DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(17), 2359-2371 (1991)

COMPARING THE COMPRESSIBILITY OF LUDIPRESS WITH THE OTHER DIRECT TABLETING AGENTS BY USING ACETAMINOPHEN AS AN ACTIVE INGREDIENT

T.BAYKARA, G.DUMAN, K.Ş.ÖZŞENER, Ş.ORDU, B.ÖZATEŞ

Department of Pharmaceutical Technology,
Faculty of Pharmacy
University of Ankara
06100 Tandoğan - ANKARA - TURKEY

ABSTRACT

Ludipress is a direct tableting agent which acts as an unique component, is really a multi component. In this study Ludipress compressibility and powder technological properties are compared with the other kind of DC agents (Avicel PH 102, Elcema G 250 and Elcema P 050) which are structurally based on cellulose. Acetaminophen has been chosen as an active ingredient.

The compression properties of powders and three direct tableting agent were investigated using the Heckel and Kawakita equations. Each formulations and compressed tablets which are compacted by hydraulic press with different pressure value were photographed by scanning electron microscope.

As a result Ludipress shows stable flow properties and the dilution potential of Ludipress is lower than the other DC agents.

INTRODUCTION

Direct tableting simply means that all of the components, active agents and auxiliaries are only blended, in other words, no granulation step is necessary. Then according to the other methods the direct tableting method is usefull for finishing the process in a short time.

Although individual properties of direct compression (DC) agents and auxiliaries affected the variability of method parameters. In that point of view, these parameters reflected the final product (1). Afterwards the production of pharmaceutical excipients as an unique component is one of the solution of the validation problems as critical parameters of pharmaceutical dosage forms (2).

Ludipress is one of the new direct tableting agent which is structurally based on sugar. Even though Ludipress is a direct tableting agent which acts an unique component, is really a multi component (3). However first of all a fundamental aspect must be mentioned: Ludipress combines three functions into one, namely that of filler, binder and disintegrant, where as Avicel PH 102 or Elcema only have one of these properties.

Ludipress contains the following components, but acts as an unique component;

Lactose monohydrate (Filler)	93.4 %
Kollidon 30 (Binder)	3.2 %
Kollidon CL (Disintegrant)	3.4 %

In this study Ludipress compressibility and powder technological properties are compared with the other different kind of (DC) agents (Avicel PH 102, Elcema G 250 and Elcema P 050) which are structurally based on cellulose. Inspite of a difficulty in direct compression, Acetaminophen has been chosen as an active ingredient.

TABLE 1

The codes and compositions of formulations.

Formulations	F1	F2	F3	F4	F5	F6
Material			%			
Acetaminophen	160	160	160	160	160	160
Lactose EP D 30	100	100	100	100	100	-
Kollidon CL	10	10	10	10	10	-
Avicel PH 102	70	-	-	-	-	-
Elcema G 250+P 050*	-	70	-	-	-	-
Ludipress	-	-	70	105	140	350
Running Powder**	10	10	10	10	10	20

* : Elcema G 250 and Elcema P 050 (4/1)

** : Running Powder: Boeson VP 50 %
Kollidon CL 30 %
Aerosil 300 20 %

EXPERIMENTAL

Materials:

Ludipress (BASF), Povidone (Kollidon 30, Kollidon CL, BASF), Microcrystalline Cellulose (Avicel PH 102, FMC Corp.), Powdered Cellulose (Elcema G 250 and Elcema P 050, Degussa), Aerosil-300 (Degussa), Lactose EP D 30 (Meggle), Boeson VP (Boehringer Ingelheim), Acetaminophen (Atabay Drug Company, İstanbul).

Methods:

The formulations which were shown in Table 1, was mixed 25 min. with an Erweka cubic mixer. Tablets were compressed with

a radius 10 mm and 12 mm flat face punch at a speed of 36 rpm, in a Korsch (EK-0) single punch machine.

1. - The controls for powders:

1.1- Determination of consolidation properties of powders:

The consolidation of 10 ml of each powder mixture was realised in a 10 cm^3 graduated cylinder by using funnel, in order to avoid percolation and the weight of the 10 ml was determined, the bulk density (BD) being calculated there from. The graduated cylinder was tapped from a height of 20 mm and the resulting reduction in volume was measured after repeating this procedure 5, 10, 20, 30, 50, 75, 100, 120, 175, 200, 300, 400 times. The natural logarithm of the tapping values, thus obtained were plotted against the ln, ln value of the relative density change (TD^* - BD/TD). The parameters of regression lines calculated with a computer programme (Basic 80) were investigated (4, 5). Similarly the assays were repeated for three direct tableting agents.

* : TD: Tapp Density

1.2- Determination of the flow properties of powders:

The flow properties of the mixed powders were determined using with the rotating drum method in order to avoid segregation of the dry mixed components (6).

1.3- Determination of the compressibility of powders:

The compression properties of the each mixed powder were investigated using the Heckel and Kawakita equations. For this purpose a 10 mm diameter flat face punch and a hydraulic press were used. Equal volumes of powders (1315 mm^3) were pressed at 306.8 , 767.0 , 1150.5 , 1534.0 , 1917.5 , 2301.0 , 2684.5 , 3068.1 and 3835.1 $kgf.cm^{-2}$. Pressure which maintained at the required value

for 30 seconds. The volume of the tablet, V_p, formed at each pressure level was calculated. Results were calculated with a computer programme written by using Heckel and Kawakita equations(7). Similarly the assays were repeated for three direct tableting agents.

2. - The pharmaceutical controls for tablets:

2.1- Weight variation:

The weight variation was calculated by using 20 tablets.

2.2- Hardness:

By using 10 tablets and Strong-Cobb apparatus, hardness was measured. The first time measurements were made just following the compression and they were repeated after 24 hours and 7 days.

2.3- Friability:

The friability tests were made by using Roche friabilator. 10 tablets were used for the measurements.

3. - Electron microscope studies:

F6 formulations and compressed tablets of F1 , F2 and F6 formulations which are compacted by hydraulic press with different pressure value (767.0 , 1150.5 , 1534.0 , 1917.5 $kgf.cm^{-2}$) were photograraphed by scanning electron microscope. The micrographs were photographed after the surface of tablets were coated with gold material (Magnif. 3000).

RESULTS AND DISCUSSION

F3 , F4 , F5 , F6 formulations which are coded on the Table 1, gives the best consolidation (r^2) value and its near to one. F6

TABLE 2

Consolidation parameters of formulations.

Formulations	(r^2)	Slope	Intercept	HI*
F1	0.8572	$0.1420 \pm 1.179 \times 10^{-3}$	$-0.9449 \pm 51.58 \times 10^{-3}$	1.429
F2	0.8795	$0.1461 \pm 12.30 \times 10^{-3}$	$-0.7541 \pm 51.60 \times 10^{-3}$	1.563
F3	0.8806	$0.1165 \pm 8.725 \times 10^{-3}$	$-0.7758 \pm 38.17 \times 10^{-3}$	1.449
F4	0.8773	$0.1423 \pm 10.82 \times 10^{-3}$	$-0.9603 \pm 47.35 \times 10^{-3}$	1.409
F5	0.8941	$0.1574 \pm 11.02 \times 10^{-3}$	$-0.9249 \pm 48.21 \times 10^{-3}$	1.515
F6	0.9765	$0.09573 \pm 3.022 \times 10^{-3}$	$-0.9045 \pm 13.22 \times 10^{-3}$	1.316

*: HI: Hausner Index

shows the highest (r^2) value in all formulations. The slope value of the formulations is the lowest value, it is $0.09573 \pm 3.022 \times 10^{-3}$ in Table 2. Because of the Ludipress' particles are spherical. The confidence limits of slope value is the lowest value according to the others (probability 95 %). That is the reason of the Ludipress particle sizes' distribution limit is narrow. If this limit is so wide;

* Powders bulk density shows continuous variability.
* At the end of the final tablet weight variation is the highest value.

At the same Table , HI value is lower. It maintains, the consolidation value F6. During the consolidation stage, higher(r^2), lower slope and HI value express the following statements;

* Less energy lost during compression.
* Homogeneous and stable distribution on particle size.
* Powder's particle shape is almost spherical or spherical(8).

The three (DC) agents' consolidations are supported to the formulation results, which were shown in Table 3. The Ludipress'

TABLE 3

Consolidation Parameters of Direct Tableting Agents.

Formulations	(r^2)	Slope	Intercept	HI*
Avicel PH 102	0.9206	$0.1024 \pm 6.115 \times 10^{-3}$	$-0.8227 \pm 26.75 \times 10^{-3}$	1.389
Elcema**	0.9392	$0.1403 \pm 7.265 \times 10^{-3}$	$-0.7980 \pm 31.78 \times 10^{-3}$	1.563
Ludipress	0.9886	$0.08123 \pm 1.777 \times 10^{-3}$	$-0.061 \pm 7.775 \times 10^{-3}$	1.205

* : Hausner Index

** : Elcema G 250+P 050

slope value is the lowest one which is $0.08123 \pm 1.777 \times 10^{-3}$. The HI value of Ludipress is also the lowest one. The consolidation figures as shown in Fig 1 and Fig 2.

The other methods (angle of repose by pouring, flow rates) were not used. For the observing of powder flow properties in the direct tableting method, being of the unit which is the mass of tableting powder mixture can be together with the component of their surface enery (9). Rotating drum method has been used to avoid the segregation of the powder mixture. The F1 formulation is rotating drum angle is the lowest one but the F6 formulations confidence limit is the lowest one. For this reason, Ludipress shows stable flow properties es shown in Table 4.

According to the Heckel equation, the F6 formulation (r^2) value is the best one. This value is 0.9907 as shown in Table 5. The logarithm of relative volume changes are plotted against applied pressure values. After calculation regression lines the slope value is important. The yield pressure (P_y) values of formulations which obtained from the reciprocal values of the slope of regressions plots were investigated. Ludipress is giving the lowest P_y value which is 450.70 $kgf.cm^{-2}$, but this reason is

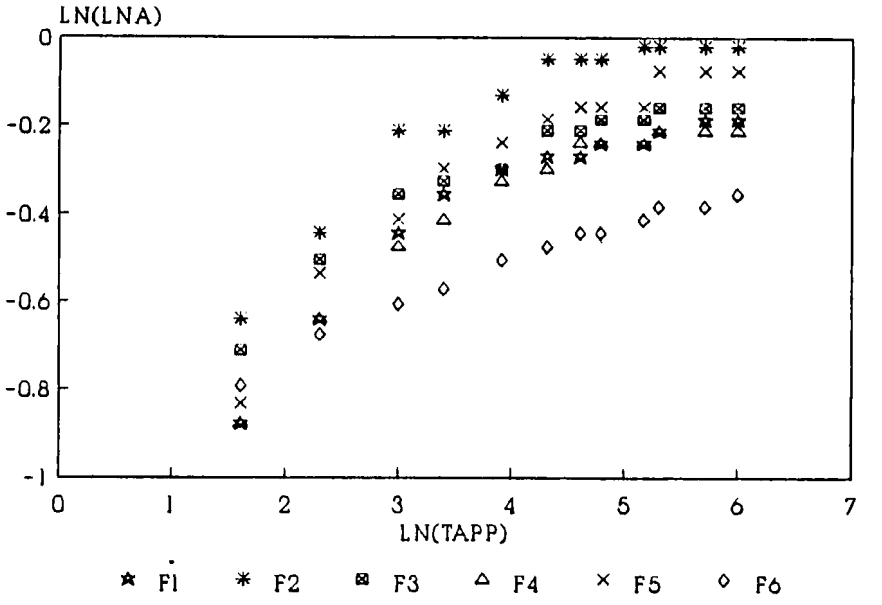

FIGURE 1

Consolidation of Formulations.

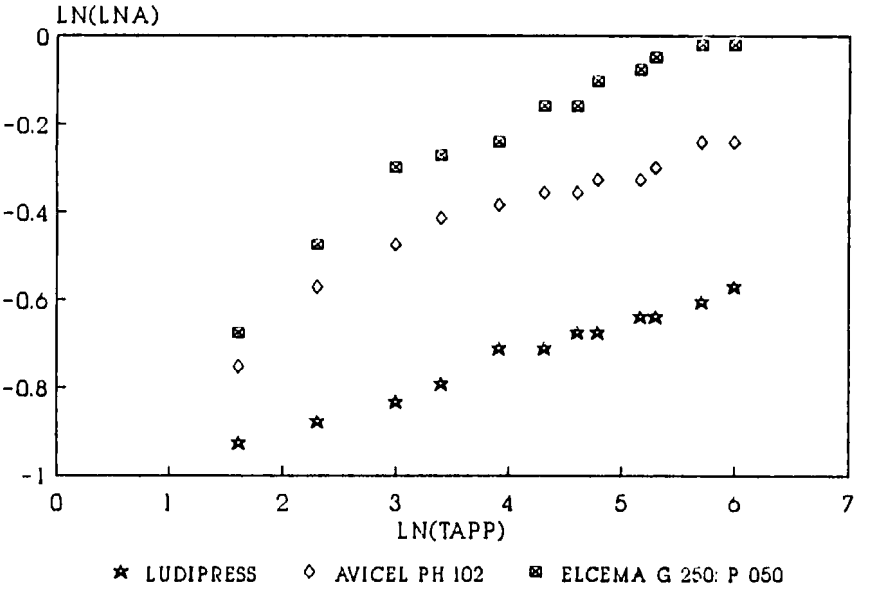

FIGURE 2

Consolidation of direct Tableting Agents.

TABLE 4

Flow Properties of Formulations.

Formulations	Rotating Drum(Degree)
F1	32.8 ± 2.52
F2	42.0 ± 2.50
F3	33.4 ± 1.88

TABLE 5

Compressibility Parameters of Formulations.

Formulations	Heckel (r^2)	P_y ($kgf.cm^{-2}$)	Kawakita (r^2)	$ax10^{-2}$
F1	0.9300	736.80	0.9999	95.87
F2	0.9801	1386.0	0.9999	95.55
F3	0.9744	1039.4	0.9999	97.33
F4	0.9583	1088.7	0.9999	97.40
F5	0.8336	734.50	0.9999	97.43
F6	0.9907	450.70	1.000	97.63

TABLE 6

Compressibility of Direct Tableting Agents.

Formulations	Heckel (r^2)	P_y ($kgf.cm^{-2}$)	Kawakita (r^2)	$ax10^{-2}$
Avicel PH 102	0.7508	499.81	0.9999	98.92
Elcema*	0.8845	974.80	0.9999	98.38
Ludipress	0.7391	871.82	0.9999	97.90

* : Elcema G 250 and Elcema P o50 (4/1)

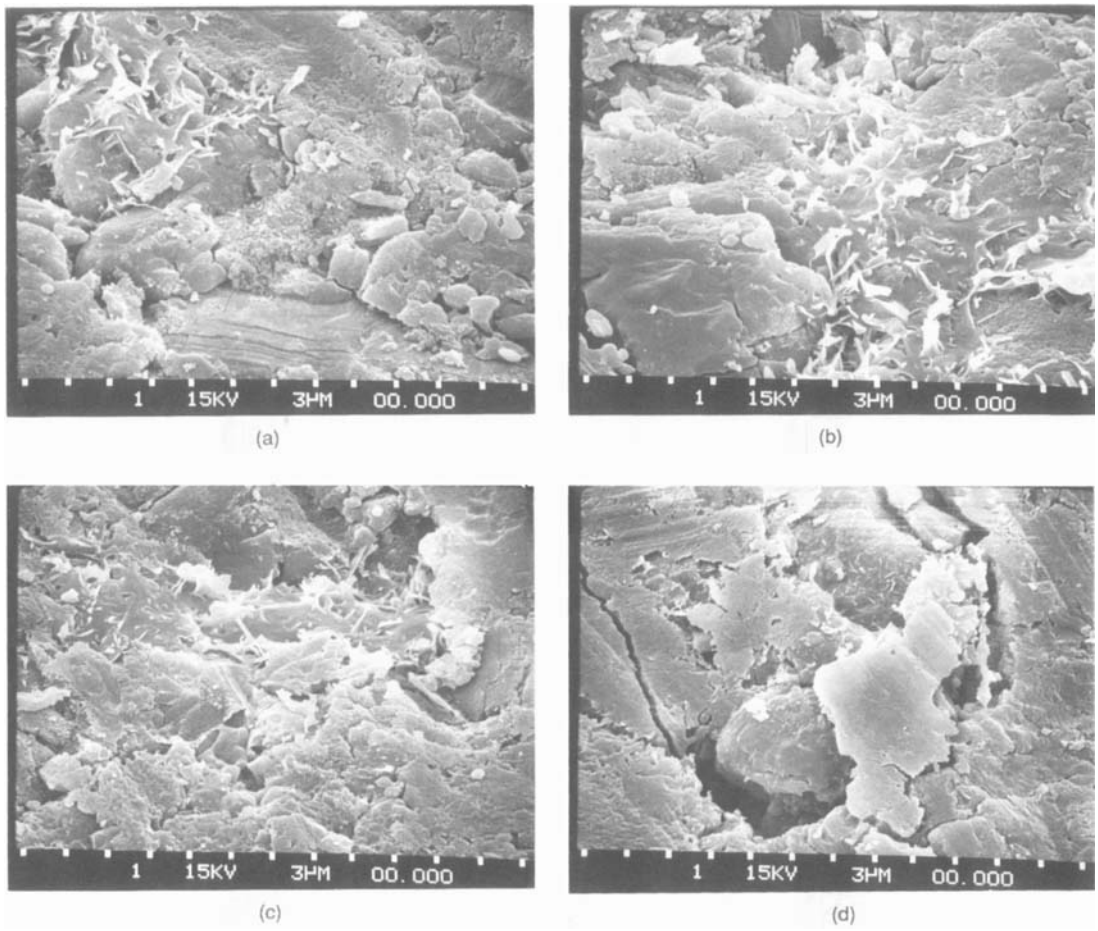

FIGURE 3

The Scanning electron micrographs of F6 formulations which are compacted by hydraulic press with different pressure values. (Mag. 3000X) a- 767.0 kgf.cm^{-2}, b- 1150.5 Kgf.cm^{-2}, c- 1534.0 Kgf.cm^{-2}, d- 1917.5 Kgf.cm^{-2}

apparent. F1 and F2 formulations'(DC) agents amounts are three times lower than the F6 formulation. When this amount is used the tablets were compressed. The results were shown in Table 6.

The scanning electron micrographs of F6 formulations which are compressed by hydraulic press in different pressure values are shown

TABLE 7

Physico-pharmaceutical Properties of Compressed Tablets.

Formulations		F1	F2	F6
Hardness(SCU),	Initially	$10.6 \pm 43.9 \times 10^{-2}$	$9.00 \pm 47.6 \times 10^{-2}$	$13.5 \pm 84.2 \times 10^{-2}$
	24 th hour	$12.8 \pm 34.5 \times 10^{-2}$	$9.70 \pm 75.7 \times 10^{-2}$	$13.4 \pm 85.3 \times 10^{-2}$
	7 th day	$11.5 \pm 50.5 \times 10^{-2}$	$9.90 \pm 69.0 \times 10^{-2}$	$14.8 \pm 89.5 \times 10^{-2}$
Disintegration Time(Min.)		0.380 ± 0.258	2.09 ± 2.51	$1.01 \pm 5.58 \times 10^{-3}$
Weight Variation(g)		$0.348 \pm 1.58 \times 10^{-3}$	$0.348 \pm 2.08 \times 10^{-3}$	$0.529 \pm 1.10 \times 10^{-3}$
Thickness(cm)		$0.346 \pm 2.26 \times 10^{-3}$	$0.341 \pm 2.26 \times 10^{-3}$	$0.463 \pm 30.5 \times 10^{-3}$
Friability(w/w %)		0.37	0.14	0.36

in Fig.3(a,b,c,d).When the pressure value was 767.0 kgf.cm^{-2}, the particular deformation has begun.Fig.3(b,c)indicated that,if the pressure values are reached at 1150.5 and 1534.0 kgf.cm^{-2},the compact structure has been shown. But, the plastic deformation point has been over come and the cracks has been occured when the pressure value reached over the value of 1917.5 Kgf.cm^{-2}. In other words, the compact system is reached to fragmentation stage.

When the three DC agents were used alone, the P_y values will change. The P_y value of Avicel PH 102 is 469.81 Kgf.cm^{-2} and Ludipress' is 871.82 Kgf.cm^{-2} as shown in Table 6. The "a" value of Kawakita equation is indicated that the initial porosity of compression mass(10). In this case, there are not any differences between the formulations. As a result, the dilution potential of Ludipress is lower than the other DC agents. Ludipress adding ratio is increased and is compressed by 12 mm punch.

Compressed tablet's hardness is not changed by the time. The Ludipress weight variation is lower than the others and Ludipress' friability is positive as shown in Table 7.

FOOTNOTE

This paper has been presented at the 5th International Pharmaceutical Technology Congress, in 30.May-1.June.1989,in Paris-France.

ACKNOWLEDGEMENT

The authors would like to thank "BASF" Company for scientific and financial support.

REFERENCES

1 - B.B.Sheth, F.j.Bandelin and F.R.Shangraw, "Compressed Tablets", H.A.Lieberman and L.Lachman,(Eds.)., "Pharmaceutical Dosage Forms:Tablets", Vol.1, P.147-161, Marcel Dekker Inc.,New York, 1980.

2 - H.Sucker, "Praxis der Validierung", Wissenschaftliche Verlagsgesellschaft mbH, Stutgart, 1983.

3 - BASF, Market Information, No.64, 1986.

4 - T.Baykara, G.Duman und M.M.Süleyman, "Stampf-Kompressionseigenschaften vo Pharmazeutischen Pulvern und Pressmassen", presented at the 49th. Int.Pharm.Sci.Congress-F.I.P., Munich, September 4-9, 1989.

5 - M.M.Süleyman and T.Baykara, "A microcomputer programme series for use in tablet technology", at the 3rd. Int.Pharm.Technology Symposium, Ankara, September 9-11, 1986.

6 - I.N.Staniforth, Int.J.Pharm.Tech.and Prod.Mfr., 3,(Suppl.)1 (1982).

7 - R.W.Heckel, Trans.Met.Soc.A.I.M.E., 221, 671 (1961).

8 - T.Baykara and F.Acartürk, Drug Devel.Ind.Pharm., 15, 1341(1989).

9 - R.J.Lantz, "Mixing", H.A.Lieberman and L.Lachman,(Eds.), "Pharmaceutical Dosage Forms:Tablets", Vol.2, Marcel Dekker Inc., New York, 1981.

10- A.Michael, K.Peeters, P.Rombaut and R.Kinget, Pharm.Ind., 48, 961(1986).