American Journal of Medical Sciences and Medicine, 2014, Vol. 2, No. 4, 71-76
Available online at http://pubs.sciepub.com/ajmsm/2/4/2
© Science and Education Publishing
DOI:10.12691/ajmsm-2-4-2

Technological Excipients of Tablets: Study of Flow Properties and Compaction Behavior

J. Conceição*, M. Estanqueiro, M. H. Amaral, J. P. Silva, J.M. Sousa Lobo

Research Centre for Pharmaceutical Sciences, Laboratory of Pharmaceutical Technology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
*Corresponding author: jmgmconceicao@ff.up.pt

Received September 04, 2014; Revised September 09, 2014; Accepted September 11, 2014

Abstract The physical properties of pharmaceutical powders/granules are very important in the development of oral solid dosage forms. The aim of this paper was, in a first stage, to carry out an evaluation of the flow properties (angle of repose, flow time, compaction capacity, compressibility index, Carr index and Hausner ratio) of technological or primary excipients of tablets (microcrystalline cellulose and dibasic calcium phosphate dihydrate) which behave differently during compaction, either pure and in binary mixtures, whose composition varied between 20% (w/w) and 80% (w/w) at intervals of 20% (w/w). In a second stage, using an instrumented eccentric tableting machine, energies and exerted forces during compaction of these materials were measured and the compressibility curves were registered. In addition, plasticity index and lubrication coefficient were calculated and weight uniformity, thickness, hardness and tensile strength of the manufactured tablets were also evaluated. The obtained results demonstrated that the binary mixtures and the pure excipients showed similar flow properties. On the other hand, the obtained tablets with the plastic excipient had lower values of exerted force by the upper punch and apparent net energy, and higher values of plasticity index and time periods of the force/time compression profiles.

Keywords: *excipients, binary mixtures, flowability, compaction, tablet instrumentation*

Cite This Article: J. Conceição, M. Estanqueiro, M. H. Amaral, J. P. Silva, and J.M. Sousa Lobo, "Technological Excipients of Tablets: Study of Flow Properties and Compaction Behavior." *American Journal of Medical Sciences and Medicine*, vol. 2, no. 4 (2014): 71-76. doi: 10.12691/ajmsm-2-4-2.

1. Introduction

Drug delivery systems are physical systems whose properties depend, among others, on the individual contributions of active pharmaceutical ingredient(s) and excipients. Some advantages like high-precision dosing, manufacturing efficiency, and patient compliance make tablets the most popular dosage forms [1]. Direct compression is the preferred method for the preparation of tablets but this process is extremely dependent on the powders characteristics and it is estimated that less than 20% of pharmaceutical materials can be compressed directly into tablets [2,3].

The propensity of powders to flow under given circumstances (flow ability) affects a large number of industrial applications [4]. In pharmaceutical industry, the knowledge of the compressibility characteristics of powders/granules is crucial in the development of oral solid dosage forms. However, these tests are usually performed with pure excipients and there are only a few published studies concerning mixtures of excipients.

Pharmaceutical powders are described as heterogeneous systems characterized by their particle size, morphology, density, specific area, roughness, porosity and interparticle forces [5]. The flow properties used in order to predict the compression ability of a powder and their criteria of analysis are the following [6-10]: angle of repose (< 25-30°), flow time (< 10 s/100 g), compaction capacity (CC) (<20 ml), compressibility index (CI) (< 15%), Carr index (C_rI) (< 15%) and Hausner ratio (HR) (< 1.25).

Officially the compression process was first started in 1843 by William Brockedon and since then, few changes were made [11]. Nevertheless, the knowledge of the process of tableting changed radically in the early 1950s, when Higuchi introduced the instrumented compression machines that allowed to measure the forces that intervened in the process [12,13]. The use of instrumented tablet machines is essential for basic research in compression physics, as it facilitates product development, optimization and scale up, and enables monitoring and control of production [14].

The production of tablets is a complex process involving many variables and a number of engineering principles [1]. According to Marshall, the set of phenomena that occur during the preparation of tablets is called compaction and is divided in two phases, namely, compression (reduction in bulk volume and particle rearrangement) and consolidation (increase in the mechanical strength and particle-particle interactions formation) [15].

Commonly, the applied force in materials compression exceeds the elastic limit, and fracture or plastic deformation is the main compression mechanisms [16,17]. Particles deformation can be reversible (elastic deformation) or irreversible (plastic deformation).

Force, time and displacement curves have usually been studied to acquire information on the compaction properties of pharmaceutical materials [18,19,20]. Mathematical equations, such as those of Heckel (1961), Cooper and Eaton (1962) and Kawakita and Lüdde (1970/1971), have been generated to describe force profiles [18,21,22,23].

The major objectives of this article were: (i) to evaluate the flow properties (angle of repose, flow time, CC, CI, C_rI and HR) of technological excipients used in tablets manufacturing which behave differently during compaction, either pure and in binary mixtures; (ii) to measure energies and exerted forces during compaction of these materials using an instrumented alternative machine DOTT Bonapace (model CPR-6) coupled to a computer; (iii) to calculate the plasticity index (PI), according to Stamm and Mathis, and the lubrication coefficient (R); (iv) to register the force/time, force/displacement, work/time, work/displacement and the position of the upper punch/time compression profiles; (v) to determine the periods (consolidation time, dwell time and contact time) of the force/time compression curves; (vi) to characterize the manufactured uncoated tablets (evaluation of weight uniformity, thickness, hardness and tensile strength).

2. Materials and Methods

2.1. Materials

The tested materials were microcrystalline cellulose (Avicel® PH-200 (AV), FMC Corporation, United States) and dibasic calcium phosphate dihydrate (Emcompress® (EMC), JRS Pharma, Germany).

2.2. Preparation of Powder Mixtures

Four binary mixtures of AV with EMC were prepared, whose composition varied between 20% (w/w) and 80% (w/w) at intervals of 20% (w/w). The mass of each powder mixture was 150 g and the mixture was performed in a Turbula WAB mixer (T2F, Switzerland) for 15 minutes. No lubricant was used.

2.3. Flow Properties Measurements

For each mixture and pure excipient, the apparent volumes (mean ± standard deviation (SD), n = 3) were evaluated using a Tap Density Tester (Electrolab ETD-1020, India) according to the European Pharmacopoeia 8 [8]. Afterwards, the values of apparent volume were used to calculate apparent density, CC, CI, C_rI and HR by the following equations(mean ± SD, n = 3) [6-10]:

$$d(g/ml) = \frac{m}{V} \quad (1)$$

$$CC(ml) = V_{10} - V_{500} \quad (2)$$

$$CI(\%) = \frac{(V_0 - V_{500})}{V_0} \times 100 \quad (3)$$

$$C_rI(\%) = \frac{(d_{500} - d_0)}{d_{500}} \times 100 \quad (4)$$

$$HR = \frac{d_{500}}{d_{10}} \quad (5)$$

where d is the apparent density, m is the weight of the sample, V is the apparent volume, V_0 is the apparent volume before tapping, $V_{10}$is the apparent volume after 10 taps, $V_{500}$is the apparent volume after 500 taps, d_0 is the apparent density before tapping, d_{10} is the apparent density after 10 taps, and d_{500} is the apparent density after 500 taps.

The angle of repose (mean ± SD, n = 3) and flow time (mean ± SD, n = 3) were evaluated with a granulate flow tester (Erweka GT, Germany) according to the European Pharmacopoeia 8 [8]. The funnel used can have different diameter apertures and the tested diameter was 10 ± 0.01 mm (nozzle 1) [8].

2.4. Compaction Procedures

Pure excipients and the binary mixtures were directly compressed and the study of the physicalparameters of compression (mean ± SD, n = 10) was performed using an instrumented alternative machine (DOTT Bonapace, model CPR-6, Italy) coupled to a computer. The volume of the compression chamber was kept constant for all samples. At the same time, the upper punch displacement was adjusted in order to obtain tablets with adequate hardness and this position was maintained during the experiments. The punches had 11 mm diameter with plane surface and all assays were done at room temperature and 60-70% relative humidity.

With software Cosalt-write, Cosalt-read and FIMA Compression Data Analysis, it was possible to measure the energies (total energy supplied by the upper punch (E_S); expansion energy (E_{EXP}), i.e., the energy lost by instantaneous elastic recovery; and apparent net energy (E_{LA}), i.e., the energy effectively expended in obtaining tablet) and forces during compaction (exerted force by the upper punch (F_S) and applied force in the lower punch (F_I)) and to register compression curves (force/time, force/displacement, work/time, work/displacement and the position of the upper punch/time). The time periods of the force/time cycle of compression were evaluated according to the following definitions [24,25]: dwell time is the time between the points corresponding to 90% maximum force; contact time with the compression force is the time between the points corresponding at 10% maximum force; and consolidation time corresponds to the necessary time to reach maximum force.

The PI, according to Stamm and Mathis, and the R were also evaluated using the following equations [26,27]:

$$PI(\%) = \frac{E_{LA}}{E_S} \times 100 = \frac{(E_S - E_{EXP})}{E_S} \times 100 \quad (6)$$

$$R = \frac{F_I}{F_S} \quad (7)$$

2.5. Characterization of the Tablets

Weight uniformity (mean ± SD, n = 10, analytical balance Mettler AE 200, Mettler Toledo, Switzerland), thickness immediately after ejection, after 1 hour and 15

days later (mean ± SD, n = 10, electronic digital micrometer, Mitutoyo, Japan) and hardness (mean ± SD, n = 10, Erweka TBH 28, Erweka GmbH, Germany) were evaluated in the obtained tablets.

Tensile strength (mean ± SD, n = 10) was assessed using equation 8, as it takes into account the dimensions of the tablets [28].

$$\text{Tensile strength} = \frac{2P}{\pi Dt} \quad (8)$$

where P is the hardness (N), D and t are the diameter (mm) and thickness (mm) of the tablet, respectively.

3. Results

In this work, two technological excipients of tablets commonly used in pharmaceutical industry, and their binary mixtures, that behave differently during compaction were studied, i.e., AV is an insoluble diluent with plastic behavior and EMC is an insoluble diluent with fragment able behavior. They are direct compression excipients and an important tool in formulation and design of tablets [19,29,30,31].

Table 1. Results of flow properties (mean ± SD, n =3), compaction behavior (mean ± SD, n = 10), weight uniformity, hardness, thickness and tensile strength of tablets (mean ± SD, n = 10)

Parameter		AV	Mixture 80:20	Mixture 60:40	Mixture 40:60	Mixture 20:80	EMC
CC (ml)		16 ± 1	14 ± 2	12 ± 0	11 ± 2	9 ± 0	8 ± 2
C_rI (%)		16.7 ± 0.4	15.5 ± 0.8	15.2 ± 0.9	14.7 ± 0.9	14.7 ± 0.4	16.2 ± 2.7
CI (%)		16.7 ± 0.4	15.5 ± 0.9	15.1 ± 0.8	14.7 ± 0.9	14.7 ± 0.4	16.2 ± 2.7
HR		1.08 ± 0.01	1.07 ± 0.01	1.07 ± 0	1.07 ± 0.02	1.08 ± 0	1.08 ± 0.02
Flow time (s/100 g)		20.3 ± 0.1	20.1 ± 0.2	16.0 ± 0	13.3 ± 0.1	10.4 ± 0	10.1 ± 0
Angle of repose (degrees)		39.3 ± 1.2	39.7 ± 0.8	40.7 ± 0.6	39.6 ± 0.9	39.9 ± 0.6	44.4 ± 0.2
F_S (N)		2501 ± 32	3391 ± 18	4594 ± 161	7289 ± 622	19795 ± 1114	-
F_I (N)		2060 ± 44	2879 ± 17	3731 ± 117	5778 ± 460	14475 ± 804	-
R		0.82 ± 0.01	0.85 ± 0.0	0.81 ± 0.01	0.79 ± 0.01	0.73 ± 0.0	-
E_S (J)		3.41 ± 0.05	4.19 ± 0.02	5.21 ± 0.17	6.96 ± 0.44	14.25 ± 0.79	-
E_{EXP} (J)		0.08 ± 0.01	0.10 ± 0.02	0.15 ± 0.01	0.24 ± 0.03	1.20 ± 0.16	-
E_{LA} (J)		3.33 ± 0.04	4.09 ± 0.02	5.06 ± 0.15	6.72 ± 0.43	13.05 ± 0.64	-
PI (%)		97.7 ± 0.3	97.6 ± 0.4	97.1 ± 0.1	96.6 ± 0.4	91.6 ± 0.7	-
Consolidation time (ms)		116.4 ± 0.4	116.2 ± 0.4	114.5 ± 0.5	109.3 ± 0.8	98.9 ± 1.9	-
Dwell time (ms)		39.1 ± 0.2	36.2 ± 0.2	34.1 ± 0.1	31.6 ± 0.3	29.4 ± 0.9	-
Contact time (ms)		177.9 ± 0.3	174.5 ± 0.4	169.7 ± 0.5	161.8 ± 0.8	152.5 ± 1.7	-
Weight (mg)		322 ± 2	371 ± 1	426 ± 4	505 ± 11	645 ± 9	-
Hardness (N)		75 ± 2	88 ± 2	93 ± 3	88 ± 5	84 ± 9	-
Tensile strength (N/mm^2)		1.13 ± 0.03	1.37 ± 0.03	1.46 ± 0.06	1.38 ± 0.08	1.29 ± 0.14	-
Thickness (mm)	0 minutes	3.833 ± 0.004	3.718 ± 0.005	3.686 ± 0.004	3.680 ± 0.005	3.774 ± 0.016	-
	1 hour	3.854 ± 0.003	3.729 ± 0.006	3.699 ± 0.003	3.687 ± 0.004	3.777 ± 0.015	-
	15 days	3.890 ± 0.004	3.754 ± 0.009	3.746 ± 0.004	3.724 ± 0.005	3.792 ± 0.017	-

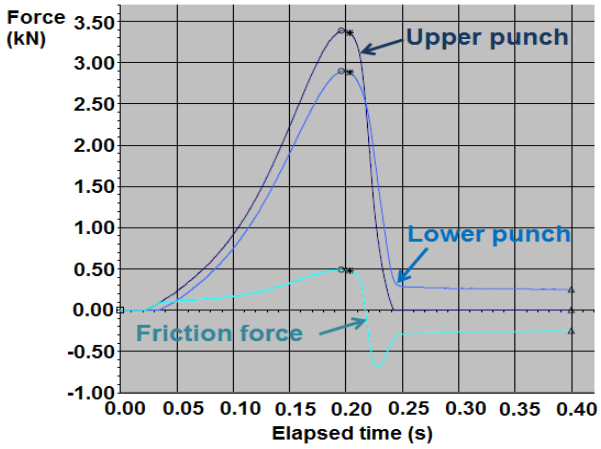

Figure 1. Force (kN)/time (s) compression profile obtained from one tablet of mixture 80:20

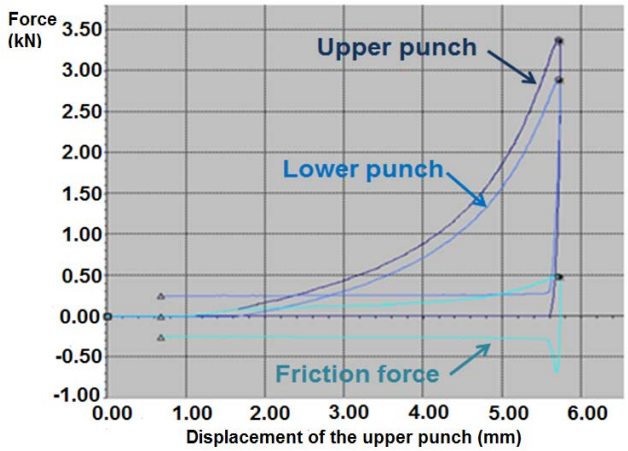

Figure 2. Force (kN)/displacement (mm) compression profile obtained from one tablet of mixture 80:20

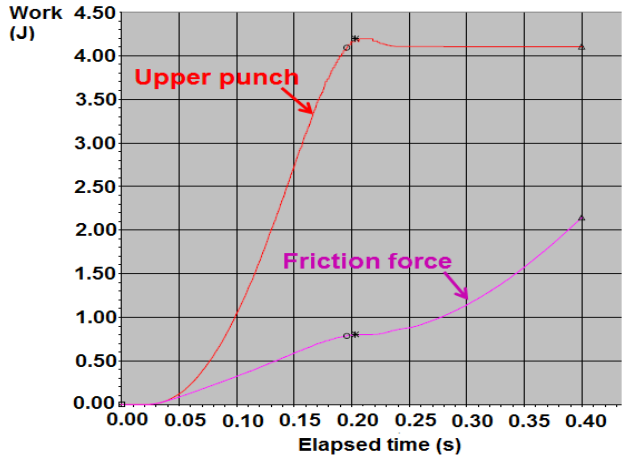

Figure 3. Work (J)/time (s) compression profile obtained from one tablet from mixture 80:20

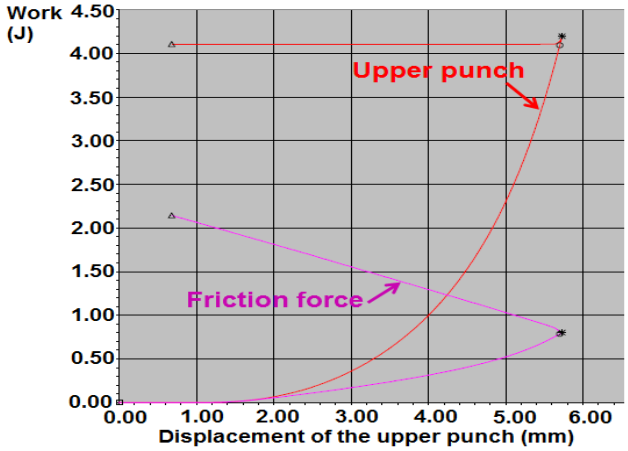

Figure 4. Work (J)/displacement (mm) compression profile obtained from one tablet from mixture 80:20

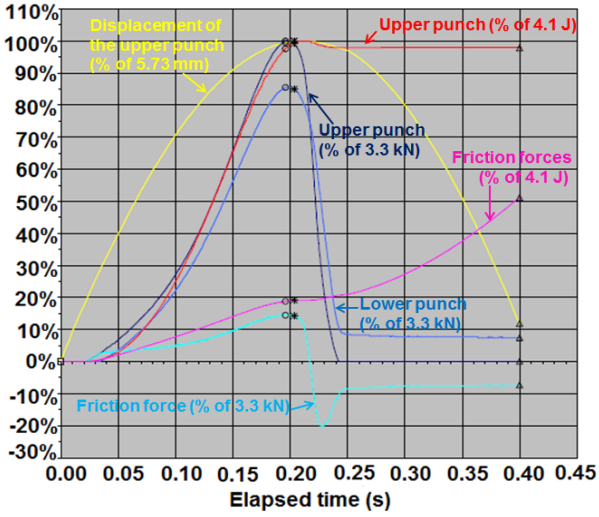

Figure 5. Compression profile obtained from one tablet of mixture 80:20

The obtained results of the flow properties (mean ± SD, n =3), compaction behavior (mean ± SD, n =10), weight uniformity, hardness, thickness immediately after ejection, after 1 hour and 15 days later, and tensile strength of tablets (mean ± SD, n =10) are shown in Table 1. Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6 and Figure 7 exhibit an example of recorded compression profile.

Uncoated tablets with acceptable physical properties were produced. But it was not possible to prepare tablets with EMC keeping constant the volume of the compression chamber and the upper punch displacement (conditions maintained constant during the experiments).

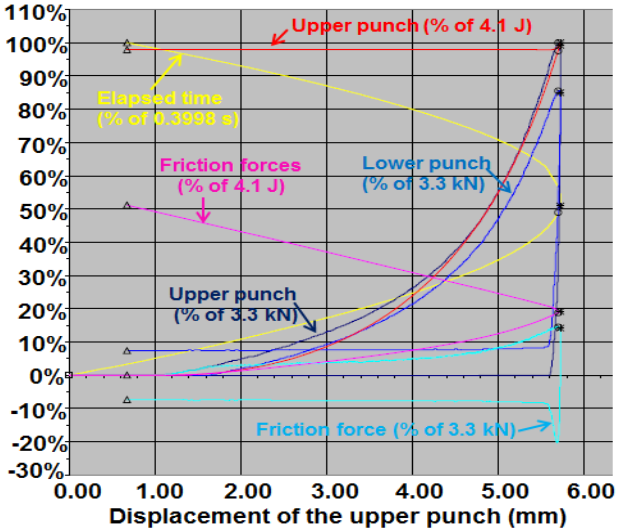

Figure 6. Compression profile obtained from one tablet of mixture 80:20

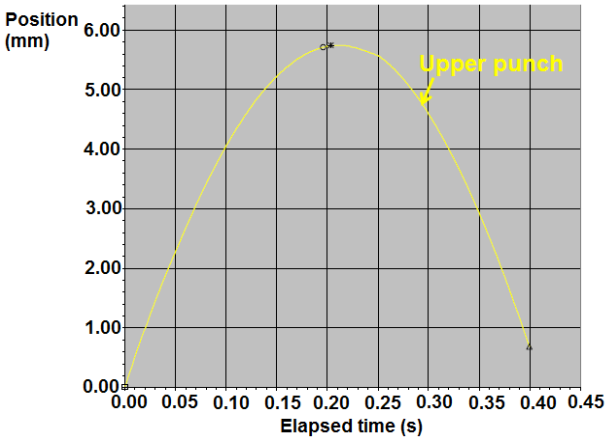

Figure 7. Position of the upper punch(mm)/time (s) compression profile obtained from one tablet of mixture 80:20

4. Discussion

Many researchers have attempted to study the compaction behavior and compressibility of binary mixtures of some pharmaceutical excipients during compression [19,32-36]. For instance, Busignies *et al.* [34] observed that the specific compaction energy was proportional to the mixture composition expressed in mass, but this was not the case for the specific expansion energy.

It can be seen from Table 1 that pure excipients and their binary mixtures presented similar CI and C_rI (<16.7%), CC (<20 ml), HR (<1.25) and angle of repose (39.3-44.4°) values. However, the flow time value determined with EMC was about half of the value obtained with AV. Increasing the amount of EMC decreased the flow time. Values of CI and C_rI below 15% indicate good flow properties but values above 25% mean poor flow [15], and values of HR of about 1.00–1.25 indicate free-flowing powder, 1.26–1.45 indicate poor flow, and >1.46 an extremely poor flow [8]. A value of angle of repose less than 30° usually indicates free

flowing material, up to 40° indicates reasonable flow potential, and above 50° means that the powder flows with great difficulty [9].

From the values of the F_S, it was possible to differentiate the tested materials. In this way, as the amount of EMC and the average weight of the tablets increased, the value of F_S also increased. Besides, as F_S increased, the E_{LA} also increased.

All the analyzed materials presented a value of R < 0.9. In a correctly lubricated pharmaceutical powder/granule, the R value is greater than 0.9 [27]. Values of R lower than 0.8 indicate an inadequate lubrication, as verified for mixtures 40:60 and 20:80, as expected due to the lack of lubricant [27].

All the obtained compaction curves showed the same configuration and Figures 1, 2,3, 4, 5, 6 and 7 illustrate an example. As far as the periods measured in the force/time compression curves are concerned, it was observed that they decreased when the amount of EMC increased.

The values of PI, calculated according to Stamm and Mathis, were high (> 91.6%) and similar for all the tested materials. AV presented the highest value (PI = 97.7%). As the amount of EMC in the binary mixtures increased, the PI decreased.

The mechanical strength of tablets is an important issue that affects, for example, further processing such as film-coating, packaging and encapsulation [37]. A consistent relationship between F_S and the tablets hardness was not observed. It is well known that the greater are the compaction forces used in tablets manufacturing, less porous and harder they are. The values of tensile strength ranged between 1.13-1.46 N/mm^2, and the tablets obtained from AV (< F_S value) showed lower tensile strength.

The tablets thickness is determined by die diameter, by amount of particulate material that performs it, by compaction characteristics of powders/granules and by applied force during compression [38]. Regarding the obtained results from thickness, the tablets showed a variation lower than 2% through analyzed time.

5. Conclusions

The technological excipients have an important role in the success of any pharmaceutical formulation, because they contribute, significantly, for the final characteristics of the drug product. In this way, the study of the compression physics of binary mixtures of excipients is very useful, since it allows analyzing the influence of the single materials and the mass proportion of each component in the mixture.

In this work, the compression ability and compaction behavior of AV and EMC and their binary mixtures were investigated. The outcomes demonstrated that the binary mixtures and the pure excipients showed similar flow properties. On the other hand, the obtained tablets with the plastic excipient (AV) had lower values of F_S and E_{LA}, and higher values of PI and time periods of the force/time compression profiles.

Statement of Competing Interests

The authors have no competing interests.

List of Abbreviations

AV - Avicel® PH-200
CC - Compaction capacity
CI - Compressibility index
C_rI - Carr index
E_{EXP} - Expansion energy
E_{LA} - Apparent net energy
EMC - Emcompress®
E_S- Total energy supplied by the upper punch
F_I - Applied force in the lower punch
F_S-Exerted force by the upper punch
HR - Hausner ratio
PI - Plasticity index
R- Lubricationcoefficient

References

[1] Patel, S., Kaushal A.M., Bansal A.K., "Compression physics in the formulation development of tablets", *Crit Rev Ther Drug Carrier Syst*, 23 (1). 1-65. 2006.

[2] Rojas, J., Buckner, I., Kumar, V., "Co-proccessed excipients with enhanced direct compression functionality for improved tableting performance", *Drug Dev Ind Pharm*, 38 (10). 1159-70. 2012.

[3] Gohel, M.C., Jogani, P.D., "A review of co-processed directly compressible excipients", *J Pharm Pharmaceut Sci*, 8 (1). 76-93. 2005.

[4] Santomaso, A., Lazzaro, P., Canu, P., "Powder flowability and density ratios: the impact of granules packing", *Chem Eng Sci*, 58 (13). 2857-74. 2003.

[5] Fatah, N., "Study and comparison of micronic and nanometric powders: Analysis of physical, flow and interparticle properties of powders", *Powder Technol*, 190 (1-2). 41-7. 2009.

[6] Carr, R.L., "Evaluating flow properties of solids", *Chem Eng*, 72. 163-8. 1965.

[7] Carr, R.L., "Powder and granule properties and mechanics", *Chem Eng*, 8. 13-88. 1976.

[8] *European Pharmacopoeia*, 8th ed., EDQM, Council of Europe, Strasbourg, 2014.

[9] Davies, P., "Oral solid dosage forms", in Gibson, M., *Pharmaceutical Preformulation and Formulation*, Interpharm, Colorado, 2001.

[10] Hausner, H.H., "Friction conditions in a mass of metal powder", *Int. J. Powder Metall*, 3. 7-13. 1967.

[11] Çelik, M., "The past, present and future of tableting technology", *Drug Dev Ind Pharm*, 22 (1). 1-10. 1996.

[12] Higuchi, T., Nelson, E., Busse, L.W., "The physics of tablet compression. III. Design and construction of an instrumented tableting machine", *J Am Pharm Assoc*, 43 (6). 344-8. 1954.

[13] Higuchi, T., *et al.*, "The physics of tablet compression. I. A preliminary report", *J Am Pharm Assoc*, 41 (2). 93-6. 1952.

[14] Doelker, E., Massuelle, D., "Benefits of die-wall instrumentation for research and development in tabletting", Eur J Pharm Biopharm, 58 (2). 427-44. 2004.

[15] Marshall, K., "Compression and consolidation of powdered solids", in Lachman, L., Lieberman, H.A., Kanig, J.L., *The Theory and Practice of Industrial Pharmacy*, 3rd ed., Lea & Febiger, 1986.

[16] Khossravi, D., Morehead, W.T., "Consolidation mechanisms of pharmaceutical solids: a multi-compression cycle approach", *Pharm Res*, 14 (8). 1039-45. 1997.

[17] Hiestand, E.N., *et al.*, "Physical processes of tableting", *J Pharm Sci*, 66 (4). 510-9. 1977.

[18] Lakio, S., *et al.*, "New insights into segregation during tabletting", *Int J Pharm*, 397 (1-2). 19-26. 2010.

[19] Schmidt, P.C., Leitritz, M., "Compression force/time-profiles of microcrystalline cellulose, dicalcium phosphate dihydrate and their binary mixtures - a critical consideration of experimental parameters", *Eur J Pharm Biopharm*, 44 (3). 303-13. 1997.

[20] Sousa Lobo, J.M., *Contribuição para o estudo da tecnologia de fabrico, estabilidade e biodisponibilidade de formas farmacêuticas contendo dipirona*, Porto, PhD Thesis, 1989.

[21] Denny, P.J., "Compaction equations: a comparison of the Heckel and Kawakita equations", *Powder Technol*, 127 (2). 162-72. 2002.

[22] Heckel, R.W., "Density-pressure relationship in powder compaction", *Transaction of the Metallurgical Society of AIME*, 221. 671-5. 1961.

[23] Kawakita, K., Lüdde, K.H., "Some considerations on powder compression equations", *Powder Technol*, 4 (2). 61-8. 1971.

[24] Levin, M., "Tablet Press Instrumentation", in *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, INC, New York, 2002.

[25] ones, T.M., "The physicochemical properties of starting materials used in tablet formulation", *Int J Pharm Tech Prod Manuf*, 2. 17-24. 1981.

[26] Stamm, A., Mathis, C., "Verpressbarkeit von festen Hilfsstoffen für Direkttablettierung", *Acta Pharm Technol*, 22. 7-16. 1976.

[27] Aulton, M.E., *The Design and Manufacture of Medicines*. Third ed., Churcill Livingstone, London, 2007.

[28] Fell, J.T., Newton, J.M., "Determination of tablet strength by the diametral-compression test", *J Pharm Sci*, 59 (5). 688-91. 1970.

[29] Wells, J.I., Langridge, J.R., "Dicalcium phosphate dihydrate-microcrystalline cellulose systems in direct compression tableting", *Int J Tech Prod Manuf*, 2. 1-8. 1981.

[30] Sousa Lobo, J.M., *et al.*, "Volume, flow and compression ability of microcrystalline cellulose and dibasic calcium phosphate in the presence of lubrificants", in *14th Pharmaceutical Technology Conference*, 1995.

[31] Khan, F., Pilpel, N., Ingham, S., "The effect of moisture on the density, compaction and tensile strength of microcrystalline cellulose", *Powder Technol*, 54 (3). 161-4. 1988.

[32] Kása, P., *et al.*, "Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression", *Chem Eng Process*, 48 (4). 859-63. 2009.

[33] Mazel, V., *et al.*, "Original predictive approach to the compressibility of pharmaceutical powder mixtures based on the Kawakita equation", *Int J Pharm*, 410 (1-2). 92-8. 2011.

[34] Busignies, V., *et al.*, "Compaction behaviour and new predictive approach to the compressibility of binary mixtures of pharmaceutical excipients", *Eur J Pharm Biopharm*, 64 (1). 66-74. 2006.

[35] Amin, M.C.I.M., Albawani, S.M., Amjad, M.W., "A comparative study of the compaction properties of binary and bilayer tablets of direct compression excipients", *Trop J Pharm Res*, 11 (4). 585-594. 2012.

[36] Conceição, J., *et al.*, "Binary Mixtures of Pharmaceutical Excipients: Evaluation of Flow Properties and Compaction Behaviour", in *6th International Congress on Pharmaceutical Engineering*, 2014.

[37] Podczeck, F., Drake, K.R., Newton, J.M., "Investigations into the tensile failure of doubly-convex cylindrical tablets under diametral loading using finite element methodology", *Int J Pharm*, 454 (1). 412-24. 2013.

[38] Allen, L.V., Popovich, N.G., Ansel, H.C., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*, Ninth ed, Lippincott Williams & Wilkins, 2011.