DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(12), 1369-1377 (1993)

COMPRESSION BEHAVIOR OF ACETYLSALICYLIC ACID PELLETS

F.J. López-Rodríguez[1], J.J. Torrado[1]*, S. Torrado[1], C. Escamilla[2], R. Cadórniga[1] and L.L. Augsburger[3]

1 Dpto. Farmacia y Tecnología Farmacéutica
Facultad de Farmacia. Universidad Complutense.
Avda. Complutense s/n. 28040. MADRID. SPAIN
2 Dpto. Tecnología Farmacéutica
ENEP Zaragoza. Universidad Nacional Autónoma de México
México D.F.
3 Department of Pharmaceutics
School of Pharmacy.
University of Maryland at Baltimore. USA

ABSTRACT

An instrumented tablet press was used to study the compression behavior of different acetylsalicylic acid (AAS) formulations. Formulations of AAS crystals and uncoated AAS pellets have compression behavior similar to formulations of AAS pellets coated with acrylic resins (Eudragit RS) and mixed with a 20% of microcrystalline cellulose. Formulations of AAS coated pellets without any excipient exhibited a more plastic compression behavior then the other formulations. Matrix tablets of AAS were produced by compression of formulations of AAS coated pellets without any excipients.

The drug release profile of the pellets before and after compression was also studied. Microcrystalline cellulose concentrations higher than 15% w/w were required to obtain tablets of coated pellets with drug release profiles similar to the coated pellets

* to whom correspondence should be addressed

before compression. It can be concluded from the present work that compression data of coated particles can be useful to study the possible damage of the film coat of the particles during tableting. Futhermore, instrumented tablet press data can be a good complement of in vitro drug release studies.

INTRODUCTION

Compression is the process of applying pressure to a material[1]. The effect of compression on the physical characteristics of tablets has been studied by different pharmaceutical scientists. To this end, several kinds of instrumented tablet presses have been used[2].

The techniques and methods available to interpret powder compaction data are often based on force-displacement and force-time compression curves[3-7].

The purpose of the present work was to study the effect of coating on the compression behavior of acetylsalicylic acid (AAS) pellets. In order to delay drug release and to reduce gastrointestinal mucosal irritation, the AAS pellets were coated by an acrylic resin (Eudragit RS). The effect of coating on the compression characteristics of the pellets was studied using force-displacement and force-time compression curves. The drug release profile of the pellets before and after compression was also studied.

MATERIALS

Acetylsalicylic acid (Merck), di-n-butylphthalate (Griffin & George Ltd), ethanol and isopropyl alcohol (Panreac) were of reagent grade.

Acrylic resins (Eudragit^R E 100 and RS 12.5, Röhm Pharma) and microcrystalline cellulose^R (Avicel PH 102, FMC) were of pharmaceutical grade.

METHODS

Pelletization process.

AAS crystal, size 350-450 μm, were milled to reduce the particle size to 100-125 μm. 400 g of these particles were then granulated in a coating pan with 400 ml of a 10% w/v ethanol solution of Eudragit E. The pellets were produced by a conventional

pan coating method. The size selection of the pellets were made by sieving between 400 and 500 μm.

Pan coating of the pellets.

300 g of AAS pellets were coated in a coating pan with 600 ml of a solution of Eudragit RS 12.5% w/v containing 7.5 g of dibutylphthalate as a plasticizer agent. The size selection of the pellets was made by sieving between 400 and 700 μm.

Compression.

Four different formulations were tableted by an instrumented eccentric tablet machine (Mondel, Spain).

- Formulation A. AAS crystals. Particle size 0.5-0.71 mm.
- Formulation B. AAS pellets. Particle size 0.4-0.5 mm.
- Formulation C. AAS pellets coated with a 20% w/w Eudragit RS. Particle size 0.6-0.85 mm.
- Formulation D. Formulation C mixed with a 20% w/w of microcrystalline cellulose.

The tablet press was instrumented with piezoelectric transducers in the eye bolt and ejection cam to measure compression and ejection forces. Inductive displacement transducers were used to measure punch movement and tablet thickness during compression. The tablet press was interfaced with a computer using an analog-to-digital converter to process the signals. The analysis of the experimental compression curves was performed on a computer using a program written at the University Complutense of Madrid. The die cavity and punches were 14 mm in diameter and the punches were flat-faced.

Elastic Recovery (ER).

It was calculated by a modification of the method used by Wong and Pilpel[8].

$$ER\ (\%) = \frac{H_f - H_m}{H_m} \times 100$$

Where, H_f is the final thickness of the tablet and H_m is the thickness of the compressed formulation when the upper punch has reached its maximum displacement.

Lubricant Efficiency (LE).

The lubricant efficiency was quantitatively expressed as the ratio of the maximum lower punch force (M.L.P.F.) to the maximum upper punch force (M.U.P.F.)[9].

$$LE = \frac{M.L.P.F.}{M.U.P.F.}$$

Evaluation of Tablets:

Uniformity of weight. For each of the formulation tested, ten tablets were weighed individually and the mean and standard deviation of the ten values were calculated.

Thickness. For each formulation the crown thickness of at less ten tablets was measured with a micrometer.

Diametral crushing strength. For each formulation, ten tablets were tested individually in an Erweka mechanical strength tester.

Dissolution rate. For each formulation, three tablets were assayed in 900 ml of phosphate buffer (pH 6.8) at 100 rpm in a Turu-Grau Dissolutest apparatus complying with USP XXII Method 2 specifications. Samples were taken at different times, filtered and assayed by spectrophotometry at 265 nm (isosbestic point for AAS, USP XXII).

RESULTS AND DISCUSSION

Table 1 shows the compression data of the four different tested formulations. AAS crystals (formulation A), AAS pellets (formulation B) and AAS coated pellets with Avicel (formulation D) have similar compression characteristics, while AAS coated pellets without Avicel (formulation C) has a very different compression behavior.

Leight et al.[10] have reported that under compression AAS crystals undergo elastic deformation. This effect can be studied with the elastic recovery value of the different formulations (Table 1). All the AAS tested formulations have elastic recovery values higher than 10, with the exception of AAS coated pellets without Avicel (formulation C).

The poor lubricant efficiency of coated pellets without Avicel contrasts with the values of the other formulations. Although the lubricant efficiency can be improved by the proper selection of lubricant agents, no lubricant agent was used in the present formulations to avoid possible modifications in the compression behavior of the tested materials[1].

Table 2 shows the tablet characteristics of the four different formulations. The weight differences of the tablets were due to the different bulk densities of the formulations. Tablets of coated pellets without Avicel (formulation C) and coated

Table 1. Compression data of the four different formulations. Key: Formulation A. AAS crystals; Formulation B. AAS pellets; Formulation C. AAS coated pellets and Formulation D. AAS coated pellets with a 20% w/w of Avicel.

	FORMULATION			
	A	B	C	D
Maximum Upper Punch Force (KN)	8.6	11.1	3.7	9.6
Maximum Lower Punch Force (KN)	7.2	9.6	2.4	8.5
Elastic Recovery (%)	11.3	11.9	6	13.6
Lubricant Efficiency	0.84	0.87	0.65	0.88

Table 2. Tablet characteristics of the four different formulations. Values in parentheses are standard deviations of the parameters. Standard deviations for thickness values were too small to report. Key: (see table 1). * Crushing strength of formulation D was out of range.

	FORMULATION			
	A	B	C	D
Weight (mg)	705.4 (16.1)	593.8 (8)	494.4 (9.1)	493.4 (15.3)
Thickness (mm)	4 (<.1)	3.5 (<.1)	3.1 (<.1)	3.1 (<.1)
Crushing strength	8.7 (.7)	10.8 (.4)	13.9 (1.3)	>15*

pellets with Avicel (formulation D) have very similar characteristics. The only difference is the higher crushing strength of the pellets with Avicel (formulation D). This higher value is probably due to the use of Avicel. The use of Avicel and other direct compression excipients usually increase the hardness of the tablets. A similar result was reported by Saleh and Stamm[2].

Figure 1 shows the force-displacement curves of the four different formulations. Coated pellets without Avicel (Figure 1C) has a diferent compression behavior than the others formulations (Figure 1A, 1B and 1D). This different tableting behavior was also

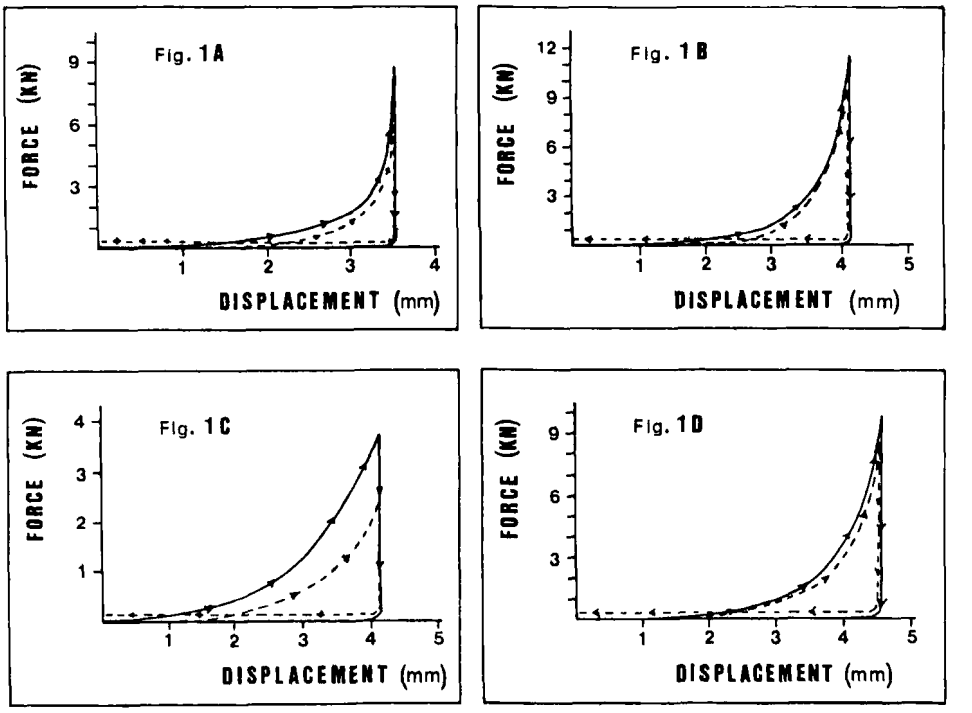

FIGURE 1
Force-Displacement compression curves of the four different formulations. The force exerted by the upper punch is drawn in continuous line and the force transmitted by the lower punch is drawn in discontinuous line. Key: Fig. 1.A. Formulation A; Fig. 1.B. Formulation B; Fig. 1.C. Formulation C and Fig. 1.D. Formulation D.

seen in the force-time compression curves (Figure 2). Coated pellets without Avicel (formulation C) requires lower punch forces than the other formulations, possibly due to a process of fusion among the acrylic membranes on the surface of the coated pellets.

Compression of coated pellets can lead to matrix tablets when the film layers come into intensive contact with one another and fuse during compression. Although fillers and disintegrants can be used to separate the coated pellets, there is still the danger of breaking the film coat which could destroy the controlled-release profile[12]. In order to avoid the formation of a matrix tablet, Avicel was added to the coated pellets.

An indirect method to check the integrity of the film layers is to study the controlled-release profile of the different formulations. Figure 3 shows the in vitro drug

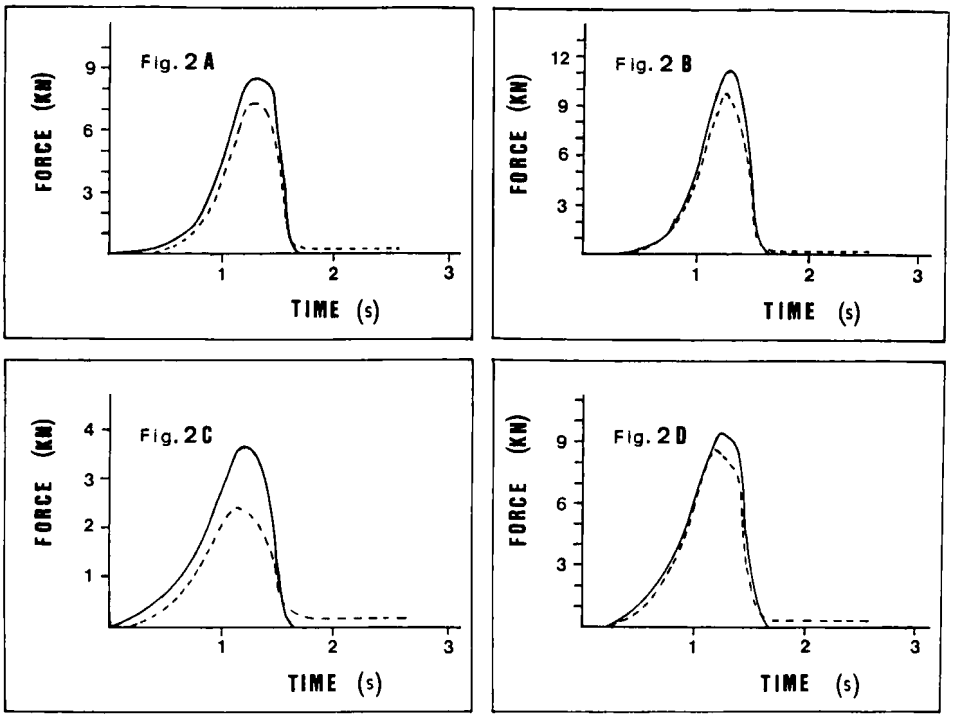

FIGURE 2
Force-Time compression curves of the four different formulations. The force exerted by the upper punch is drawn in continuous line and the force transmitted by the lower punch is drawn in discontinuous line. Key: Fig. 2.A. Formulation A; Fig. 2.B. Formulation B; Fig. 2.C. Formulation C and Fig. 2.D. Formulation D.

release of the different formulations. A matrix tablet of slow release was produced when Avicel was not added to the formulation and when Avicel was used at low concentrations (5%). Coated pellets with 15, 20 and 25% w/w of Avicel have a similar drug release profile to the coated pellets before compression.

The results of the in vitro dissolution experiments agree with the compression data obtained with the instrumented tablet press. Figure 3 shows that formulations of AAS coated pellets with less than a 15% w/w of Avicel have a release profile slower than the coated pellets before compression. As was suggested from the data obtained by the instrumented tablet press, this effect may be due to of fusion of the acrylic membranes of the coated pellets (formulation C in Figures 1 and 2).

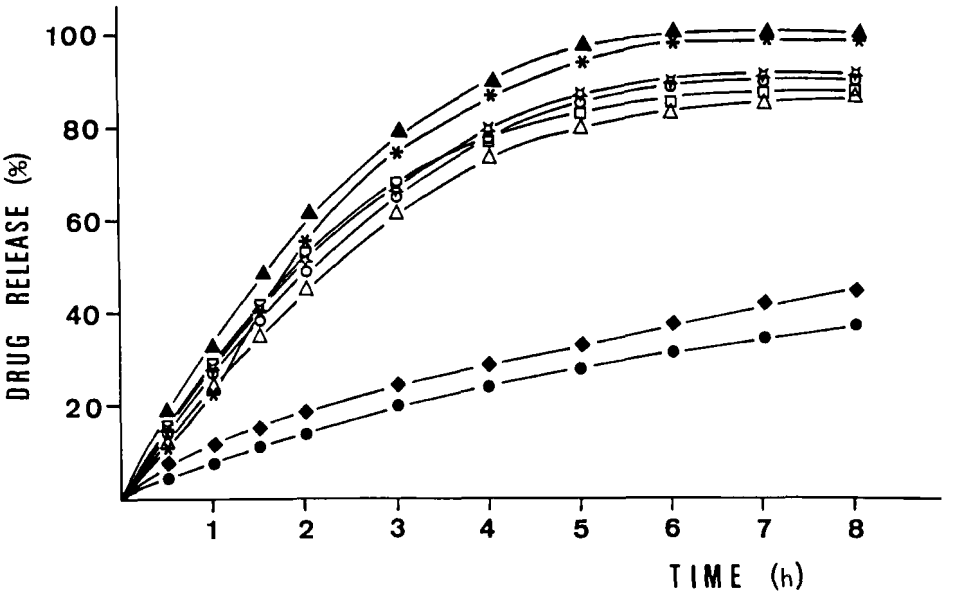

FIGURE 3
Dissolution curves of the different formulations. Key: ○ — AAS coated pellets; ▲ — —Tablet of AAS crystals (Formulation A); ✱ — Tablet of AAS pellets (Formulation B); ● —Tablet of AAS coated pellets without Avicel (Formulation C); ◆ —Tablet of AAS coated pellets with a 5% w/w of Avicel; △ –Tablet of AAS coated pellets with a 15% w/w of Avicel; ✡ ——Tablet of AAS coated pellets with a 20% w/w of Avicel (Formulation D) and □ —Tablet of AAS coated pellets with a 25% w/w of Avicel.

Lehmann[12] has reported that when the amount of excipients is lower than 30%, there is an increasing amount of coated particles which can break during compression. Futhermore, formulations with less than a 25% of Avicel have poor disintegration characteristics (> 3 hours during the dissolution test). For these reasons, and in order to obtain tablets of multiparticulate AAS coated pellets with good disintegration characteristics (< 15 minutes), Avicel proportions of at least 25% w/w was required.

It can be concluded from the present work that data obtained by instrumented tablet presses can be useful in evaluating the integrity of the film layers when multiparticulate tablets of coated pellets are going to be formulated. Futhermore, data obtained by instrumented tablet presses can be a good complement to in vitro drug release studies.

REFERENCES

1. E.L. Parrot, in "Pharmaceutical Dosage Forms: Tablets. Vol. 2" H.A. Lieberman and L. Lachman, eds., Marcel Dekker Inc., New York, 1981, p. 153-184.
2. P.R. Watt, "Tablet machine instrumentation in pharmaceutics. Principles and practice", Elis Horwood Ltd., Chichester, West Sussex, England. 1988, p. 397-428.
3. I. Krycer, D.G. Pope and J.A. Hersey, Drug Dev. Ind. Pharm. 8, 307 (1982).
4. H. Leuenberger and B.D. Rohera, Pharm. Res. 3, 12 (1986).
5. N.A. Armstrong, Int. J. Pharm. 49, 1 (1989).
6. J.R. Hoblitzell and C.T. Rhodes, Drug Dev. Ind. Pharm. 16, 201 (1990).
7. J.R. Hoblitzell and C.T. Rhodes, Drug Dev. Ind. Pharm. 16, 469 (1990).
8. L.W. Wong and N. Pilpel, Int. J. Pharm. 59, 145 (1990).
9. E. Nelson, S.M. Naqvi, L.W. Busse and T. Higuchi, J. Am. Pharm. Assoc., Sci. Ed. 43, 596 (1954).
10. S. Leigh, J.E. Carless and B.W. Burt, J. Pharm. Sci. 56, 888 (1967).
11. S.I. Saleh and A. Stamm, S.T.P. Pharma 4, 10 (1988).
12. K.O.R. Lehmann, in "Aqueous polymeric coatings for pharmaceutical dosage forms", J.W. McGinity, ed., Marcel Dekker Inc, New York, 1989, p. 153-245.