DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(14), 2519-2527 (1987)



# THE USE OF COMPRESSION FORCE TO CONTROL THE QUALITY OF DIRECTLY COMPRESSED PHENOBARBITAL FORMULATIONS

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## ABSTRACT

The friability and dissolution rate of various directly compressed phenobarbital formulations with microcrystalline cellulose as excipient are closely correlated with the compression force used in punching the tablets. Compliance with tolerance limits set for such technological characteristics can therefore be ensured by suitable control of compression force.

## INTRODUCTION

In recent years the homogeinity of pharmaceutical products has been improved by applying quality control to each succesive stage of the manufacturing process. An example of this strategy is provided by the development of process validation techniques. One of the areas in which quality control is most difficult is the production of tablets, since the large number of tablets per lot increases the probability that substandard tablets may escape detection by routine sampling ( 1 ), and it may accordingly be hoped that in this field modern methods may prove of greatest efficacy.

One of the parameters most affecting the characteristics of tablets is the compression force used in punchin them ( 2; 3; 4 ), and knowledge of the relationship between compression

force and the weight of tablets has allowed the latter to be controlled automatically during the manufacturing process ( 5; 6 ) by means of devices enabling the compression force employed in the production of each individual tablet to be monitored. It may be expected that automatic control of other characteristics may likewise be implemented by controlling compression force if the two variables are found to be sufficiently well correlated. This article discusses the use of compression force to control the quality of directly compressed phenobarbital tablets.

## MATERIALS AND METHODS

Materials-. Phenobarbital ( C. Barcia lot B-522 ), Microcrystalline cellulose ( Avicel PH 101, C. Barcia lot 831 ) and Magnesium Stearate ( C. Barcia lot 832 ).

Formulations-. Table 1 lists the differential characteristics of the formulations studied, which were all prepared as follows. After sifting through a 0.5 mm sieve, the active principle, excipient and lubricant were mixed at 30 r.p.m. in a Turbula T2C mixer for 30 minutes before tablets were produced using flat punches 9 mm in diameter in an excentric press equipped with piezoelectric transducers ( 7 ). In all cases the depth of charge was adjusted to produce tablets with a mean weight of 200 mg.

Tests-. The following characteristics were measured for each formulation:

Friability-. Ten tablets were subjected to 15 minutes in an Erweka TAP apparatus at 20 r.p.m. The loss of weight was expressed as a percentage of the initial weight.

Dissolution rate-. Assays were carry out using a Prolabo Dissolutest ( France ) complying with USP XXI Ed. Method II specifications. The dissolution medium was distilled water stirred at 50 r.p.m., and the concentration of phenobarbital in samples taken every 5-10 minutes was determined in 0.1 N NaOH by spectrophotometry at 256 nm ( $E^{1\%}_{1\ cm}$ = 323 ). The measure of dissolution rate used was $D_{45}$, the percentage of phenobarbital dissolved in 45 minutes. Three assays were carried out for each formulation.

TABLE 1

Characteristics of the various formulations studied

| Formulation | Phenobarbital ( % ) | Microcrystalline Cellulose ( % ) | Magnesium Stearate ( % ) | Compression Force ( Nw ) |
|---|---|---|---|---|
| A | 0 | 99.5 | 0.5 | 650 |
| B | 0 | 99.5 | 0.5 | 1300 |
| C | 5 | 94.5 | 0.5 | 650 |
| D | 5 | 94.5 | 0.5 | 1300 |
| E | 10 | 89.5 | 0.5 | 650 |
| F | 10 | 89.5 | 0.5 | 1300 |
| G | 15 | 84.5 | 0.5 | 650 |
| H | 15 | 84.5 | 0.5 | 1300 |
| I | 20 | 79.5 | 0.5 | 650 |
| J | 20 | 79.5 | 0.5 | 1300 |

Experimental Design and Statistical Analysis-. The formulations described in Table 1 were established so as to allow the effects of compression force and the proportion of drug to be tested in a 2 x 2 x 5 factorial design ( 8 ). Dissolution rate data were analysed by the corresponding analysis of variance ( 8 ). The use of equally spaced levels of the active principle facilitates separation of the effects of this variable both its direct effects and its combined effect with compression force, into linear, quadratic and other terms ( see Table 3 ). The dependence of $D_{45}$ on compression force and phenobarbital content was estimated by linear regression.

No analysis of variance could be applied to the friability data because these assays were not replicated. Instead, the corresponding response surface was obtained by applying the stepwise multiple linear regression program BMDP.P2R ( 9 ) to the set of all the terms accesible with the experimental design employed.

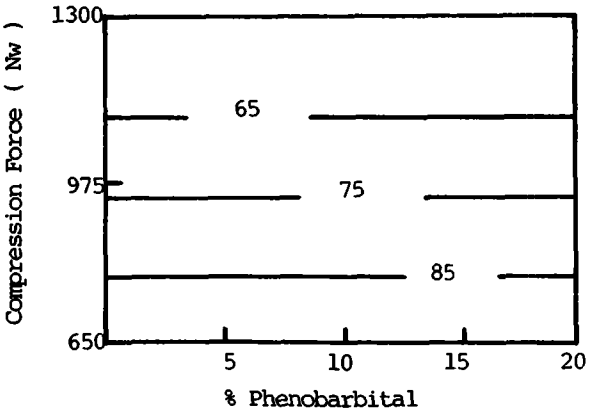



FIGURE 1

Response surface for $D_{45}$

The predictive capacity of the response surfaces obtained was measured by the regression parameter $R^2$.

## RESULTS AND DISCUSSION

Table 2 lists the dissolution rate and friability data obtained for the various formulations tested.

Table 3 shows the analysis of variance results for the parameter $D_{45}$ and Figure 1 displays the corresponding response surface. The high value of $R^2$ for the regression of $D_{45}$ on the compression force F

$$D_{45} = 133.10 - 0.0614\ F \qquad R^2 = 0.9782$$

means that it should be possible to control $D_{45}$ closely by controlling compression force. The value of $R^2$ is also very high for the regression equation obtained by applying the stepwise program to the friability data ( Figure 2 ):

$$Fr\ (\ \%.10^3\ ) = 309.36 + 144.66\ Ph - 0.225.F - 0.105.Ph.F$$

$$R^2 = 0.952$$

Fr = Friability; Ph = % Phenobarbital; F = Compression Force (Nw)

TABLE 2

Mean values of $D_{45}$ and loss of weight due to friability for the various formulations studied.

| Formulation | $D_{45}$ | % Friability |
|---|---|---|
| A | - | 0.11 |
| B | - | 0.01 |
| C | 91.9 | 0.81 |
| D | 51.3 | 0.06 |
| E | 95.5 | 0.65 |
| F | 56.4 | 0.08 |
| G | 92.1 | 1.29 |
| H | 54.0 | 0.15 |
| I | 93.1 | 1.77 |
| J | 51.2 | 0.17 |

TABLE 3

Analysis of variance for the parameter $D_{45}$

| Source of Variation | D.F. | Mean Square | F |
|---|---|---|---|
| Compression Force | 1 | 9568.03 | 1162.87* |
| % Phenobarbital | 1 | 0.43 | $5.3.10^{-2}$ |
| ( % Phenobarbital )$^2$ | 1 | 41.08 | 4.99 |
| ( % Phenobarbital )$^3$ | 1 | 26.70 | 3.25 |
| ( % Phenobarbital )$^4$ | - | - | - |
| Force. % Phenobarbital | 1 | 0.53 | $6.5.10^{-2}$ |
| Force. ( % Phenobarbital )$^2$ | 1 | 10.94 | 1.33 |
| Force. ( % Phenobarbital )$^3$ | 1 | 1.41 | 0.17 |
| Force. ( % Phenobarbital )$^4$ | - | - | - |
| Residual | 16 | 8.23 | |
| Total | 23 | 425.25 | |

* Significant at the $\alpha < 0.01$ level

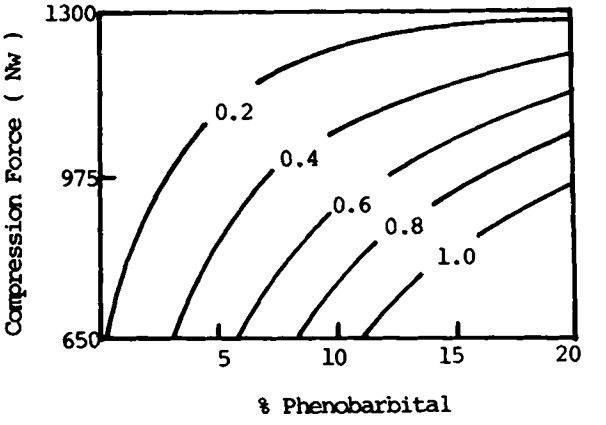



FIGURE 2

Response surface for Friability

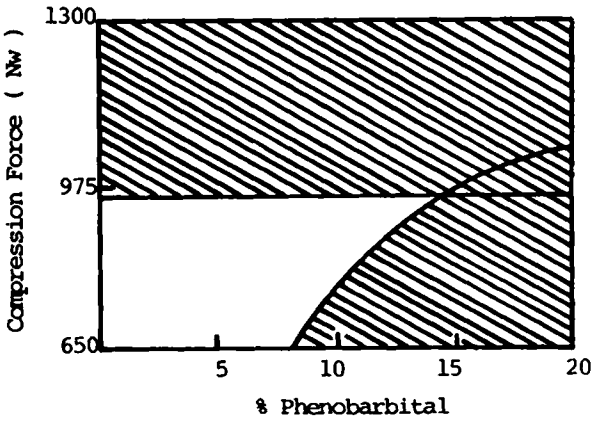



FIGURE 3

Ranges of maximum compression force and phenobarbital content in which the quality requisites are both complied with ( unshaded )

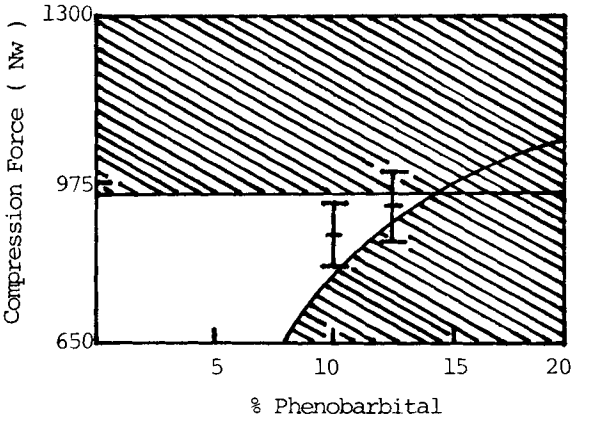
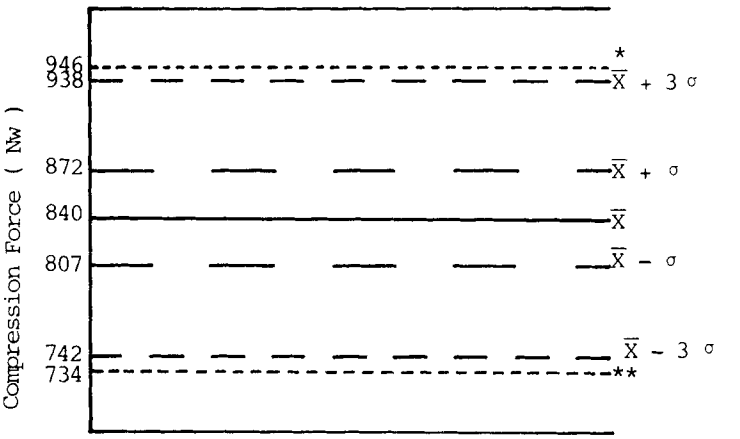



FIGURE 4

Mean ± 3 standard deviations of the maximum compression force used in punching tablets of formulations containing 10 and 12.5% of Phenobarbital




* Limit for dissolution ( USP XXI Ed. )

** Limit for friability ( 0.8% )

FIGURE 5

Control chart for acceptable maximum and minimum compression force for formulations containing 10% of Phenobarbital.

The USP XXI Ed. limit for $D_{45}$ is 75%, and the usual tolerated friability 0.8%. Figure 3 shows the intersection of the compression force and phenobarbital content ranges in which these limits are complied with according to Figures 1 and 2. It is clear that, of the formulations studied, only those with phenobarbital contents lower than 15% are admissible. Figure 4 shows that the value of 3.9% for the coefficient of variation of the compression force for formulations with 10% of phenobarbital allows the production of acceptable tablets to be ensured by using this concentration of phenobarbital and setting the compression force to 840 Nw ( the midpoint of the range of joint compliance with the tolerance limits ); whereas if the phenobarbital content is 12.5% ( and assuming the same coefficient of variation for the compression force ), about 23% of the tablets produced would be unacceptable.

Now that a suitable formulation has been chosen, the quality of individual tablets can be controlled by ensuring that the compression force lies within limits corresponding to the set of restrictions on the characteristics of the tablets. Figure 5, for example, shows a control chart with limits for formulations containing 10% of phenobarbital. Tablets punched with a force outside these limits can be automatically discarded, and the quality of the whole lot thus guaranteed.

This work was supported by grant 2777-83 from the Comisión Asesora de Investigación Cientifica y Técnica. Ministry of Education ( Spain ).

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