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DETERMINATION OF PRECOMPRESSION AND COMPRESSION FORCE LEVELS TO MINIMIZE TABLET FRIABILITY USING SIMPLEX

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ABSTRACT

Pilot simplex experiments for improving the tablet strength of three aspirin tablet formulations based on precompression and compression forces were presented. As each simplex moved towards the direction of the optimum, the friability was being minimized and the crushing strength was concomittantly being maximized. Because it followed a systematic direction, simplex process would locate a local optimum rapidly. The appropriate levels of precompression and compression forces that produced tablets with the desired strength were attained in five trials. By contrast, random search for this force combination required at least ten trials. Simplex technique is a cost and time effective means for determining the precompression and compression forces that will reduce the friability or increase the hardness of a tablet formulation. Results appeared to also indicate that crushing strength might be a more reliable measure of tablet strength than friability.

INTRODUCTION

Tablets for coating need sufficient strength to withstand rigorous process conditions to avoid product loss. One of the properties that has been traditionally accepted as a measure for tablet strength is friability.

An earlier study (1) has shown that by adjusting the levels of precompression and main compression forces, tablet strength can be increased. Lamination and capping observed in compressing a highly mixed powder were reduced by applying the appropriate level of precompression force (2). By and large, in tablet manufacturing, the appropriate levels of these forces are set on the press by trial and error random approach. For formulations which have a narrow compression range, this technique can be too time-consuming and costly. An alternative to random setting is the simplex method (3-9) which has been applied to other pharmaceutical formulations (10-12).

This paper presents pilot simplex experiments with respect to minimizing the friability of aspirin tablets based on precompression and compression forces. These experiments were conducted in connection with a full-fledged optimization for determining, in the absence of any background, the experimental region (13-15) of interest. The results reported are not intended to be the final solution of an optimization study.

MATERIALS

Crystalline aspirin 40 mesh, microcrystalline cellulose (Avicel PH101), pregelatinized starch (Starch I500) and corn starch.

METHODS

Tablet Preparation - Bulk mixes of aspirin (Formula A or B: 90.3%w/w; Formula C: 82.2%w/w), microcrystalline cellulose (Formula A or B: 3.0%w/w; Formula C: 11.7%w/w), pregelatinized starch (Formula A or B: 3.0%w/w; Formula C: 2.8%w/w), and corn starch (Formula A or B: 3.6%w/w; Formula C: 3.3%w/w) were prepared by bag mixing the

materials for five minutes. Tablets were prepared on a rotary machine (Betapress Manesty Machines Ltd. UK) using normal concave round tooling (8.73 mm diameter for Formula A and I0.3 mm diameter for Formula B/C) on four stations at a constant speed of 60 rpm.

Simplex Procedure - The factors investigated were compression and precompression forces measured with strain gauges with the data transmitted through a digital oscilloscope (Model 4094, Nicolet Instrument Corporation). The responses observed were friability (primary) and crushing strength (auxilliary).

(a) Friability was measured in duplicate on 25 tablets in a Roche Friabilator for 12 minutes (300 drops) determining the per cent weight loss on intact tablets. Using conventional calculations, it was observed in some tests that even though the incidence of capping could be as high as 25% in the test sample, the friability could be less than 1%. Thus, in this study, to demonstrate more clearly the condition of the tested samples and to effectively differentiate the friabilities between test samples, friability was calculated based on the total weight loss which consisted of weight loss due to abrasion and fracture and weight of capped tablets, if any.

(b) Tablet crushing strength was measured on ten tablets using the Schleuniger Hardness tester (Vector Corporation).

(c) The desired responses were not more than 1% for friability and not less than 3.5 kp for crushing strength.

Three points or vertices of the initial simplex were chosen and plotted graphically. The tablets were compressed using the factor levels of these three vertices. Responses of these tablets were then determined. The point with the worst response was eliminated and reflected to obtain the fourth point which generated the next simplex. Tablets were compressed using the factor levels of the fourth point. The

Table 1. Results of Simplex Experiments

		Factor Level		Response	
Simplex No.	Vertices	C (kN)	PC (kN)	F (%)	H (kp)
Figure 1					
1	A	6.7	0.0	63	3.6
1,2	B	9.8	7.8	36	5.1
1,2,3	C	14.5	1.1	3.9	6.2
2,3	D	17.6	8.7	16	5.5
3	E	22.4	2.2	0.18	6.7
Figure 2					
1	A	6.7	0.0	48	3.9
1,2	B	11.6	13.2	18	5.6
1,2,3	C	20.7	1.9	0.26	6.6
2,3	D	23.3	13.3	10	5.6
3	E	32.2	2.2	0.29	8.4
Figure 3					
1	A	7.6	7.3	62	2.7
1,2	B	12.2	1.1	26	3.7
1,2	C	14.9	8.5	40	3.2
2	D	19.1	2.0	1.6	4.9

C = Compression Force
PC= Precompression Force
F = Friability
H = Hardness

responses of this point were evaluated and the process was repeated until an optimum was reached.

Note, in this study, optimum refers to the point where the tablets produced showed the desired response.

RESULTS AND DISCUSSION

The results of the simplex experiments are shown in Table I. The simplex series generated in this study are shown in Figs. 1-3. The simplexes are numbered

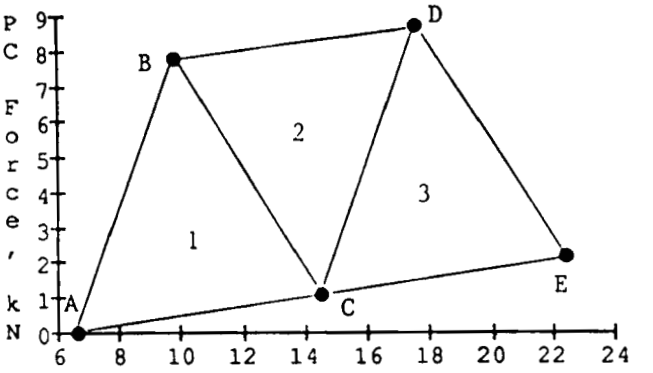

FIGURE 1. Simplex experiments for Formula B

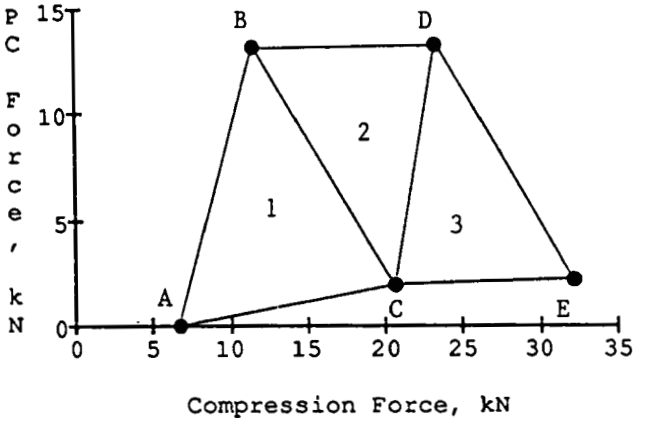

FIGURE 2. Simplex experiments for Formula C

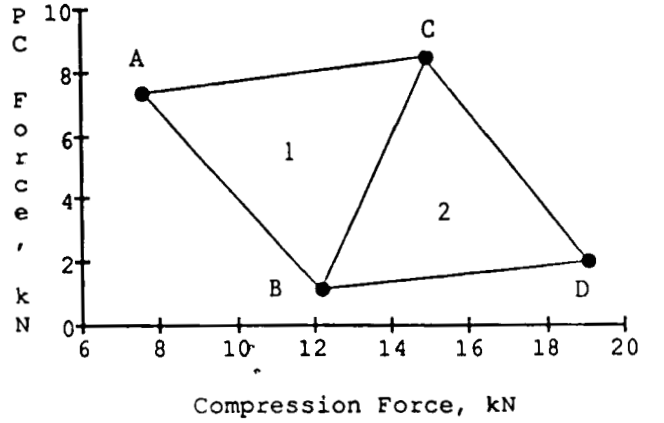

FIGURE 3. Simplex experiments for Formula A

consecutively to show their stepwise formation and their movement towards the optimum response.

In Figure 1, Vertex A (C=6.7 kN, PC=0 kN) of simplex 1 (ABC) yielded tablets with the highest friability (63%) and lowest crushing strength (3.6 kp) and therefore this point was eliminated and reflected to point D (C=17.6 kN, PC=8.7 kN) forming simplex 2 (BCD). In simplex BCD, the tablets produced at Point B (C=9.8 kN, PC=7.8 kN) showed the highest friability (36%) and the lowest crushing strength (5.1 kp). This point was consequently eliminated and reflected to E (C=22.4 kN, PC=2.2 kN) forming simplex 3 (CDE). At point E setting, the friability of the tablets generated dropped drastically to 0.18% and their hardness increased to 6.7 kp. These tablets were considered the best tablets in this simplex series. In this set of experiments, the optimum was reached in five trials.

In Figure 2, in the first simplex, ABC, one of the vertices which was chosen arbitrarily for the first simplex, point C (C=20.7 kN, PC=1.9 kN), yielded tablets with the friability (0.26%) and the hardness (6.6 kp) desired. This meant the local optimum was reached in three experiments. However, the simplex was made to proceed for further investigation. Since vertex A (C=6.7 kN, PC=0) of simplex 1 produced tablets with the highest friability (48%) and the lowest crushing strength (3.9 kp), it was eliminated and expanded to point D. In the new simplex (BCD), because tablets at point B (C=11.6 kN, PC=13.2 kN) were the most friable (18%), this point was eliminated and reflected to point E (C= 32.2 kN, PC=2.2 kN) generating simplex 3 (CDE). At point E, the tablets obtained showed satisfactory (0.29%) friability and the highest crushing strength (8.4 k). These tablets were considered the best in the series. Note that a satisfactory setting was obtained in three experiments in this series.

Because a setting of low compression force with no precompression force in the two previous simplex series indicated poor reponse, this point was not used in the third

simplex series (Fig. 3). Instead, a reflection of this point setting (vertex C: C=14.9 kN, PC=8.5 kN)) was chosen for one of the vertices of the first simplex. In simplex 1, at vertex A (C=7.3 kN, PC=7.3 kN), the tablets generated were highly friable (62%) and soft (2.7 kp). This point was therefore eliminated and reflected to point D (C=19.1 kN, PC=2.0 kN). At point D, the tablets showed the lowest friability (1.6%) and the highest crushing strength (4.9 kp) in the series.

As shown in Figs. 1-3, as each simplex moved towards the direction of the optimum, the friability was being minimized and the crushing strength was concomittantly being maximized. This demonstrated that tablet strength lends itself to simplex optimization based on precompression and compression forces.

At compression forces of 20 kN and greater, when the ratio of compression force to precompression force was about 10 or larger, strong tablets were produced from the aspirin formulations studied.

Although friability testing following the compendial procedure could demonstrate the ultimate weakness of tablets, it would not generate meaningful results at all times. The results from the crushing strength test, by contrast, showed good precision, indicating that crushing strength might be a more reliable measure of tablet strength.

Because it followed a systematic direction (as shown in Figures 1-3), simplex process would locate a local optimum rapidly. In this study, this technique needed only up to five trials to improve tablet strength, demonstrating its efficiency. By contrast, random search to attain the appropriate precompression and compression settings that reduced the friability of the tablets of this study required at least ten trials.

In conclusion, it would appear that because it can find the experimental region and the center point rapidly and efficiently, the simplex method can effectively act as an adjunct to a full-fledged formulation optimization. Unlike random trials, it is a more 'cost

and time' effective means for determining the precompression and compression forces that will reduce the friability or increase the hardness of a tablet formulation. Further, by visual inspection of the response surface simplex method can provide insights into the general behaviour of a formulation relative to a process parameter. The extension of simplex to process improvement including scale-up operation and possibly in equipment calibration or validation warrants investigation.

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