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THE EFFECT OF MAXIMUM COMPRESION FORCE AND DRUG CONTENT ON COMPRESSION FORCE-TIME PROFILE PARAMETERS

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ABSTRACT

Compression force-time profiles have been obtained for three series of directly compressed tablets containing various quantities of prednisone, phenobarbital and isoniazide in a microcrystalline cellulose matrix. The tablets were punched in an excentric press equipped with piezoelectric transducers, and the profiles were characterized by the parameters: area under curve, width at half height, inflection point ordinate and maximum positive slope, whose dependence on maximum compression force and drug content was evaluated. Since the effects of maximum compression force overwhelmed those of drug content, it was found preferable to normalize the variables area under curve, inflection point ordinate and maximum positive slope by dividing them by the maximum compression force. The strong correlation between the width at half height and the normalized area under the curve as regards their dependence on maximum compression force and drug content suggest that it is redundant to use both these variables.

INTRODUCTION

For the characterization of the compression behaviour of various tablet materials and their mixtures, *Chilamkurti* et al. (1-4) have recently proposed a

series of parameters derived from compression force-time profiles, and have suggested that these parameters, which contain more information than the value of the maximum compression force alone, may be useful for estimating the energy absorbed by tablets during compression and hence their disintegration, dissolution and associated properties. The present article reports mutual correlations among Chilamkurti parameters and their dependence on maximum compression force and drug content in three series of direct compression microcrystalline cellulose matrix formulations in which the active principle was prednisone, phenobarbital or isoniazide.

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.

Preparation of tablets

Table 1 lists the compositions of the formulations studied. Drug levels were chosen so as to correspond roughly to the usual doses of the drugs used while at the same time conforming to the experimental design described below.

Once the separate components had been sifted through 0.5 mm sieves they were mixed for 30 minutes in a Turbula T2C mixer operated at 30 r.p.m.. Tablets were produced using 9 mm flat punches and a maximum compression force of either 650 or 1300 N in a Korsch EKO excentric tablet press equipped with piezoelectric transducers (5). Punch stroke was adjusted for a tablet weight of 200 mg. For each formulation, three punch cycles were monitored at the upper punch.

Characterization of compression profiles

Of the various parameters proposed by Chilamkurti et al., the following were used to characterize compression curves in the present study: *maximum height (M.H.), width at half height (W.H.H.), area under the curve (A.U.C.), inflection point ordinate (I.P.O.)* and *maximum slope on the upward curve (M.S.).*

Table 1.- Characteristics of the various formulations studied.

Formulation	Drug	Drug content(%)	Microcrystalline cellulose(%)	Magnesium stearate(%)	Compression force(N)
1		0.0	99.5	0.5	650
2		0.0	99.5	0.5	1300
3		2.5	97.0	0.5	650
4		2.5	97.0	0.5	1300
5	Prednisone	5.0	94.5	0.5	650
6		5.0	94.5	0.5	1300
7		7.5	92.0	0.5	650
8		7.5	92.0	0.5	1300
9		10.0	89.5	0.5	650
10		10.0	89.5	0.5	1300
11		0.0	99.5	0.5	650
12		0.0	99.5	0.5	1300
13		5.0	94.5	0.5	650
14		5.0	94.5	0.5	1300
15	Phenobarbital	10.0	89.5	0.5	650
16		10.0	89.5	0.5	1300
17		15.0	84.5	0.5	650
18		15.0	84.5	0.5	1300
19		20.0	79.5	0.5	650
20		20.0	79.5	0.5	1300
21		0.0	99.5	0.5	650
22		0.0	99.5	0.5	1300
23		10.0	89.5	0.5	650
24		10.0	89.5	0.5	1300
25	Isoniazide	20.0	79.5	0.5	650
26		20.0	79.5	0.5	1300
27		30.0	69.5	0.5	650
28		30.0	69.5	0.5	1300
29		40.0	59.5	0.5	650
30		40.0	59.5	0.5	1300

Experimental design and statistical analysis

A 2x5 factorial design was employed (maximum compression force x % drug) and the results were subjected to the corresponding analysis of variance (6). The equally spaced drug percentages allowed the use of orthogonal polynomials (6) to separate the effects of this variable (alone or combined with compression force) into the various terms listed in Table 3. Since the interpretation of these results was in most cases hampered by the large number of significant terms, the stepwise multiple linear regression program *BMDP.P2R* (7) was used to identify those terms necessary for the prediction of the various compression profile parameters. Correlations among the latter were investigated using the method proposed by Llabrés et al. (8) for In vivo- In vitro correlations which in the present case consists in the use of linear regression analysis to examine the relationship among corresponding coefficients of the response surfaces of the profile parameters.

RESULTS AND DISCUSSION

The mean values of the Chilamkurti parameters studied are listed for each series of tablets in Table 2. The existence of significant terms involving drug content (Table 3) confirms the thesis of Chilamkurti et al.(2) that the compression parameter usually cited, the maximum compression force, is insufficient to represent the information content of the compression profile parameters.

In order to obtain figures that would be easier to interpret then the analysis of variance data, which not only exhibited numerous significant terms but also widely varying F values within the significance levels employed, the stepwise multiple linear regression program *BMDP.P2R* was used.

The results (Table 4) show that for fewer terms are necessary than those which are significant for the analysis of variance. All the Chilamkurti parameters except W.H.H. can in fact be predicted adequately from the maximum compression force alone, whose increase produced the almost proportional increases in AUC, I.P.O. and M.S. reported by Chilamkurti et al.(2).

Table 2.- Mean values of the various parameters used to characterize compression force-time curves.

Formulation	W.H.H.(ms)	AUC(N.s)	I.P.O.(N)	M.S.(N/ms)
1	57.80	39.70	436.37	10.12
2	53.91	78.23	1001.42	20.94
3	58.62	38.47	409.33	9.95
4	54.15	74.26	906.31	19.70
5	56.91	43.13	457.81	11.29
6	52.90	77.84	958.52	22.48
7	55.83	36.45	413.99	9.85
8	47.79	67.57	880.20	23.83
9	54.83	37.85	452.22	10.52
10	48.18	70.88	917.50	24.70
11	57.80	39.70	436.37	10.12
12	53.91	78.23	1001.42	20.94
13	57.62	40.05	450.35	10.59
14	52.91	72.60	898.85	21.59
15	55.78	37.96	524.02	10.44
16	53.15	73.02	938.01	21.00
17	55.38	36.51	422.38	10.13
18	52.71	76.36	904.44	22.90
19	54.11	37.09	459.68	10.91
20	49.99	68.33	873.78	22.80
21	57.80	39.70	436.37	10.12
22	53.91	78.23	1001.42	20.94
23	56.54	36.60	403.74	9.89
24	51.69	74.69	967.47	22.71
25	54.02	40.07	511.90	11.56
26	48.23	78.01	1136.80	26.89
27	49.85	34.53	497.91	11.67
28	48.86	78.46	1027.52	25.32
29	50.28	32.43	459.68	10.95
30	47.07	73.25	987.91	27.03

Table 3.- Analysis of variance results for the parameters indicated. F= *compression force;* D= *% drug.*

Source of Variation	W.H.H.	AUC	I.P.O.	M.S.
		Prednisone		
F	901.15*	4330.74*	1409.11*	1945.32*
D	433.97*	52.97*	2.81	41.32*
D^2	18.92*	1.49	2.41	0.54
D^3	56.60*	4.86**	0.07	4.12
D^4	5.62**	75.39*	12.14*	9.44*
FxD	51.04*	17.74*	6.01**	32.41*
FxD^2	0.14	2.39	0.75	2.87
FxD^3	11.84*	1.07	0.17	7.07**
FxD^4	20.93*	1.54	0.54	0.31
		Phenobarbital		
F	484.15*	2522.44*	655.94*	2964.37*
D	232.33*	24.68*	3.24	17.20*
D^2	12.49*	0.02	0.14	0.67
D^3	5.63**	6.74**	0.22	0.42
D^4	2.75	0.95	6.11**	3.60
FxD	1.83	2.13	4.37**	6.97**
FxD^2	6.10**	0.25	1.73	0.09
FxD^3	13.87*	19.26*	2.89	2.78
FxD^4	3.52	0.52	0.58	5.37**
		Isoniazide		
F	560.40*	1666.96*	480.71*	1443.91*
D	1169.80*	13.52*	0.92	50.93*
D^2	25.53*	1.83	3.89	7.75**
D^3	17.57*	2.62	2.71	0.54
D^4	3.07	5.97**	6.16**	10.02*
FxD	21.85*	1.42	0.35	19.79*
FxD^2	5.95**	0.15	0.53	1.20
FxD^3	39.62*	0.50	0.03	1.99
FxD^4	38.90*	0.43	0.96	3.68

* Significant at the α <0.01 level.
** Significant at the α <0.05 level.

Table 4.- Regression equations fitted using the program BMDP.P2R. F= *Compression force;* D= *% Drug.*

	Prednisone	
W.H.H.(ms)	$= 62.21 - 0.5596\ 10^{-2}\ F - 0.5465\ 10^{-3}\ FxD$	R^2=0.9118
AUC (Nxs)	$= 4.48 + 0.0533\ F$	R^2=0.9606
I.P.O. (N)	$= - 64.90 + 0.7674\ F$	R^2=0.9690
M.S. (N/ms)	$= -1.64 + 0.0184\ F$	R^2=0.9427
	Phenobarbital	
W.H.H.(ms)	$= 61.05 - 0.5549\ 10^{-2}\ F - 0.8680\ 10^{-2}\ D^2$	R^2=0.9303
AUC (NxS)	$= 2.815 + 0.0545\ F$	R^2=0.9713
I.P.O. (N)	$= - 6.179 + 0.7446\ F$	R^2=0.9516
M.S. (N/ms)	$= - 0.969 + 0.018\ F$	R^2=0.9811
	Isoniazide	
W.H.H.(ms)	$= 62.84 - 0.2698\ D - 0.0074\ F + 0.8046\ 10^{-4}\ FxD$	R^2=0.9208
AUC (Nxs)	$= - 2.739 + 0.060\ F$	R^2=0.9729
I.P.O. (N)	$= - 100.39 + 0.8651\ F$	R^2=0.9310
M.S. (N/ms)	$= - 2.903 + 0.0211\ F$	R^2=0.9257

In order to prevent more interesting influences being obscured by this effect, the data were re-analysed after all the dependent variables (except W.H.H., of course) were normalized by dividing them by the maximum compression force. Table 5 lists the mean values of the normalized parameters (subindex $_n$), and Table 6 the corresponding analysis of variance results, which suffer from the same interpretative difficulties as before. The multiple regression results (Table 7) show that except for I.P.O.$_n$ the Chilamkurti parameters are not predictable solely from the maximum compression force.

Table 5.- Mean values of the normalized Chilamkurti parameters.

Formulation	AUC_n(ms)	$I.P.O._n 10^2$	$M.S._n$($ms^{-1}x10^3$)
1	60.65	66.59	15.46
2	58.42	74.86	15.64
3	61.21	65.26	15.83
4	58.73	71.68	15.58
5	59.85	63.61	15.67
6	57.35	70.61	16.55
7	58.52	66.53	15.80
8	50.61	65.92	17.86
9	57.09	68.20	15.88
10	51.45	66.61	17.92
11	60.65	66.59	15.46
12	58.42	74.86	15.64
13	60.42	67.95	15.97
14	57.10	70.71	16.98
15	58.41	80.64	16.07
16	57.24	73.60	16.46
17	57.84	66.87	16.04
18	56.65	67.11	17.04
19	56.74	70.56	16.69
20	53.22	68.22	17.81
21	60.65	66.59	15.46
22	58.42	74.86	15.64
23	58.94	65.20	15.92
24	55.77	72.46	16.96
25	56.77	72.48	16.38
26	51.77	75.46	17.85
27	52.51	75.75	17.76
28	52.51	70.83	17.45
29	52.69	74.68	17.79
30	50.88	68.64	18.76

Table 6.- Analysis of variance results for the normalized parameters. F= *Compression force;* D= *% Drug.*

Source of variation	AUC_n	$I.P.O._n$	$M.S._n$
	Prednisone		
F	253.42*	5.27**	36.67*
D	1409.10*	2.19	44.55*
D^2	43.89*	1.07	0.03
D^3	12.69*	0.04	2.48
D^4	3.03	0.02	0.48
FxD	13.76*	4.97**	27.79*
FxD^2	15.76*	0.21	0.41
FxD^3	29.97*	0.12	5.80**
FxD^4	55.24*	0.64	0.01
	Phenobarbital		
F	264.00*	0.03	14.59*
D	456.45*	0.43	25.83*
D^2	17.84*	1.35	$4.0\ 10^{-3}$
D^3	8.78*	0.20	5.36**
D^4	3.58	8.30*	0.87
FxD	0.03	2.45	1.86
FxD^2	13.95*	1.63	0.02
FxD^3	30.21*	0.13	0.51
FxD^4	4.37**	1.47	1.47
	Isoniazide		
F	253.42*	0.47	55.97*
D	1409.10*	0.66	438.68*
D^2	43.89*	0.33	2.85
D^3	12.69*	1.05	1.58
D^4	3.03	0.74	0.17
FxD	13.56*	6.99**	0.16
FxD^2	15.76*	0.04	3.36
FxD^3	29.97*	0.42	30.09*
FxD^4	55.24*	0.07	17.66*

*Significant at the α <0.01 level.
**Significant at the α <0.05 level.

Table 7.- Regression equations for the normalized parameters fitted using the program BMDP.P2R.

	Prednisone	
AUC_n(ms)	$= 63.62 - 0.3064\ 10^{-2}\ F - 0.6645\ 10^{-3}\ FxD$	R^2=0.8583
$I.P.O._n$	= 0.6799	
$M.S._n$($ms^{-1}\ 10^3$)	$= 15.46 - 0.1640\ D + 0.0003\ FxD$	R^2=0.7840
	Phenobarbital	
AUC_n(ms)	$= 62.60 - 0.3469\ 10^{-2}\ F - 0.1020\ 10^{-1}\ D^2$	R^2=0.8963
$I.P.O._n$	= 0.7071	
$M.S._n$($ms^{-1}\ 10^3$)	$= 14.62 + 0.0694\ D + 0.0011\ F$	R^2=0.5733
	Isoniazide	
AUC_n(ms)	$= 64.02 - 0.2634\ D - 0.0050\ F + 6.144\ 10^{-5}\ FxD$	R^2=0.9027
$I.P.O._n$	= 0.7170	
$M.S._n$($ms^{-1}\ 10^3$)	$= 14.67 + 0.0662\ D + 0.0010\ F$	R^2=0.8670

Table 8.- Analysis of variance of the regression between corresponding response surface coefficients for W.H.H. and normalized AUC.

Source of variation	D.F.	Sum of squares	Mean square	F	α	R^2
			Prednisone			
Total	8	3588.50				
Regression	1	3587.40	3587.40	17937.0	<0.01	1.0000
Residual	7	1.10	0.20			
			Phenobarbital			
Total	6	3511.40				
Regression	1	3510.40	3510.40	17625.2	<0.01	1.0000
Residual	5	1.00	0.20			
			Isoniazide			
Total	8	3460.00				
Regression	1	3460.00	3460.00	$173.0.10^5$	<0.01	1.0000
Residual	7	$1.4.10^{-3}$	$2.0.10^{-4}$			

In all three series of tablets, W.H.H. and normalized AUC decreased with increasing drug percentage, showing that compressibility increases with drug content (2). Normalized I.P.O. was virtually constant, i.e. it could be predicted ade quately without using any of the significant analysis of variance terms. For all three drugs, an increase in drug content increased normalized M.S., which reflects the rate of energy exchange between the tablet and its environment during compression (2). In spite of these general trends, it may nevertheless be pointed out that the set of terms contained in the prediction equation for each Chilamkurti parameter varied from one drug to another.

Examination of the analysis of variance tables shows that the significant terms for W.H.H. and normalized AUC are generally the same, as is the distribution of significance among these terms.

Calculation of correlations between corresponding response surface coefficients for the two parameters shows that W.H.H. and normalized AUC are practically equivalent as far as their dependence of maximum compression force and drug content is concerned (Table 8).

This is logical, since normalized AUC is in fact the mean width of the normalized compression profile, and implies that it is redundant to use both parameters.

In a subsequent article we shall examine the use of Chilamkurti et al. parameters to predict various tablet properties.

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