	6·93	27·13	48·05	44·75	26·25	27·25	55·70
40	24·93	38·38	89·38	22·68	31·03	81·73	26·93	41·03	62·90
	20·63	25·13	17·45	29·80	52·90	78·73	31·70	27·10	69·50
	8·50	7·33	8·50	39·50	57·13	55·05	36·40	39·68	67·00

but the presence of diluent, the addition of magnesium stearate again causes a reduction in drug release (Fig. 1b, c) but the inclusion of both wetting agent and diluent provides the non-predictable pattern observed in Fig. 1b, c and the small differences in average affect seen in Fig. 2. Thus the overall effect of lubricant is overcome by the presence of the other additives and, in terms of statistics, contributes mainly to the interaction term.

Comparison of the results for each combination of additives at the two capsule fill weights indicates that similar quantities of drug are released for both low and high capsule filling densities (Table 2). The magnitude of the effects of each factor, shown for low capsule fill weights in Fig. 2 are, therefore, very similar. The variance

Table 3. *Statistical significance of results for drug release from capsules.*

Source of error	5 min Mean square S^2	5 min F ratio	20 min Mean square S^2	20 min F ratio	40 min Mean square S^2	40 min F ratio
			Low capsule fill weight			
Dilent D	1844·28	8·30‡	7843·2	77·95†	9935·96	16·93†
Lubricant L ..	117·68	*	503·3	5·00‡	1146·68	1·90
Wetting agent W ..	1908·47	8·60‡	5521·91	54·80†	5318·16	9·06†
D × L	514·49	2·32	1659·47	16·19†	1297·02	2·21
D × W	195·43	*	1231·88	12·24†	440·2	*
L × W	389·73	1·76	1510·96	15·02†	2057·59	3·51
D × L × W ..	221·66	8·51†	100·61	2·49‡	586·89	12·27†
Residual	26·05		40·30		47·84	
			High capsule fill weight			
Diluent D	2497·62	19·15†	8831·86	10·65†	7242·8	12·99†
Lubricant L ..	743·89	5·70‡	632·98	*	542·42	*
Wetting agent W ..	979·2	7·51‡	4460·99	5·37‡	6120·89	10·98†
D × L	281·22	2·16	828·52	1·0	1278·9	2·29
D × W	154·43	1·18	449·75	*	410·58	*
L × W	430·59	3·30	1158·09	1·40	2665·35	4·78‡
D × L × W ..	130·42	4·39†	829·25	25·60†	557·66	14·5†
Residual	29·69		32·29		41·32	

The F ratio for the interaction error D × L × W is the ratio mean square D × L × W: mean square residual. As these are always significant at the 5% level, the F ratio for all other factors is the ratio mean square for the factor: mean square D × L × W.

† F values significant at 1% level.

‡ F values significant at 5% level.

* The value of the mean square for this source of variation is less than that for the interaction, hence the F ratio is less than 1—indicating that the variation in question is probably of a random nature.

ratios (Table 3) also show a similar pattern of significance and hence the effect of additives can be considered independent of capsule filling conditions.

The failure to exclude interactions from the complete 3 way analysis of variance, suggests that the use of this approach to evaluate the effect of combined additives on the release of drug from capsules is not satisfactory if but three levels are used. Increasing the number of levels within the same range of concentration of additives would define the main effects in greater detail and also elucidate the contribution of the different factors to the interactions. Unfortunately, increasing the number of levels increases the number of experiments to be made, e.g. the use of 5 levels requires 125 different combinations of factors compared with the 27 of the present experiment. Reduced forms of designed experiments can, however, be used and measurements of factors other than drug release should also be considered when optimum levels of additives are sought.

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