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PREDICTION OF TABLET PROPERTIES BY COMPRESSION FORCE-TIME PROFILE PARAMETERS

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ABSTRACT

The compression force-time profile parameters proposed by Chilamkurti el al. (1) have proved to be no better than maximum compression force for prediction of the properties of three series of direct compression microcrystalline cellulose tablet formulations containing various proportions of prednisone, phenobarbital or isoniazide and punched under various compression forces. The usefulness of the Chilamkurti parameters is nevertheless not ruled in the case of formulations for which maximum compression force has little predictive value.

INTRODUCTION

For the characterization of the compression behaviour of various tablet materials and their mixtures, Chilamkurti el al. (1-3) have recently proposed a series of parameters derived from compression force-time profiles. In a previous article (4) we studied these parameters' dependence on drug/matrix ratio and maximum compression force in the case of three series of direct compression microcrystalline cellulose formulations containing prednisone, phenobarbital or isoniazide. In the present article we evaluate the utility of the Chilamkurti parameters for prediction of the technological properties of these formulations.

MATERIALS AND METHODS

Materials

Prednisone, Phenobarbital and Isoniazide were of U.S.P. XX grade. Microcrystalline cellulose (Avicel PH 101) and Magnesium Stearate were of pharmaceutical grade.

Methods

Tablet preparation, calculation of Chilamkurti parameters and statistical analysis have been described elsewhere (4).

WEIGHT: For each of the formulations tested, ten tablets were weighted individually and the mean and coefficient of variation of the ten values calculated.

CRUSHING STRENGTH: For each formulation, ten tablets were tested individually in an *Erweka TB24* durometer.

FRIABILITY: Ten-tablet samples were tested for 15 minutes in an *Erweka TAP* friabilometer operated at 20 r.p.m..

DISINTEGRATION: For each formulation, six tablets were disintegrated in distilled water in an apparatus complying with U.S.P. XXI Ed. specifications.

DISSOLUTION RATE: For each formulation, three tablets were assayed in distilled water at 50 r.p.m. in a *Prolabo Dissolutest* apparatus complying with U.S.P. XXI Ed. Method II specifications. Samples were drawn every 5-10 minutes and analysed by the following methods: for prednisone, U.V. spectrophotometry at 239 nm. in distilled water ($E_{1\%,1\ cm}$=420); for phenobarbital, U.V. spectrophotometry at 256 nm. in 0,1 N NaOH ($E_{1\%,1\ cm}$=323); for isoniazide, U.V. spectrophotometry in 0,01 N HCl ($E_{1\%,1\ cm}$=416). The dissolution rates of prednisone and phenobarbital were expressed following U.S.P. XXI Ed., by the percentage of the drug dissolved after 30 and 45 minutes. The dissolution rate of isoniazide was expressed by the time taken for 90% of the drug to dissolve.

RESULTS AND DISCUSSION

For each of the formulations studied, Table 1 lists the mean values of weight, crushing strength, friability, disintegration time and dissolution rate, and the coefficient of variation of the weight. Table 2 shows the analysis of variance results for crushing strength, disintegration time and dissolution rate, and Table 3 the regression equations calculated by the stepwise program *BMDP.P2R* for

Table 1.- Mean values of weight, crushing strength, friability, disintegration time and dissolution rate and coefficient of variation of weight for each of the formulations studied.

Formulation	Weight mg	Coefficient of variation of weight (%)	Crushing Strength Kg	Disintegration Time (s)	Friability %	Dissolution Rate([a],[b],[c])
			Prednisone[a]			
1	197.7	0.90	3.93	6.6	0.11	--
2	203.4	1.05	6.73	18.5	0.01	--
3	196.4	0.90	3.00	9.8	0.51	77.5
4	197.5	0.67	5.83	19.3	0.05	34.0
5	196.5	0.73	3.20	9.7	0.61	91.0
6	195.4	0.47	5.80	16.5	0.09	39.4
7	193.7	0.65	2.65	13.0	0.92	89.9
8	190.8	0.47	5.95	18.3	0.08	26.7
9	194.1	0.71	2.50	9.7	1.11	87.3
10	195.0	0.73	6.20	15.5	0.04	32.2
			Phenobarbital[b]			
11	197.7	0.90	3.93	6.6	0.11	--
12	203.4	1.05	6.73	18.5	0.01	--
13	197.0	0.60	2.70	10.7	0.81	91.9
14	196.9	1.16	5.80	18.5	0.06	51.3
15	199.4	0.91	2.73	10.8	0.65	95.5
16	198.5	0.44	5.03	14.5	0.08	56.4
17	200.6	1.31	2.40	10.8	1.29	92.1
18	201.7	0.67	5.15	14.5	0.15	54.0
19	197.2	0.89	2.05	10.3	1.77	93.1
20	197.1	0.30	4.50	15.3	0.17	51.2
			Isoniazide[c]			
21	197.7	0.90	3.93	6.6	0.11	--
22	203.4	1.05	6.73	18.5	0.01	--
23	193.0	1.15	1.95	8.8	1.25	15.1
24	192.6	1.31	4.30	12.7	0.24	33.4
25	198.4	0.43	1.80	8.2	2.01	11.6
26	200.2	1.00	4.25	11.2	0.33	25.8
27	194.1	1.13	1.13	6.7	10.45	6.1
28	195.2	1.17	2.70	8.2	0.71	19.8
29	198.6	0.73	0.98	5.2	13.79	5.9
30	196.5	0.93	2.55	7.7	1.10	11.2

[a] Dissolution rate expressed as % dissolved after 30 min.
[b] Dissolution rate expressed as % dissolved after 45 min.
[c] Dissolution rate expressed as time (min) to dissolve 90% of dose.

Table 2.- Results of analysis of variance for crushing strenght, disintegration time and dissolution rate. *F= Maximum Compression Force; D= Percentage Drug Content.*

Source of Variation	Crushing Strength	Disintegration Time	Dissolution Rate
	Prednisone		
F	2385.94*	1168.91*	929.24*
D	87.57*	2.05	0.43
D^2	39.43*	40.87*	5.14**
D^3	11.58*	6.80**	9.89*
D^4	9.80*	64.89*	--
FxD	26.64*	100.36*	8.69*
FxD^2	10.31*	13.17*	5.31**
FxD^3	0.01	1.90	2.17
FxD^4	4.24**	0.02	--
	Phenobarbital		
F	1658.35*	1349.95*	1162.87*
D	387.29*	4.66*	0.05
D^2	27.16*	6.30**	4.99**
D^3	21.27*	44.63*	3.25
D^4	0.11	21.78*	--
FxD	4.83**	212.46*	0.07
FxD^2	$2.00\ 10^{-3}$	105.39*	1.33
FxD^3	0.41	1.32	0.17
FxD^4	13.02*	4.70**	--
	Isoniazide		
F	1192.49*	822.62*	47.24*
D	1445.65*	771.94*	39.82*
D^2	142.33*	0.39	0.09
D^3	25.66*	0.93	0.04
D^4	78.18*	8.36*	--
FxD	54.75*	356.05*	5.62**
FxD^2	0.01	173.84*	0.34
FxD^3	0.73	17.93*	0.46
FxD^4	8.94*	13.95*	--

* Significant at the $\alpha < 0.01$ level
** Significant at the $\alpha < 0.05$ level

Table 3.- Coefficients of the regression equations fitted using program BMDP.P2R. *(F= Maximum Compression Force; D= % Drug).*

Prednisone		
Coefficient of variation of weight	= 0.73	
Crushing strength (Kgf)	$= 0.4225 - 0.0825\ D + 0.4685\ 10^{-2}\ F$	$R^2 = 0.9280$
Disintegration time (s)	$= 1.87 + 0.012\ F$	$R^2 = 0.8067$
Friability (% 10^3)	$= 298.5 + 190.14\ D - 0.1989\ F - 0.1441\ FxD$	$R^2 = 0.9861$
% Dissolved 30 min.	$= 139.75 - 0.0821\ F$	$R^2 = 0.9512$
Phenobarbital		
Coefficient of variation of weight	= 0.82	
Crushing strength (Kgf)	$= 0.9875 - 0.0918\ D + 0.4131\ 10^{-2}\ F$	$R^2 = 0.9288$
Disintegration time (s)	$= 3.43 + 0.9872\ 10^{-2}\ F$	$R^2 = 0.9475$
Friability (% 10^3)	$= 309.36 + 144.66\ D - 0.2253\ F - 0.1052\ FxD$	$R^2 = 0.9518$
%Dissolved 45 min.	$= 133.10 - 0.0614\ F$	$R^2 = 0.9782$
Isoniazide		
Coefficient of variation of weight	= 0.98	
Crushing strength (Kgf)	$= 1.92 - 0.1721\ D + 0.33\ 10^{-2}\ F + 0.22\ 10^{-2}\ D^2$	$R^2 = 0.9150$
Disintegration time (s)	$= -0.70 + 0.1617\ D + 0.0135\ F - 0.3256\ 10^{-3}\ FxD$	$R^2 = 0.8802$
Friability (% 10^3)	$= 76.70 + 17.52\ D^2 - 0.0130\ FxD^2$	$R^2 = 0.9610$
Time to dissolve 90% (min.)	$= -3.16 + 0.0335\ F - 0.5479\ 10^{-3}\ FxD$	$R^2 = 0.8450$

crushing strength, disintegration time, dissolution rate, friability and coefficient of variation of weight (the absence of replicates prevents analysis of variance for the latter two parameters, whose dependence on maximum compression force F and percentage drug content D was investigated submitting all possible terms for initial consideration by the stepwise program). It should be pointed out that in view of the inherent difficulties in measuring disintegration times with accuracy, the low values recorded in the present study mean that the results for this parameter can only be accepted with reserve.

In spite of the fact that for most parameters and drugs there are a large number of significant analysis of variance terms, good predictivity is in most cases achieved by regression equations involving far fewer terms. Furthermore, whereas the significant analysis of variance terms for a given parameter vary more or less strikingly from one drug to another, the corresponding regression equations are very similar, the exceptional behaviour of isoniazide in this respect probably being due to the large proportions of drug included in some of the isoniazide formulations. The good fit between the experimental data and the model implicit in the experimental design contrasts with the results obtained by other authors in similar studies (5-7).

Figure 1 shows the response surfaces calculated for crushing strength. For each of the three drugs used, increasing drug concentration reduces the crushing strength of the tablets, which reflects a corresponding reduction in the comprimability of the tablet mixtures and hence in their suitability for tablet formation. Figure 2 shows that for prednisone and phenobarbital formulations the equation for the response surface for friability involves maximum compression force (F), drug content (D) and FxD terms, whereas for isoniazide the terms involved are D^2 and FxD^2. As mentioned above, this difference may due to the high drug/matrix ratio of some of the isoniazide formulations. The fact that of the three drugs, isoniazide is also the only one for which percentage drug content affects dissolution rate (Figure 3) may be attributed to the same cause and also the high hidrosolubility of this drug. The most surprising results, given the high drug/matrix ratios of some formulations, is that the coefficient of variation of weight is independent of both maximum compression force and percentage drug content.

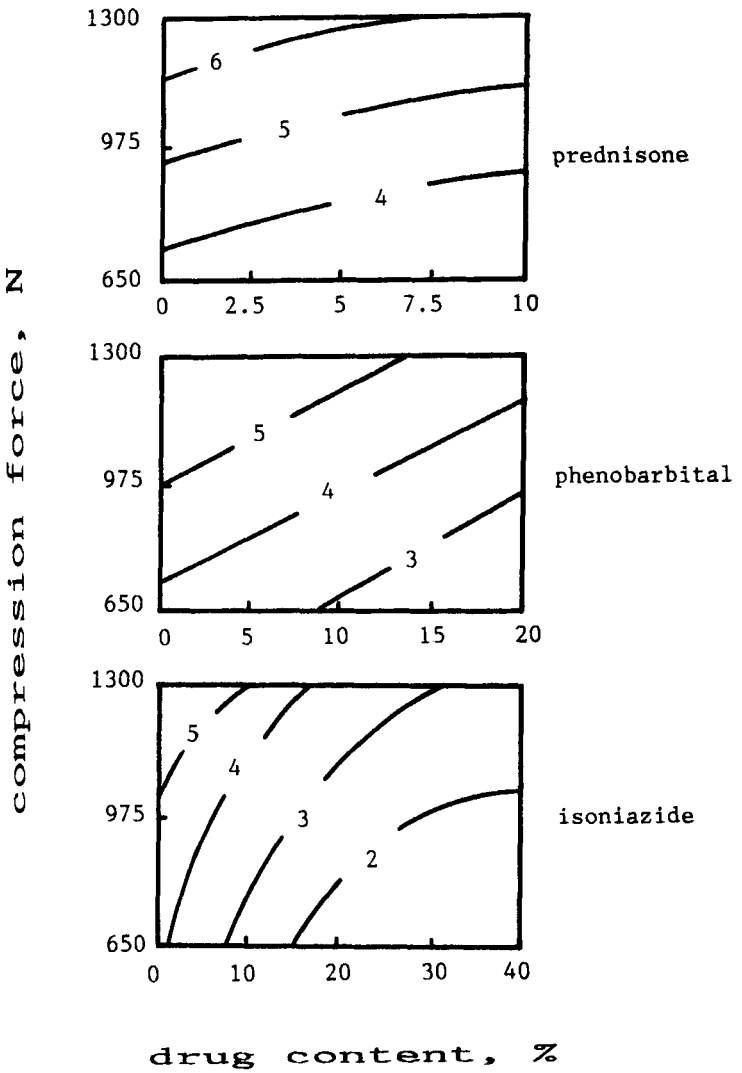

Figure 1
Response surfaces for crushing strenght (Kg).

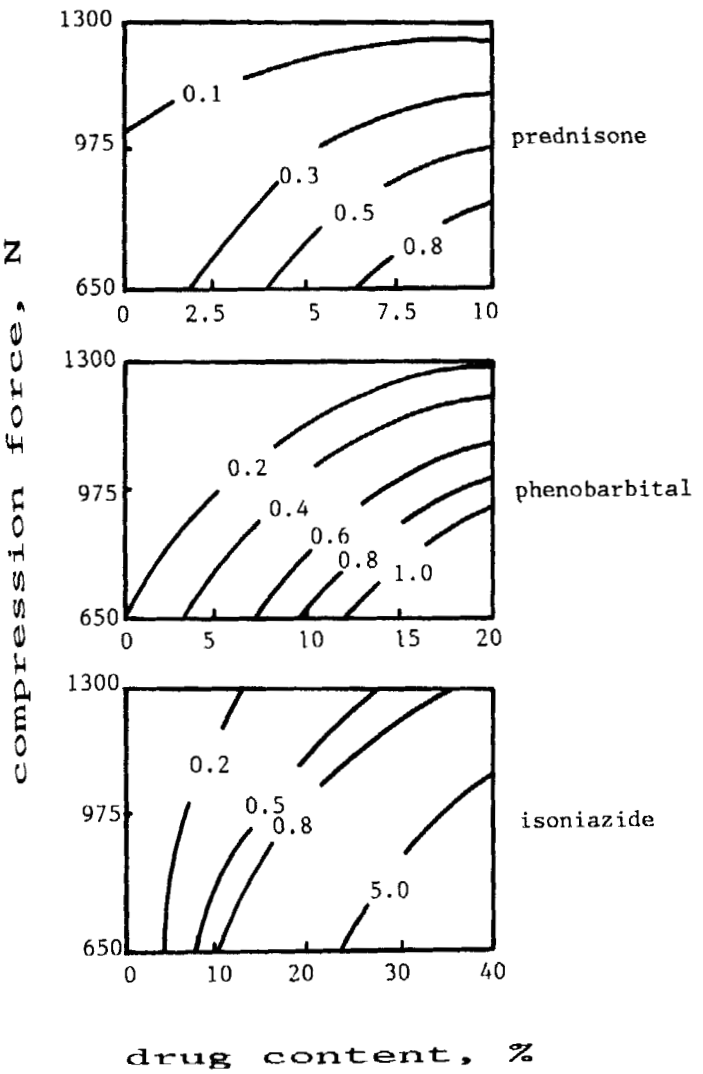

Figure 2
Response surfaces for friability (%).

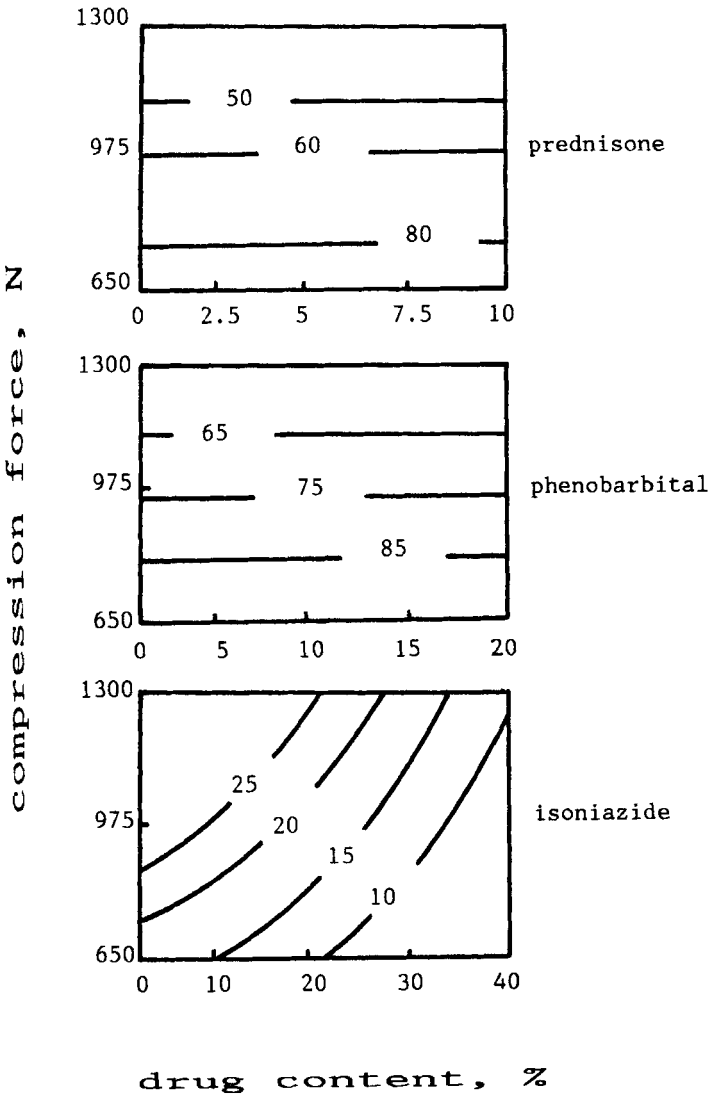

Figure 3
Response surfaces for dissolution rate *(Prednisone= % dissolved after 30 min.; Phenobarbital= % dissolved after 45 min.; Isoniazide= time*$_{min}$ to dissolve 90% of dose).

The regression equations expressing the dependence of the Chilamkurti parameters on percentage drug content and maximum compression force in the formulations tested in the present study were reported in a previous article (4). It was originally intended to estimate the capacity of each of the Chilamkurti parameters to predict technological properties by examining the correlation between corresponding terms of these equations and the regresion equations expressing the influence of maximum compression force and drug content on the technological properties in question (Table 3). However, no formal analysis of this kind is possible because the terms in the two sets of equations are quite different, which in itself shows that there can be no correlation between the Chilamkurti parameters and the technological properties investigated. Since the latter are almost completely determined by maximum compression force and percentage drug content, it is evident that none of the technological parameters can be adequatelly predicted by any single Chilamkurti parameter. These parameters likewise fail to improve the predictivity of the response surfaces for the tecnological parameters when used instead of maximum compression force as one of the independent variables, the only cases in which values of R^2 comparable with those achieved be the pair F and D are attained being those involving the Chilamkurti parameters maximum positive slope and AUC, both of which are in any closely correlated with maximum compression force.

In view of the above results it may be concluded that the Chilamkurti parameters are insuitable for predicting the technological properties of tablet formulations with technological characteristics similar to those of the formulations employed in the present study. It should nevertheless by pointed out that this finding does not rule out the possible utility of these parameters for predicting the properties of tablets with other characteristics. In particular, there are many kinds of tablets whose technological properties, unlike those of the formulations used in this study, cannot be predicted by maximum compression force (either alone or in conjuction with percentage drug content). It is quite possible that in these cases the Chilamkurti parameters may have a predictive role to play.

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