# The effect of additives on the release of drug from hard gelatin capsules

The release of drugs from hard gelatin capsules has been shown to be affected by the presence of additives (Paikoff & Drumm, 1965; Withey & Mainville, 1969, Samyn & Jung, 1970). In these studies a single factor was varied at any one instance. To study the effect on drug release produced by combining a drug (ethinamate) with a diluent (0, 10 and 50% lactose), a lubricant (0, 1 and 5% magnesium sterate) and a wetting agent (0, 1 and 10% sodium lauryl sulphate) a preliminary experiment has been undertaken. The design used is set out in Table 1. The drug release from capsules has also been shown to be dependent on the capsule fill weight and the particle size of the drug (Newton & Rowley, 1970). The design in Table 1 was carried out with a 76–105 and a 251–420 $\mu$m size fraction at a low and high capsule fill weight. The drug availability was assessed by the dissolution test described by Newton & Rowley (1970), employing eight capsules from each combination of drug, diluent, lubricant and wetting agent.

The results for the percentage of drug released from the capsule into solution were treated by an analysis of variance. The values of the variance ratios are given in Table 2. An important feature of the results is the presence of significant interaction between diluent, lubricant and wetting agent. The restricted design of the experiment is such that when interactions are present, it is only possible to obtain indications of how additives influence drug release. To assess the effect of each factor, the average value for each level of the factor is compared with the overall mean for one series of experiments (i.e. one particle size, one capsule density, one time interval).

Table 1. *Combinations of additives tested.*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $D_0$ | $L_0$ | $W_0$ | $D_{10}$ | $L_0$ | $W_1$ | $D_{50}$ | $L_0$ | $W_{10}$ |
| $D_0$ | $L_1$ | $W_1$ | $D_{10}$ | $L_1$ | $W_{10}$ | $D_{50}$ | $L_1$ | $W_0$ |
| $D_0$ | $L_5$ | $W_{10}$ | $D_{10}$ | $L_5$ | $W_0$ | $D_{50}$ | $L_5$ | $W_1$ |

Where D represents diluent, L lubricant and W wetting agent. The subscript represents the % of additive present.

Table 2. *Results of analysis of variance of the effect of additives on the release of ethinamate from capsules.*

| Size fraction of Drug | Time (mins) | Variance ratio | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Low capsule denstiy | | | | High capsule density | | | |
| | | $F_D$ | $F_L$ | $F_W$ | $F_{DLWI}$ | $F_D$ | $F_L$ | $F_W$ | $F_{DLWI}$ |
| 251–420 $\mu$m | 5 | 0·60 | 8·43 | 47·82 | 18·32 | 1·77 | 17·94 | 42·00 | 5·54 |
| " | 10 | 14·90 | 21·35 | 93·23 | 44·42 | 2·70 | 3·76 | 31·04 | 3·71 |
| " | 20 | 8·31 | 25·91 | 75·73 | 26·32 | 1·21 | 3·34 | 9·52 | 0·32 |
| " | 30 | 1·05 | 3·11 | 10·69 | 0·82 | 3·57 | 0·81 | 1·28 | 2·63 |
| " | 40 | 5·91 | 5·55 | 15·15 | 0·02 | 4·53 | 0·51 | 0·39 | 3·28 |
| 76–105 | 5 | 16·19 | 10·59 | 33·71 | 11·39 | 7·43 | 25·28 | 28·08 | 0·04 |
| " | 10 | 61·09 | 27·30 | 91·76 | 26·62 | 28·82 | 28·34 | 73·63 | 7·48 |
| " | 20 | 80·76 | 28·16 | 96·71 | 19·62 | 70·73 | 34·76 | 188·05 | 5·88 |
| " | 30 | 69·06 | 22·93 | 68·08 | 11·81 | 78·53 | 33·69 | 206·68 | 1·93 |
| " | 40 | 72·54 | 26·96 | 68·14 | 8·81 | 81·43 | 33·23 | 206·00 | 0·53 |

Variance ratio—this is obtained from the mean square calculated as follows:

$$F_D = \frac{S^2_D}{S^2_O},\ F_L = \frac{S^2_L}{S^2_O},\ F_W = \frac{S^2_W}{S^2_O} \text{ and } F_{DLWI} = \frac{S^2_{DLWI}}{S^2_O}$$

where the subscript gives the source of variation: D, diluent; L, lubricant; W, wetting agent; DLWI interaction and O, residual error.
The tabulated values for the variance ratio for 2 and 60 degrees of freedom at the 5, 1 and 0·1% probability levels are 3·15, 4·98 and 7·76 respectively.

Table 3. *Magnitude and significance of the effects of diluent, lubricant and wetting agent on the release of ethinamate from capsules.*

| Time (min) | Average % drug released for all factors | Diluent content 0 | Diluent content 10% | Diluent content 50% | Lubricant content 0 | Lubricant content 1% | Lubricant content 5% | Wetting agent content 0 | Wetting agent content 1% | Wetting agent content 10% | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 5·75 | +0·41* | −0·02* | −0·39* | +1·36 | +0·17 | −1·18 | −2·20 | +0·68 | +1·53 | |
| 10 | 12·69 | +0·69* | +0·33* | −1·01* | +1·22 | −0·70 | −0·51 | −3·42 | +1·07 | +2·36 | |
| 20 | 22·27 | +1·04* | −1·05* | +0·01* | +0·67 | −1·99 | +1·30 | −3·35 | +1·16 | +2·29 | A1 |
| 30 | 29·83 | −0·31 | −2·44 | +2·73 | −0·11* | −1·19* | +1·29* | −1·57* | +0·09* | +1·46* | |
| 40 | 35·53 | −0·61 | −3·10 | +3·72 | +0·33* | −1·28* | +0·95* | −0·97* | +0·08* | +1·05* | |
| 5 | 5·31 | +0·25* | +0·01* | −0·23* | +0·97 | −0·12 | −0·96 | −2·38 | +0·55 | +1·83 | |
| 10 | 12·89 | +1·84 | −0·10 | −1·75 | +2·20 | −2·09 | −0·12 | −4·45 | −0·07 | +4·52 | |
| 20 | 21·45 | +2·27 | −0·40 | −1·88 | +3·83 | −3·59 | −0·24 | −5·51 | −1·44 | +6·94 | A2 |
| 30 | 28·68 | +1·02* | −1·91* | +0·90* | +3·29 | −1·39 | −1·89 | −2·29 | −3·76 | +6·07 | |
| 40 | 34·82 | +0·03 | −3·51 | +3·48 | +3·62 | +0·18 | −3·80 | −0·16 | −6·06 | +6·22 | |
| 5 | 12·86 | −0·81 | −2·55 | +3·35 | +6·22 | −4·62 | −1·61 | −6·55 | +1·64 | +4·89 | |
| 10 | 17·95 | +0·28 | −7·13 | +6·86 | +7·38 | −6·40 | −1·09 | −11·97 | +1·78 | +10·20 | |
| 20 | 24·88 | +1·00 | −9·89 | +8·83 | +6·06 | −6·99 | −0·92 | −16·62 | +3·31 | +13·48 | B1 |
| 30 | 29·34 | +1·76 | −11·05 | +9·29 | +5·84 | −7·37 | +1·54 | −18·01 | +3·11 | +14·91 | |
| 40 | 33·40 | +2·05 | −11·84 | +9·79 | +6·29 | −7·54 | +1·26 | −18·66 | +2·78 | +15·88 | |
| 5 | 12·59 | +0·47 | −4·43 | +3·95 | +3·85 | −1·25 | −2·61 | −6·55 | +1·09 | +5·65 | |
| 10 | 17·83 | −0·88 | −8·33 | +9·22 | +6·07 | −5·69 | −0·38 | −12·10 | +3·49 | +8·63 | |
| 20 | 24·31 | −1·47 | −10·47 | +11·93 | +6·05 | −7·13 | +1·07 | −14·02 | +4·81 | +9·20 | B2 |
| 30 | 28·81 | −0·91 | −11·42 | +12·35 | +6·64 | −7·06 | +0·43 | −13·35 | +4·21 | +9·15 | |
| 40 | 32·96 | −1·28 | −11·81 | +13·10 | +7·80 | −7·44 | −0·35 | −13·00 | +4·19 | +9·48 | |

The figures in the Table represent the difference between the mean of the percentage of drug released, under the influence of each level of each factor and the grand mean, at each time interval. All the results were found to be significant at the 5% level except those marked *.

A = 251–410 μm size fraction. B = 76–105 μm size fraction.
1 = high capsule fill weight. 2 = low capsule fill weight.

The results in Table 3 provide the following indications.

(i) All the additives have a greater effect on drug release when the finer particle size fractions are used. This can be related to the less permeable structure of powder beds formed by small particle size fractions (Newton & Rowley, 1970).

(ii) The addition of 50% of diluent is required to increase the drug release. The lower level of diluent is presumably insufficient to change the hydrophobic nature of the powder bed.

(iii) The presence of the lubricant at a 1% concentration reduces drug release, but there is no further decrease when the content is increased to 5%. The lubricant will enhance the hydrophobic character of the powder mass, however, it appears that there is a limit to this effect.

(iv) The presence of wetting agent increases drug release, the higher level producing a greater increase. The mechanism is no doubt associated with the wetting of the hydrophobic drug.

(v) The range of capsule fill weights used does not appear to greatly influence the effect which additives have on drug release. The results show the complex way in which combining additives influences the release of drugs from capsules. Further studies are required in which it is possible to evaluate the contribution of interactions.

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