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Effect of Mode of Incorporation of Disintegrants on the Characteristics of Fluid-bed Wet-granulated Tablets

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Abstract—A full factorial experimental design was employed to investigate the effects of mode of disintegrant incorporation and concentration in wet-granulated paracetamol tablets manufactured by top-spray fluid-bed. Disintegrants (croscarmellose sodium, sodium starch glycolate, or crospovidone) were incorporated either intragranularly, extragranularly, or distributed equally between the two phases. The results were analysed by a general quadratic equation and response surfaces generated. On examining the results for dissolution studies the combined mode resulted in significantly faster dissolution rates than did the extragranular mode which, in turn, was superior to the intragranular mode of inclusion. These results were reflected in the disintegration studies where the combined mode exhibited the shortest disintegration times for all the disintegrants. Tablet crushing strength was not affected by the mode of incorporation of concentration of the disintegrants. Main as well as interaction effects between the types, mode of incorporation and percent disintegrant employed were significant ($P<0.05$) for disintegration time and percent release at 15 min. Croscarmellose sodium exhibited the shortest while crospovidone displayed significantly ($P<0.05$) longer disintegration times. Formulations containing crospovidone did not meet official compendial (USP XXII) requirements of 80% in 30 min. In general, croscarmellose sodium and sodium starch glycolate were found to be less sensitive to the mode of incorporation than crospovidone.

For most solid dosage forms disintegration is a necessary first step for release from the tablet matrix. The use of disintegrants such as croscarmellose sodium, sodium starch glycolate, and crospovidone is common to enhance the rate of disintegration, thereby improving the drug release profile (Shangraw et al 1980). Wet granulation is an often-used technique for manufacture of tablets. The disintegrant in wet granulation can be incorporated either extragranularly [e], intragranularly [i], or distributed between the two phases [i+e]. Much work has been done on the effect of mode of incorporation and concentrations of disintegrants (Sakr & Farrag 1975; Shotton & Leonard 1976; Van Kamp et al 1983; Gordon et al 1990) in wet granulation prepared by traditional methods. Fluid-bed techniques for wet granulation offer the current state of the art technology in controlling production variables, as well as meeting Good Manufacturing Practices requirements since mixing, wetting, and drying are combined in a single process (Higashide et al 1985). Hence a comparative study on the effect of mode, type and concentration of disintegrant on fluid-bed granulations is desirable. Sakr & Farrag (1975) and Gordon et al (1990) found intragranular inclusion to be superior with extragranular inclusion. Miller et al (1980) and Shotton & Leonard (1976), however, found the combined inclusion to result in faster dissolution than the separate modes of incorporation, and Van Kamp et al (1983) concluded that method of addition of disintegrants had little effect on the dissolution characteristics. These apparent differences could be attributed to the method of manufacture or to the physicochemical characteristics of the tablet ingredients.

A full factorial experimental design is an established statistical tool and can be used to study and compare the effects of the mode of incorporation and concentration of disintegrants. The present study employs techniques used in optimization studies—multiple regression analysis and response surface modelling to obtain a better visual understanding of the responses and process interactions. An understanding of these factors could lead to the development of a physically stable formulation.

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Materials and Methods

Materials

Paracetamol (acetaminophen) was from Mallinckrodt, Inc., St Louis, MO, USA; povidone was from GAF Chemical Corp., Wayne, NJ, USA; croscarmellose sodium from FMC Corp., Philadelphia, PA, USA; crospovidone, GAF Chemical Corp., Wayne, NJ, USA; sodium starch glycolate, Mendel Co., NY, USA; magnesium stearate, Mallinckrodt, Inc., St Louis, MO, USA.

Methods

Table 1 lists the general formulation used for the preparation of the paracetamol tablets.

Preparation of the tablets. Binder solutions were prepared by dissolving polyvinylpyrrolidone in distilled water. The following were the conditions maintained in the preparation of the batches in the fluid-bed (Glatt Laboratory Fluidized-

Table 1. General formula for paracetamol tablets.

Ingredient	Composition (% w/w)	Amount per tablet (mg)
Paracetamol	93·37	312·80
Polyvinylpyrrolidone	4·67	15·64
Disintegrant	1–4	3·28–12·72
Magnesium stearate	0·98	3·28
Total		335·0

Bed, Model GPCG-1, Glatt Air Technique, Ramsay, NJ, USA): inlet air temperature 45°C; liquid binder flow rate 20 mL min^{-1}; atomization air pressure 2 bar; binary spray nozzle diameter 1 mm; binary spray nozzle angle 2 * 360°; dual filter shaking interval 30 s; dual filter shaking duration 5 s; pressure drop across the bed 0–1 kPa; fluidization air flow rate 50–100 $m^3 h^{-1}$.

The resultant granules were dried in the fluid-bed to a moisture content of 2% w/w. The granules were then mixed with 1% w/w magnesium stearate powder in a Turbula mixer (Willy A., Bachofen AG Machinefabrik, Basel, Switzerland) for 10 min. In the case where disintegrants were included extragranularly, they were added along with the lubricant and mixed in the Turbula for 10 min. The final granulations were compressed at 4·45 kN in an instrumented Manesty tablet press (Manesty D3B, Manesty Machines Ltd, Liverpool, UK) to a target weight of 335 mg.

Table 2. Full factorial experimental design.

	Variable level in coded form	
Trial formulation number[a]	X_1	X_2
1	−1	−1
2	−1	−0·33
3	−1	+1
4	0	−1
5	0	−0·33
6	0	+1
7	+1	−1
8	+1	−0·33
9	+1	+1

[a] Formulations were randomized during the experimentation.

Table 3. Translation of experimental conditions to physical units.

	Variable level in coded form			
Variable	−1	−0·33	0	+1
X_1	[i]	—	[i+e][a]	[e]
X_2	1%	2%	—	4%

[a] 50% w/w of the disintegrant was added intragranularly and 50% w/w extragranularly.

Evaluation of tablets. The mechanical strength of the tablets was determined using a Key hardness tester (model HT-500 II, Key International Inc., English Town, NJ) (n = 10). The tablets were evaluated for disintegration times (Erweka ZT3-4 DT6, Erweka Instrument Corp., Milford, CT, USA) following the procedures specified in the USP XXII (n = 6).

Dissolution studies was performed using the USP XXII dissolution apparatus II. The media consisted of phosphate buffer (pH 5·8) at 37 ± 0·5°C with a paddle speed of 50 rev min^{-1}. Samples were withdrawn at 15, 30 and 60 min and replaced with fresh media. The samples were analysed using a UV spectrophotometer (Beckman DU 70, Beckman Instruments, North Kennicott, IL) at 243 nm (n = 6).

Experimental design and analysis. The experimental design used in this study was a full factorial design. The design layout is shown in Table 2. Two variables were investigated for each of the disintegrant types studied: mode of incorporation of the disintegrant (X_1), and the level of disintegrant (X_2). Table 3 describes the translation of the experimental conditions to their coded form. Second order regression models were developed for the various responses in the form shown below:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 \quad (1)$$

where Y_i is the level of response, b_i is the regression coefficient, and X_i is the coded level of the independent variable.

Analysis of variance was also performed on the resulting raw data.

Results and Discussion

Tables 4, 5 give the hardness, disintegration time and dissolution characteristics for the various batches. The data were then used to generate a second-order regression model

Table 4. Disintegration times (T_d, min) and hardness of paracetamol tablets prepared by top-spray fluid-bed with three disintegrants.

	Disintegrant					
	1%		2%		4%	
Disintegrating agent	T_d	Hardness	T_d	Hardness	T_d	Hardness
None	112 (1·37)	5·49 (0·46)				
Sodium starch glycolate						
Intragranular	22* (1·77)	4·52 (0·53)	8* (1·82)	4·29 (0·60)	4* (0·32)	4·38 (1·20)
Extragranular	42* (1·38)	4·57 (0·51)	16* (1·37)	4·26 (0·42)	6* (1·06)	4·06 (1·16)
Combined	17* (1·46)	4·36 (0·40)	12* (1·46)	4·31 (0·50)	2* (1·31)	4·11 (1·23)
Croscarmellose sodium						
Intragranular	12* (1·00)	3·96* (0·67)	8* (1·33)	4·06 (0·94)	3 (0·41)	3·62 (0·75)
Extragranular	11* (1·50)	5·27* (0·86)	6* (0·82)	4·04 (1·36)	2 (1·40)	4·17 (0·78)
Combined	7* (1·40)	5·75* (0·63)	3* (0·41)	3·88 (0·77)	2 (1·51)	4·26 (0·63)
Crospovidone						
Intragranular	26* (1·71)	3·67* (0·77)	11* (1·47)	4·44 (0·81)	9* (1·37)	4·53 (1·92)
Extragranular	28* (1·50)	3·91* (0·68)	16* (2·32)	4·52 (0·94)	12* (1·63)	4·17 (0·86)
Combined	21* (1·94)	4·05 (1·67)	10* (1·72)	4·70 (1·51)	7* (1·17)	4·23 (0·91)

* $P < 0·05$ compared with other modes of incorporation. Mean (± s.d.).

Table 5. Effect of the mode of incorporation and concentration of disintegrants on the dissolution of paracetamol tablets prepared by top-spray fluid-bed.

Disintegrants	Release (%) 15 min	30 min	60 min
None	9·77 (0·41)	19·61 (1·75)	44·52 (4·05)
Sodium starch glycolate			
1%			
Intragranular	64·83* (2·44)	89·79 (2·950)	99·87 (0·79)
Extragranular	76·61* (3·36)	94·72 (4·480)	100.00 (0·88)
Combined	84·38* (3·26)	95·80 (2·34)	98·99 (1·23)
2%			
Intragranular	82·96 (2·32)	93·40 (1·68)	99·34 (1·31)
Extragranular	81·10 (3·73)	94·47 (3·46)	100·00 (1·04)
Combined	86·30 (2·36)	97·24 (2·32)	100·00 (0·94)
4%			
Intragranular	85·28 (3·17)	96·22 (1·25)	100·00 (0·93)
Extragranular	87·64 (2·64)	96·81 (1·29)	99·86 (0·64)
Combined	89·08 (3·19)	99·25 (1·07)	100·00 (0·73)
Croscarmellose sodium			
1%			
Intragranular	67·06* (3·29)	86·08 (2·10)	98·28 (1·21)
Extragranular	76·63* (1·79)	92·49 (1·77)	99·56 (2·99)
Combined	80·64* (6·76)	94·71 (3·22)	100·00 (2·00)
2%			
Intragranular	72·17* (3·22)	89·16 (2·07)	99·86 (1·47)
Extragranular	78·37* (3·25)	94·03 (1·93)	100·00 (1·57)
Combined	82·85* (3·47)	95·83 (4·01)	100·00 (0·98)
4%			
Intragranular	80·97* (2·43)	94·65 (1·99)	100·00 (1·74)
Extragranular	82·43* (1·56)	95·44 (1·96)	99·87 (1·51)
Combined	87·28* (1·38)	97·57 (1·93)	100·00 (1·01)
Crospovidone			
1%			
Intragranular	16·98* (2·05)	43·38 (1·68)	85·49 (1·74)
Extragranular	22·11* (1·66)	43·38 (1·67)	86·24 (1·48)
Combined	29·55* (3·61)	51·52 (2·06)	88·36 (2·37)
2%			
Intragranular	14·11* (2·13)	32·81 (1·48)	78·09 (2·33)
Extragranular	29·78* (3·55)	46·85 (3·76)	85·20 (1·26)
Combined	39·27* (3·34)	56·23 (2·62)	86·87 (1·18)
4%			
Intragranular	19·38* (2·61)	47·29 (1·74)	79·80 (1·55)
Extragranular	31·79* (2·51)	54·17 (3·21)	89·07 (2·27)
Combined	48·38* (3·18)	63·90 (2·75)	92·58 (1·09)

$P<0·05$ compared with other modes of incorporation. Mean (±s.d.).

for each of the studied responses. A summary of the results of the regression analysis is shown in Table 6. Correlation coefficients, regression F-ratios, and regression confidence intervals were acceptable for the various responses. Residual analysis indicated no violation of the assumptions. Hence the model was found to be adequate for the limited range and responses studied. It should be noted that for sodium starch glycolate the model explained only 75% of the variability in the data. Variables with regression confidence intervals less than 75% were considered not to have a significant effect on the particular response. On examining the coefficients it is observed that the level of the disintegrant included has a significant effect on the dissolution, disintegration and mechanical strength of the tablets. Mode of incorporation displayed a significant effect on disintegration times of sodium starch glycolate and the percent dissolved at 15 min for croscarmellose sodium. All measured responses were significantly effected by the mode of incorporation for crospovidone. Significant interaction effects followed the regression results of the mode of incorporation. The second-order term of mode of incorporation was found to contribute significantly to the model fit and this was reflected in the apparent curvature in the contour diagrams (Figs 1, 2). There was a significant ($P<0·05$) increase in the mechanical strength when croscarmellose sodium was present extragranularly. This can be attributed to croscarmellose sodium acting as a binding agent when incorporated extragranularly or in the combined mode.

In order to further describe the behaviour of the tablet dissolution (at 15 min) and disintegration, contour plots were generated. For the analysis of percent release, the 15-min dissolution data were selected, since no studied formulation had achieved 100% release at 15 min. The resulting contour plots clearly show the impact of varying the concentrations of disintegrants as well as mode of disintegrant incorporation on the dissolution and disintegration. Fig. 1 shows the contour surface for disintegration times. A pronounced effect of the level of disintegrant on the disintegration time is observed for all three disintegrants. Examination of the slopes of the plots also indicates significant effects of the mode of disintegrant incorporation and level of disintegrant. No observable interaction effect is apparent

Table 6. Summary of regression results for measured responses (eqn 1).

Y	b_0	b_1	b_2	b_3	b_4	b_5	r[a]	F[b]	Confidence (%)[c]
Sodium starch glycolate									
Disintegration time (min)	—[d]	4·54	−11·50	−4·18	6·00	8·18	0·9210	6·92	90·4
% Dissolution (at 15 min)	90·52	—	6·03	—	−6·85	—	0·8132	2·61	76·4
Hardness (kp)	4·15	—	−0·15	−0·08	0·11	0·11	0·9029	5·57	88·3
Croscarmellose sodium									
Disintegration time (min)	2·19	—	−3·83	—	3·0	1·98	0·9427	9·85	92·7
% Dissolution (at 15 min)	84·13	2·65	4·39	−1·99	−7·32	—	0·9710	48·07	98·7
Hardness (kp)	4·04	—	−0·49	—	—	0·76	0·7594	1·89	68·4
Crospovidone									
Disintegration time (min)	5·95	1·67	−7·83	—	4·33	8·32	0·9893	55·61	97·2
% Dissolution (at 15 min)	40·73	5·69	5·15	—	−16·71	—	0·9229	7·17	90·6
Hardness (kp)	4·77	—	0·13	−0·15	−0·12	−0·59	0·9893	8·48	93·4

[a] Multiple correlation coefficient. [b] Regression F-ratio (mean square regression/mean square residual). [c] Confidence regression equation is non-zero. [d] Blanks indicate that regression confidence was less than 75%.

from the contour diagrams. Analysis of variance indicated significant interactions ($P < 0.05$) between the mode and level of disintegrants. It can be seen from Fig. 1 that for identical amounts of disintegrant, tablets containing disintegrants in the combined mode disintegrate faster than the extragranular mode followed by the intragranular mode. The differences between the extragranular and intragranular modes of inclusion can be explained (Shotton & Leonard 1976). Due to the disintegrant particles being confined to spaces between the granules in the extragranular mode, an easier passage for water penetration is present for the formation of a continuous hydrophilic capillary system throughout the tablet. Intragranular disintegrants are confined within the granules thus presenting a less wettable matrix and subsequent absence of a continuous hydrophilic network. Croscarmellose sodium exhibited the shortest disintegration time followed by sodium starch glycolate and crospovidone. Superior dissolution efficiency was achieved by incorporating the disintegrants in the combined mode. This is further substantiated by Fig. 2, where an optimum for percent release is

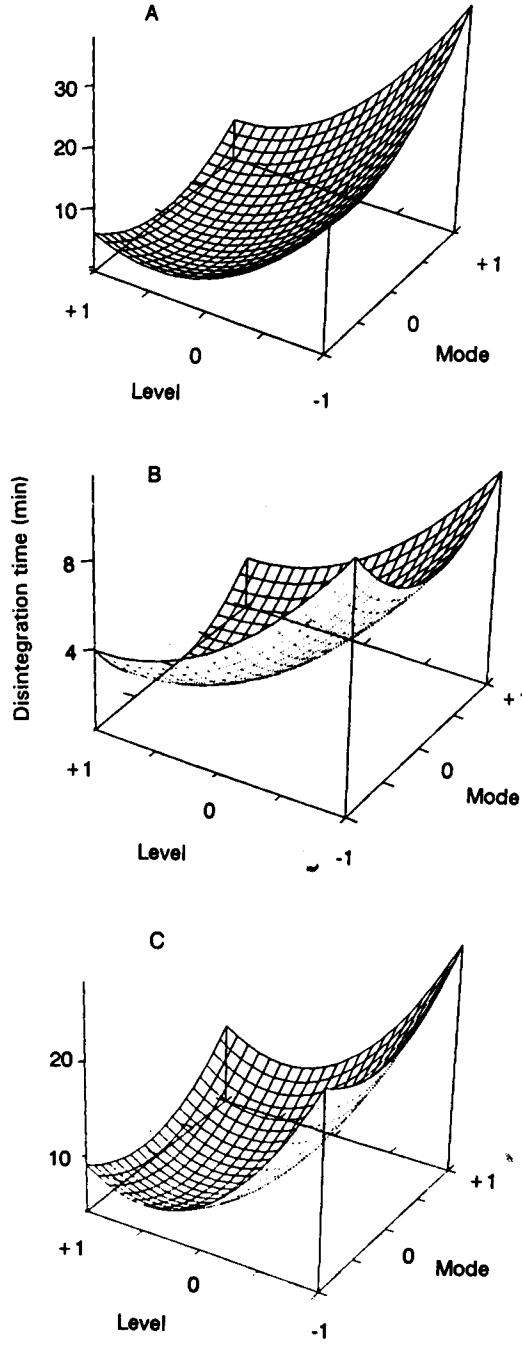

FIG. 1. Contour diagrams for the disintegration time as a function of the mode of incorporation and the level of disintegrant. Variable values are in coded form. A Sodium starch glycolate, B croscarmellose sodium, C crospovidone.

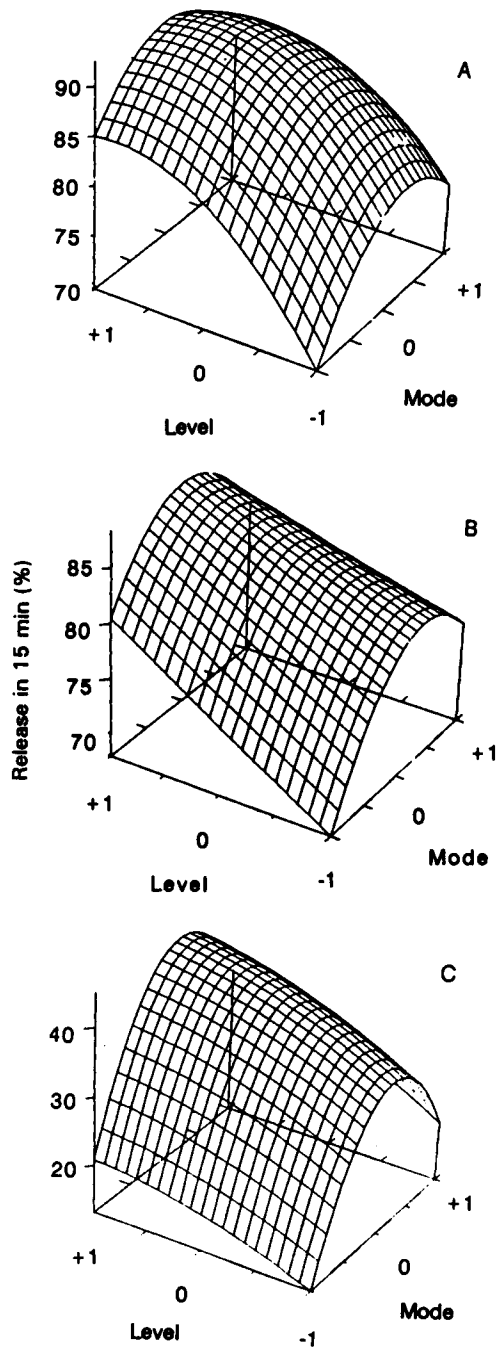

FIG. 2. Contour diagrams for the dissolution at 15 min as a function of the mode of incorporation and the level of disintegrant. Variable values are in coded form. A Sodium starch glycolate, B croscarmellose sodium, C crospovidone.

exhibited in the combined mode at a disintegrant level of 3–4% w/w. This is a trend observed with all three disintegrants. As expected, increasing disintegrant level increased percent dissolved at 15 min. Sodium starch glycolate and croscarmellose sodium in the combined mode at 4% w/w displayed the highest percent release in 15 min, while crospovidone at 2% w/w in the intragranular mode exhibited the lowest release rate. In general sodium starch glycolate and crospovidone were found to be less sensitive to the mode of incorporation.

Conclusion

The study indicates that for formulations prepared in a top-spray fluid-bed, distribution of the disintegrant in the two phases results in a faster dissolution rate and shorter disintegration time rather than intra- or extragranularly. The mechanical strength remains unaffected by the mode of incorporation of disintegrant. The generated response surfaces indicated sodium starch glycolate had an optimum region for dissolution when incorporated in the combined mode for this particular formulation. Significant interactions ($P<0{\cdot}05$) between the type, mode of inclusion and level of disintegrants is present.

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