ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 44 (1997) 283–288

European Journal of Pharmaceutics and Biopharmaceutics

Paper

The repeated compression of powders

Mohammed R.A.K. Al-Aghbar, N. Anthony Armstrong *

Welsh School of Pharmacy, University of Wales, Cardiff, UK

Received 7 November 1996; accepted 22 April 1997

Abstract

Powders were subjected to repeated compression in a tablet press, the ejection mechanism of which had been disconnected. The force detected at the upper punch was found to change with successive compressions, the magnitude of the change being dependent on the powder, the compressive force and the interval between compressions. Repeated compression also caused a change in tablet crushing strength. With compression intervals of 1.2 s, all substances showed an significant increase in strength. With longer time intervals, the increase was reduced and in some cases, a diminution in strength occurred. © 1997 Elsevier Science B.V.

Keywords: Tablet; Compression; Strength; Plasticity; Elasticity

1. Introduction

Multiple compression—compressing the same tablet more than once without ejecting it from the die—was first studied by Bessho et al. [1] who noted that the applied force may change with each successive compression. Double compression was later studied by de Blaey and Polderman [2] who, by means of a study of force–displacement curves, attempted to quantify the work involved in the compaction process. They considered that the work used in the first compression was the total work, and that work used in the second compression was that needed to overcome elastic expansion of the tablet. However, Armstrong et al. [3] later showed that third and subsequent compressions used progressively less work, indicating that factors other than elastic expansion were involved. Furthermore, they found that the behaviour of a powder undergoing multiple compression was found to be substance dependent and was also dependent on the frequency of compression. Work by Schierstedt and Muller [4] confirmed that each successive compression stored additional energy in the tablet, and so net energy could not be determined by a double compression technique.

Powders consolidate under a compressive force by a variety of mechanisms, ranging from particle fragmentation to plastic and elastic deformation. Particle fracture can be regarded as a virtually instantaneous process, but irreversible deformation resulting from plastic flow or viscoelasticity is comparatively slow, and greater consolidation can be achieved by applying the compressive force for a longer time.

The mechanism of consolidation and the time over which the consolidation process occurs can be a major influence on tablet properties [5,6]. Since there appears to be a time-dependent element in the response of powders to multiple compression, it was considered that multiple compression might afford a means of elucidating the consolidation mechanism. Several powders were selected whose consolidation mechanisms are known, together with others whose mechanism is less well established.

* Corresponding author. Welsh School of Pharmacy, University of Wales, Cardiff, P.O. Box 13, Cardiff, CF1 3XF, UK.

PII S0939-6411(97)00137-9

2. Materials and methods

The following solids were used as received.
Microcrystalline cellulose (Avicel PH102®, FMC, Cork, Ireland).
Pregelatinised maize starch (Starch 1500®, Colorcon, Orpington, UK).
Sodium chloride (BDH, Poole, UK).
Mannitol (BDH, Poole, UK).
Spray-dried lactose (Zeparox®, Borculo Whey Products, Saltney, UK).
Dicalcium phosphate dihydrate (Emcompress®, E. Mendell, Reigate, UK).
Cellactose®, (a coprocessed combination of lactose 75% and cellulose 25%, Meggle, Wasserburg, Germany).

All were stored at 54% RH until used. Repeated compression was carried out on a Manesty F3 eccentric press (BWI Manesty, Liverpool, UK) fitted with a 12.5 mm diameter die and flat-faced punches. The upper punch was fitted with strain gauges (Measurements Group, Basingstoke, UK) to permit determination of applied pressure. The separation of upper and lower punches was monitored by means of a linear variable differential transformer (LVDT, Sangamo Weston, Bognor, UK). Transducer calibration was carried out using a load cell for the strain gauges and blocks of known thickness for the LVDT.

The ejection mechanism of the press was disconnected so that the tablet remained stationary in the die between compressions.

The die walls and punch faces were lubricated with a suspension of magnesium stearate in acetone. An exact weight of powder (Table 1) was transferred into the die, and compressed repeatedly for up to ten times at time intervals of 1.2 s, 1 or 5 min. After removal from the die, tablets were stored in a sealed container for 24 h. Tablet dimensions were then measured with callipers, and the crushing strength determined on a CT40 tester (Engineering Systems, Nottingham, UK).

Table 1
Weights of powder (mg) used to achieve a specific compression force

Powder	Force (kN)		
	5	10	15
Avicel PH102®	340	385	420
Zeparox®	350	380	405
Emcompress®	495	550	590
Cellactose®	320	350	385
Starch 1500®	350	412	448
Mannitol	330	375	405
Sodium chloride	495	565	615
Avicel:Zeparox (25:75)	320	350	380

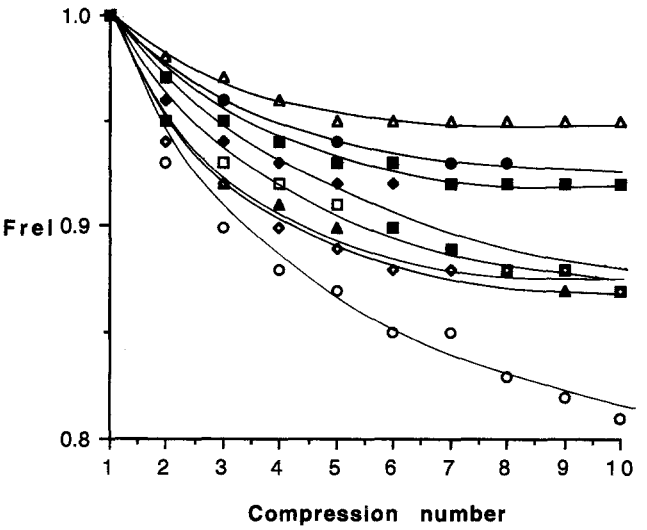

Fig. 1. The relationship between the number of compressions and Frel for a series of solids repeatedly compressed at 15 kN at intervals of 1.2 s. ○, Zeparox; ●, Emcompress; □, sodium chloride; ■, Starch 1500; △, Avicel; ▲, Mannitol; ◇, Cellactose; ◆, a mixture of Zeparox (75%) and Avicel (25%).

When operating continuously, the press prepared tablets at the rate of 50 min^{-1}, equal to an interval between compressions of 1.2 s. For compression at longer intervals, it was found that if the press was started when the upper punch was at its highest point, the same punch displacement–time profile was obtained in all cases.

3. Results and discussion

The effects of multiple compression are assessed by calculation of the parameter Frel [3] which is defined as

$$\text{Frel} = \frac{\text{Force detected at the } n\text{th compression}}{\text{Force detected at the first compression}} \quad (1)$$

Multiple compression was studied from three viewpoints

1. The effect of the initial compression force on Frel.
2. The effect of changing the interval between compressions on Frel.
3. The effect of multiple compression on tablet strength and porosity.

4. The effect of initial compression force on Frel

Fig. 1 shows the variation of Frel with the number of compressions, using an initial compressing force of 15 kN and a compression interval of 1.2 s. The flow properties of some of the solids were not good enough to give a consistent weight and hence force, and so individually weighed quantities of each powder were

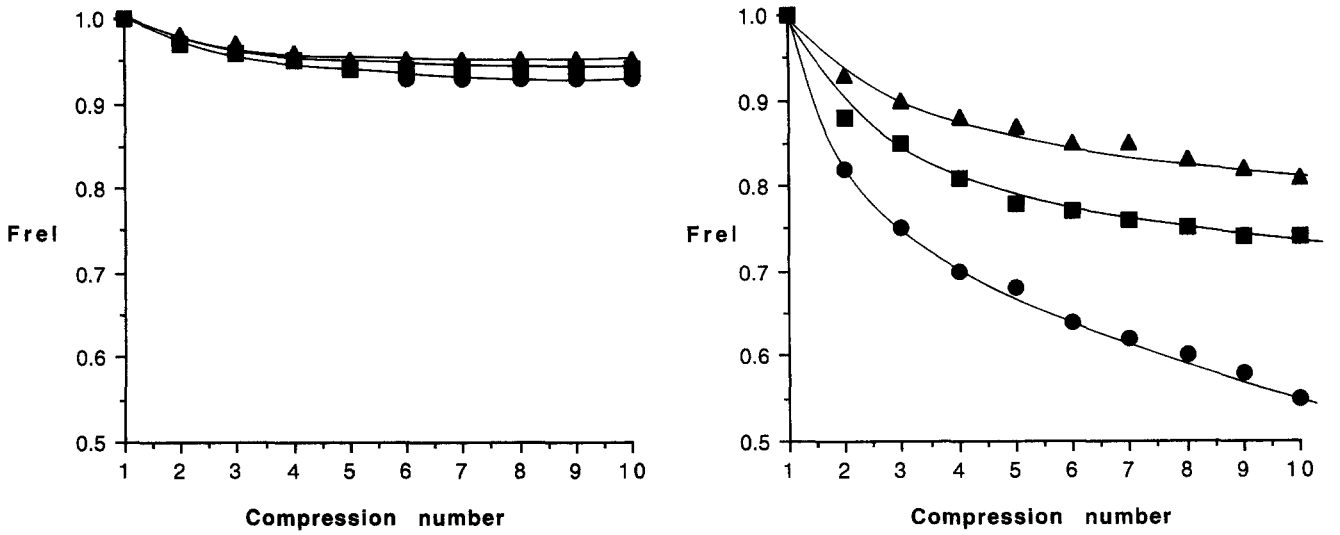

Fig. 2. The relationship between the number of compressions and Frel for Avicel (a) and Zeparox (b) after repeated compression at intervals of 1.2 s at three compression forces (●, 5 kN; ■, 10 kN; ▲, 15 kN).

transferred to the die (Table 1). The distance of minimum separation between the punch faces was kept constant. This technique gave a reproducibility of force of ± 0.1 kN.

An unavoidable consequence of changing the mass of the powder in the die is to alter the total time which elapses from the first contact between the upper punch and the powder and the point of maximum punch penetration. However, this alteration is at most 30 ms [5] which is considerably less than the intervals between compressions, even at the fastest press speed.

Considerable differences in behaviour between substances are apparent. Avicel PH102 attains a constant value of Frel of ~ 0.95 after only five compressions, whereas the Frel for Zeparox was still decreasing quite steeply beyond a Frel of 0.8 after ten compressions. This indicates that Avicel achieves its final porosity relatively easily compared with Zeparox. Since lactose is primarily a fragmenting material and cellulose deforms, it is tempting to relate this behaviour to consolidation mechanisms. However, the behaviour of Emcompress, which consolidates almost exclusively by fragmentation, resembles that of Avicel more closely than that of Zeparox.

A further contrast between substances is afforded by compression at three different forces. The Frel profiles for Avicel (Fig. 2a) are virtually superimposable, showing that the ultimate porosity attainable for a given force is readily achieved, irrespective of the force. Zeparox (Fig. 2b) shows widely separated lines. This again is what might be expected of a fragmenting substance. Repeated force applications will lead to further fracture of the particles along zones of weakness. These might be imperfections in the crystal structure or, in the case of a spray-dried product such as Zeparox, at the interface between crystalline and amorphous lactose. Each successive compression will bring about progressively less comminution, as predicted by the Griffith crack theory. This accounts for the shape of the lines in Fig. 2b. The higher the force, the greater the degree of fragmentation brought about by each compression.

Fig. 3 shows the relationship between Frel of Cellactose, a physical mixture of 75% Zeparox and 25% Avicel, and a predicted line derived from the behaviours of pure Avicel and Zeparox. The force is 15 kN and the compression interval 1.2 s. The behaviour of Cellactose differs from that of a mixture of spray-dried lactose and microcrystalline cellulose, supporting the manufacturer's claim that the co-processed product

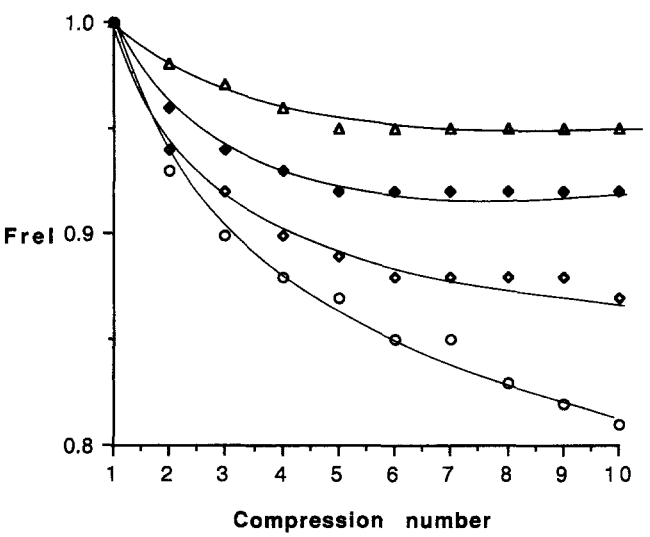

Fig. 3. The relationship between the number of compressions and Frel for Zeparox (○), Avicel (△), Cellactose (◇) and a mixture of Zeparox (75%) and Avicel (25%) (◆), all repeatedly compressed at 15 kN at intervals of 1.2 s.

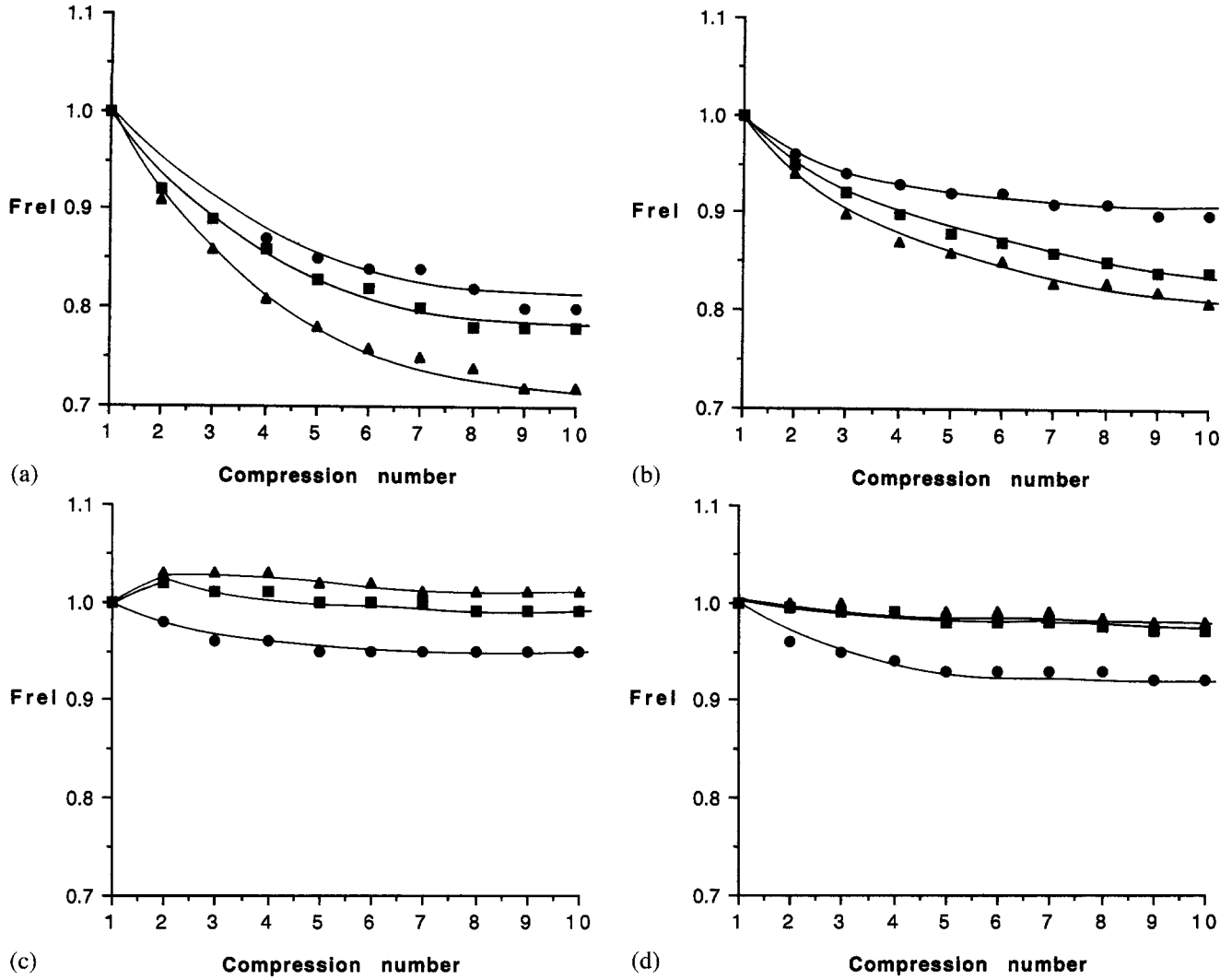

Fig. 4. The relationship between the number of compressions and Frel for Zeparox (a), Emcompress (b), Avicel (c) and Starch 1500 (d), all compressed at 15 kN and at three compression intervals (●, 1.2 s; ■, 1 min; ▲, 5 min).

possesses significantly different compression characteristics to a physical mixture of the two components. This finding agrees with the work of Belda and Mielck [7].

5. The effect of changing the interval between compressions

Fig. 4 shows the effect of altering the time interval between compressions from 1.2 s to 1 and 5 min, using a compressing force of 15 kN. Considerable differences in behaviour are apparent.

In the case of Zeparox (Fig. 4a), Frel decreases more as the time interval is increased. This means that with shorter time intervals, the descending punch meets a more resistant structure. After several minutes, however, this structure must have largely dissipated, as less resistance is encountered and Frel progressively decreases. The change in structure described above must be of a fairly transitory nature, since repeating these experiments at time intervals of 10 and 20 min gave essentially the same results as at 5 min.

Emcompress shows essentially the same behaviour (Fig. 4b). The behaviour of the other materials is quite different. With Avicel (Fig. 4c), after intervals of 1 and 5 min, the punch encounters a resistance which is greater than that encountered after 1.2 s, indicating that over these times, a structure develops by the formation of interparticulate bonds. Indeed with an interval of 5 min, Frel is actually greater than unity. Thus, on the second compression, a force is detected which is considerably greater than that on the first compression. In the case of Starch 1500, ratios of almost unity are achieved after intervals of 5 min, indicating the formation of a coherent structure. which if broken down by compression, reforms within 5 min (Fig. 4d).

If the difference in Frel at 1.2 s and 5 min is calculated for each substance, and the results arranged

Table 2
The change in tablet crushing strength after multiple compression (mean ± S.D., $n = 10$)

Powder	Crushing strength (kg)		Change in crushing strength (%)
	1 Compression	10 Compressions	
Time interval between compressions, 1.2 s			
Zeparox	7.65 ± 0.51	8.30 ± 0.32	+8.5
Emcompress	5.68 ± 0.25	6.03 ± 0.28	+6.2
Mannitol	8.04 ± 0.28	8.35 ± 0.32	+3.9
Cellactose	13.86 ± 0.60	14.40 ± 0.38	+3.9
Sodium chloride	6.63 ± 0.35	7.39 ± 0.38	+11.5
Starch 1500	10.85 ± 0.19	17.88 ± 0.44	+64.8
Avicel PH102	29.75 ± 0.47	32.54 ± 0.54	+9.4
Time interval between compressions, 1 min			
Zeparox	6.87 ± 0.44	5.95 ± 0.47	−13.4
Emcompress	5.64 ± 0.22	5.03 ± 0.38	−10.8
Mannitol	7.94 ± 0.32	7.44 ± 0.32	−6.3
Cellactose	13.90 ± 0.19	13.12 ± 0.57	−5.6
Sodium chloride	14.05 ± 0.76	14.76 ± 0.28	+5.1
Starch 1500	10.98 ± 0.38	12.63 ± 0.25	+15.0
Avicel PH102	29.38 ± 0.47	31.68 ± 0.57	+7.8
Time interval between compressions, 5 min			
Zeparox	6.67 ± 0.22	5.66 ± 0.28	−18.1
Emcompress	5.66 ± 0.22	5.14 ± 0.28	−9.2
Mannitol	8.09 ± 0.41	7.39 ± 0.44	−8.7
Cellactose	14.16 ± 0.82	12.08 ± 0.47	−10.5
Sodium chloride	13.91 ± 1.01	17.25 ± 0.82	+24.0
Starch 1500	11.38 ± 0.28	12.84 ± 0.63	+12.8
Avicel PH102	30.77 ± 0.47	31.32 ± 0.57	+1.8

in rank order, then the order is similar to that reported by Roberts and Rowe [8] in terms of strain rate sensitivity. This is therefore indicative of consolidation mechanism, in that substances which fragment show lower Frel values as the compression interval increases, whereas the opposite result is obtained with substances which deform.

6. The relationship between frel and tablet strength and porosity

The foregoing results seem to indicate the formation, however transitory, of a structure during compression, and it is therefore worth investigating if such a structure has an effect on the physical strength of the tablet. In no case could a progressive change in tablet thickness be detected. Zeparox shows the greatest change in Frel with repeated compression. By using the LVDT at its maximum sensitivity, the separation of the punches at maximum compression was found to change by < 5 μm, equivalent to a porosity change of $< 0.1\%$. Similarly attempts to detect changes in tablet dimensions after ejection were unsuccessful. As changes in tablet dimensions were not detectable, tablet strength is expressed in terms of crushing strength rather than tensile strength.

If porosity and hence interparticulate contact does not change, then changes in Frel must be due to changes in the strength of interparticulate bonds, and this should be reflected in the strength of the tablet. Evaluating changes in tablet strength due to repeated compression is complicated by the known fact that some tablets change strength with age, even after only one compression [9]. Thus with a tablet which has undergone ten compressions at 5 min intervals, 45 min have elapsed since the first compression. Therefore, a valid comparison is between a tablet compressed ten times at 5 min intervals with a tablet that has been compressed once and retained in the die for 45 min. Similarly tablets compressed ten times at 1 min intervals are compared with tablets allowed to stand for 9 min, and those compressed at 1.2 s intervals with those allowed to stand for 11 s.

As shown in Table 2, compressing a tablet ten times changes its strength, all changes being significant at $P = 0.05$. However, the magnitude of the strength change depends on the solid and on the time intervals between compressions.

When the compression interval is 1.2 s, all substances show an increase in strength, ranging from 3.86% for mannitol to 64.8% for Starch 1500. As the interval is increased to 1 min, four substances (Zeparox, Emcompress, mannitol and Cellactose) show a weakening,

whereas sodium chloride, Starch 1500 and Avicel show an increase in strength, but one which is less than that when the interval is 1.2 s. As the interval is lengthened to 5 min, the same four substances show a further reduction in breaking strength. Starch 1500 and Avicel still show an increase in strength, albeit smaller than that at 1.2 s and 1 min. Only sodium chloride shows a larger increase. However, this substance is exceptional in showing a much greater increase in strength with ageing than the other solids [9].

A possible explanation is that elastic recovery occurs with all seven solids to a greater or lesser extent, causing a weakening of interparticulate attractive forces, and a consequent reduction in tablet strength. However, this elastic behaviour is not instantaneous, and with a short time interval between compressions, does not occur to a significant extent before the next compressive force is applied. As the time intervals are prolonged, elastic expansion has more time to occur, with a resultant weakening of the tablet structure.

References

[1] S. Bessho, S. Tomioka, S. Ito, Compression of powder-like materials: IV repeated compression, Yakugaku Zasshi 89 (1969) 1130–1137.
[2] C.J. de Blaey, J. Polderman, Registration of force–displacement curves on a small computer, Pharm. Weekbl. 106 (1971) 57–65.
[3] N.A. Armstrong, N.M.A.H. Abourida, L. Krijgsman, Multiple compression of powders in a tablet press, J. Pharm. Pharmacol. 34 (1982) 9–13.
[4] D. Schierstedt, F. Muller, Ruckdehnung und relaxation wahrend der tablettierung mit exzentermaschinen, Pharm. Ind. 44 (1982) 932–937.
[5] N.A. Armstrong, Time-dependent factors involved in powder compression and tablet manufacture, Int. J. Pharm. 49 (1989) 1–13.
[6] N.A. Armstrong, L.P. Palfrey, The effect of machine speed on the consolidation of four directly-compressible tablet diluents, J. Pharm. Pharmacol. 41 (1989) 149–151.
[7] P.M. Belda, J.B. Mielck, The tabletting characteristics of Cellactose compared with mixtures of cellulose and lactose, Eur. J. Pharm. Biopharm. 42 (1996) 325–339.
[8] R.J. Roberts, R.C. Rowe, The effect of punch velocity on the compaction of a variety of materials, J. Pharm. Pharmacol. 37 (1985) 377–384.
[9] J.E. Rees, E. Shotten, Some observations on the ageing of sodium chloride compacts, J. Pharm. Pharmacol. 22 (1970) 17S–23S.