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Original Article

Development of tablet formulations of calcium carbonate by direct compression

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Abstract: Tablets are the most prescribed dosage form of pharmaceuticals due to their ease of administration, transportation, stability and low production cost. Tablets could be fabricated by direct compression which has fewer individual steps and thus is faster and less expensive than other granulation-based table fabrication processes. However, direct compression for tablets covering high drug dosage is challenging, since adequate flow and compressibility properties are difficult to achieve. The aim of this study was to obtain tablets containing 750 mg of calcium carbonate by direct compression. Calcium carbonate is used to treat and prevent diseases related to calcium deficiency and high quantities are necessary for meeting daily requirements of this nutrient. Different blends of excipients were prepared and evaluated in terms of flow and compressibility properties. Tablets were characterized by weight, hardness and friability, disintegration, dissolution, and unitary dose uniformity measurements. The final tablet formulation was in compliance with the requirements from Brazilian, British and the United States pharmacopeias, presenting satisfactory quality for further *in vivo* bioavailability studies and production at industrial scale.
Keywords: carbonate calcium, direct compression, pharmaceutical development, tablets.

Introduction

Calcium is a primordial electrolyte that plays roles in several biochemical-signaling pathways. Most of the human body cells have a set of calcium signaling tools, with many components combined that promote blood pressure regulation, blood coagulation, nerve impulse transmission, muscle contraction, and tissue resistance and integrity [1,2]. The recommended daily calcium intake of approximately 1000 mg/day prevents calcium deficiency in healthy adults with stable bone formation and resorption, but it should increase to 1200-1300 mg/day for proper bone development of adolescents, and for elderly due to bone loss and increased calcium reabsorption [3–6].

Calcium carbonate and calcium citrate are the most used salts for daily calcium supplementation [7,8]. Despite calcium carbonate is less soluble than calcium citrate their absorption profiles in humans are similar [9]. In addition, calcium carbonate has a higher percentage of calcium (40%) in relation to calcium citrate (21%), which implies in a smaller number of tablets that must be ingested to meet the daily calcium intake requirement, thus improving acceptability from users [10–12].

Supplementing diet with calcium tablets has become an important strategy to achieve the daily calcium requirements worldwide and, therefore, it is included in the World Health Organization Model List of

Essential Medicines, and adopted at the Brazilian version of this list [13,14].

Direct compression is among the industrial processes used for producing pharmaceutical tablets. It is one the most simple and advantageous processes since it consists of one compression step in which active principle and excipients are mixed without pre-formation of granules [15,16]. Direct compression is essentially affected by the properties of the components which should display high performance, quality, and consistency, but considering the scaled-up production of tablets, this method is time-saving and cheap, as it basically involves powder mixing and compression, thereby reducing losses and possible errors related to successive manipulation steps [17–19]. Therefore, the aim of this study was to produce 750 mg calcium carbonate tablets by direct compression. Different adjuvants were tested in order to enhance the compression efficiency.

Materials and Methods

Materials

The ingredients used in the tablet formulations (Table 1) were of pharmaceutical grade. Calcium carbonate (990.8 mg/g purity) and magnesium stearate were acquired from DEG, Carbosil DC90® (990.4 mg/g purity) from Erves Farmacêutica, starch 1500® (pregelatinized starch) from Colorcon, corn starch and 101 microcrystalline cellulose from Pharma Nostra, spray-dried lactose from Ciel, crospovidone from AISP, Explosol® from Embrafarma, Aerosil 200® from Henrifarma, and sodium lauryl sulfate from Emfal. All reagents and solvents used in the quality control analyses were of analytical grade.

Table 1 – Percentage composition of excipients in calcium carbonate tablets

Ingredients	F1	F2	F3	F4	F5
Starch 1500®	-	-	15	-	-
Corn starch	15	15	-	15	-
101 Microcrystalline cellulose	62	20	20	20	48
Spray-dried lactose	20	61	61	61	48
Crospovidone	-	3	3	-	-
Explosol®	2	-	-	3	3
Magnesium stearate	0.5	-	-	-	-
Aerosil 200®	0.5	-	-	-	-
Sodium lauryl sulfate	-	1	1	1	1
Tablet weight	1.5 g	1.5 g	1.5 g	1.5 g	1.0 g

Formulation Development

Five formulations of 750 mg calcium carbonate tablets were proposed (F1 to F5) to be prepared by direct compression at a pilot scale (Table 1). All formulations were prepared using Carbosil DC90® equivalent to 750 mg calcium carbonate.

Determination of Flow and Compressibility properties

Micromeritic properties of the raw materials (calcium carbonate and Carbosil DC90®) and powder mixtures (drug + excipients) were evaluated by flow, angle of repose, compressibility index (CI) and Hausner ratio (HR) determinations, as described in the British and United States pharmacopeias (Table 2) [20,21].

Table 2 – Analysis of the flow and compressibility of raw materials and mixtures of powders

Raw material/ Mixture	Flow ratio (g/s)	Angle of repose	CI (%)	HR
Calcium carbonate	0.88	34º	37	1.58
Carbosil DC90®	4.60	18º	8	1.09
F1	1.58	21º	8	1.08
F2	4.49	21º	15	1.13
F3	4.05	21º	11	1.11
F4	4.02	21º	12	1.14
F4T	1.39	21º	8	0.98
F5T	3.76	19º	10	1.11

Flow ratio was calculated by the weight variation per time unit of the powder mixture after passage through a funnel [22]. Angle of repose was also used as an indication of the powder flow capacity; this was determined by allowing an excess quantity of powder mixture to drain from a funnel. After formation of a powder cone on the base, the angle of repose was determined as the ratio between the cone height and the radius of the base.

CI and HR were calculated from the bulk density and tapped density of powder, measuring the volume of the initial unpacked powder and again after tapping the powder until no further volume changes occur, as follows:

$$HF = dt/db$$

$$CI\ (\%) = (db - dt) \times 100/dt$$

Production of pilot tablet lots

Calcium carbonate tablets were produced by direct compression. Briefly, all ingredients were weighed, sieved, and mixed in a twin shell blender (Powdermix, Brazil) in this order: Carbosil DC90®, 101 microcrystalline cellulose, spray-dried lactose, corn starch or Starch 1500®, Explosol® or crospovidone. The mixture was homogenized at 5.5 rpm for 30 minutes. Finally, Aerosil 200® and magnesium stearate or sodium lauryl sulfate was added to the mixture which was further homogenized for 10 minutes.

The tablets were compressed in an 8-station rotary compression machine (Stinfer STR-mini; São Paulo, Brazil), using a set of concave punches Stinfer STR-15 mm.

The compression pressure was set at 99,650 kgf and 1,000 tablets were produced in each pilot lot.

Characterizations of compressed tablets

Characterizations and quality analysis of the produced tablets were performed in accordance with the Brazilian, British and United States pharmacopeias [20,21,23]. Visual appearance, color, brightness, odor, and texture of each table were registered and a caliper rule (Digimess-PG2000; São Paulo, Brazil) was used to check the diameter and height of each tablet.

The mean table weight was determined from 20 individual measurements and a variation of ±5.0% was considered to be acceptable for the individual tablet units. Tablet breaking force, which is the force required to fracture a tablet, was determined from 10 tablets of each formulation using a durometer [20,21,23] (Nova Ética-298.0100; Vargem Grande Paulista, Brazil).

Friability measurements were conducted on 20 tablets of each formulation, which were weighed before and after being submitted to abrasion forces in a friabilator (Nova Ética-300; Vargem Grande Paulista, Brazil) for 4 min at 25 rpm. The powdered dust was removed before the tablets were weighed again, and weight loss percentage during testing was calculated. Tablets with friability less than or equal to 1.0% of their weight are considered acceptable [20,21,23].

Tablet disintegration time was measured on 6 tablets of each formulation using a disintegration apparatus (Nova Ética-301; Vargem Grande Paulista, Brazil). 700 mL of distilled water at 37 ± 1 ° C was used as a solvent and the test was conducted for 30 minutes. The time was recorded when all tablets left no material on the mesh [20,21,23].

Dissolution tests were performed on 6 tablets of each formulation using 900 mL of 0.1 M HCl solution at 37 ± 0.5 °C in a dissolution test apparatus (Nova Ética-299; Vargem Grande Paulista, Brazil). The USP Type II apparatus (paddle) was used at a rotation speed of 75 rpm. Samples were collected, filtered and analyzed for drug content determination. The tolerance for the labeled calcium carbonate amount dissolved after 30 minutes is of 75% (Q) [20,21,23].

Drug content was determined using the method proposed by Santana and colleagues [24], which is a variation of the monograph for calcium carbonate determination in the United States Pharmacopeia [21]. The method consists of performing a titration using 0.05 M edetate disodium volumetric solution and 150 mg hydroxy naphthol blue as an indicator until the solution presents a distinct blue color. The tablet was considered acceptable if the amount of calcium was between 90.0% and 110.0% with respect to the expected amount [20,21,23].

Uniformity of dosage units was assessed by the weight variation (WV) test. The amount of drug per unit was estimated from the results of the drug content test and individual weight measurements, assuming a homogeneous distribution of the active component in the tablet.

Acceptance value (AV) was calculated using the following equation:

$$AV = |M-X| + kS$$

where k is 2.4 while testing 10 tablets, S is the standard deviation of drug content assay values of 10 tablet units, and X is mean of the assay values. M =X when X value is between 98.5 - 101.5%. M = 98.5% if X value is below 98.5% and M =101.5% if X value is above 101.5%.

Data analysis

Statistical analyses were carried out using one-way analysis of variance followed by Tukey's test. Difference among mean values were considered to be statistically different for $p \leq 0.05$.

Results and Discussion

Flow and compressibility properties of active ingredients and formulations

Flow and compressibility properties of calcium carbonate and Carbosil DC90® were determined in order to select the best ingredient for the calcium carbonate tablets. As expected, the calcium carbonate powder exhibited a weak fluidity with a high CI [25], in addition to presenting a very low HR (1.46 to 1.59). As can be seen in Table 3, it is not interesting to use calcium carbonate in tablets produced by direct compression [20,21]. However, Carbosil DC90® showed high flow ratio, with excellent angle of repose, CI and HR. The presence of 10% starch in its composition with controlled granulometry enhanced flow and compressibility properties of calcium carbonate. Therefore, Carbosil DC90® was selected as the ingredient to be used in the tablet formulations.

Table 3 – Mean weight and variation of the tablets from the produced pilots

Pilot formulation	Mean weight (g)	Range of weight (g)	RSD (%)
F1	1.48	1.45 - 1.54	0.98
F2	1.53	1.52 - 1.55	0.65
F3	1.54	1.51 - 1.57	1.01
F4	1.47	1.45 - 1.54	0.94
F4T	1.51	1.50 - 1.55	0.54
F5T	1.00	0.98 - 1.02	0.83

Powder mixtures were evaluated in order to identify the formulation comprising the best characteristics of flow, density, and compaction for the direct compression tablet fabrication process. Formulations F1 to F4 were proposed with different compositions. Formulation F1 presented excellent angle of repose, CI and HR values, but the flow ratio was low (1.58 g/s).

Formulations F2 to F4 presented an excellent angle of repose, all below 30º, but CI and HR could not be considered excellent. Formulation F4 was further ground in a mortar, sieved through a 40 mesh drum sieve, with 420 µm opening and its properties were determined again (FAT). Clearly, F4T presented excellent angle of repose, CI and HR values, but again the flow ratio was low (1.39 g/s).

Finally, the concentration of the excipients was reduced, so that the tablet had a final mean weight of 1 g. This formulation was also ground and sieved, named F5T. This formulation presented excellent flow and compressibility characteristics and higher flow ratio (3.76 g/s).

Altogether, all the other formulations can also be considered adequate for tablet fabrication by direct compression.

Characterization of calcium carbonate tablets: Characteristics and weight variation

All tablets were homogeneous white, with characteristic brightness, smooth texture, odorless and with no break-mark. The tablet thickness was 4.0 ± 0.2 mm and the mean diameter was 15.1 ± 0.2 mm.

Formulations F1 to F4 had a theoretical weight of 1.5 g, while F5 was 1.0 g. Thus, weight variation was considered suitable if it ranged from 1.425 g to 1.575 g and from 950 mg to 1.05 g, respectively. As can be seen in Table 3, the mean weight was found to be near the theoretical value for all produced tablet pilots. Also, the minimum and maximum weights observed (Table 4) for the tablets in all pilots were within the range determined, indicating an acceptable weight variation. In addition, the relative standard deviation (RSD) of weight variation did not exceed 5%, thus the variation was also considered low.

Table 4 – Performance of the tablets in the tests of mechanical resistance and disintegration

Pilot formulation	Mean breaking force (kgf)	Friability (%)	Disintegration time
F1	6.3	20.7	27 s
F2	5.7	28.3	1.47 min
F3	4.7	55.6	1.48 min
F4	4.9	24.7	1.53 min
F4T	5.7	4.7	3.2 min
F5T	11.5	0.5	6 min

Mechanical resistance and disintegration

The results of mechanical resistance, tablet breaking force and friability percentage are described in Table 4. Tablets F1 to F4 showed low breaking force (4.9 to 6.3 kgf) and high friability (4.7 to 55%), while F5T showed the highest hardness (11.5 kgf) and low friability (0.5%). It is recommended that tablets do not present friability higher than 1.0% [20,21] then only tables F5T could be considered suitable with basis on this parameter.

One main factor determining the resistance of tablets to breaking forces is the compression pressure applied to the powder, which also directly influences the disintegration rate. Tablets should not ideally exhibit high friability so that they do not fragment into smaller pieces by friction during transportation.

Tablets that undergo high pressures during production may have adequate friability and hardness, but they may last too long times for disintegrating [26].

All tablet formulations disintegrated within a few minutes (Table 5). Considering that the general specification for disintegration of uncoated tablets is 30 minutes, all formulations were considered satisfactory. In addition, they presented lower disintegration time when compared with a previously developed oral calcium carbonate formulation [27].

Disintegration tests are important to assess the effect of processing variables on the biopharmaceutical properties of pharmaceutical tablets, as well as they serve as a control procedure for evaluating the quality reproducibility of the tablet during production. In this sense, These results were already expected, once tablets obtained by direct compression have better flow and cohesion properties, which allow direct compaction of drugs without previous granulation [16,28].

Table 5 – Percentage of calcium carbonate dissolved in the tablets

Replicate	% Dissolved
01	99.08
02	99.08
03	99.08
04	105.28
05	99.08
06	105.28
Mean	101.1 ± 3.2 %

Previous reports on development of calcium carbonate tablets by direct compression have focused in instantaneous disintegration and thus, oral dispersion tablets and effervescent tablets were developed and characterized. Although those tablets exhibited faster disintegration than the tablets developed in this study, the latter still displayed short disintegration times (less than six minutes), thus fulfilling the requirement stipulated by pharmacopoeias [29,30].

Dissolution, drug content, and uniformity of dosage units

Considering that formulations F1 to F4 were unsatisfactory in the friability test, only formulation F5T in the pilot was tested for dissolution, drug content and uniformity.

Among the 6 analyzed samples in the first stage, mean quantity dissolved was 101.1 ± 3.2 %, and each unit presented dissolution greater than Q + 5%, i.e, 80% of the labeled amount (Table 6).

Dissolution is the percentage of active compound released and dissolved in a determined medium, at a time, in this case, of 30 minutes. This is an *in vitro* physicochemical test used to estimate the *in vivo* dissolution profile. The use of inappropriate excipients entails inconsistent tablet weight, unsatisfactory tablet strength, lack of uniformity or segregation, and dissolution failure. Microcrystalline cellulose is generally considered a diluent with good dry-binding and self-disintegrating properties [31]. Once produced by direct compression, the tablets disintegrate into primary particles, rather than granules, providing an increase of surface area and consequently improving dissolution [19].

Assay for drug content in F5T pilot reported 102.96 ± 0.62 % of the expected amount, which is within the recommended range of 90.0 to 110.0% [21]. The uniformity of dosage units quantifies the active components in individual tablet units of the produced batch to verify whether this amount is uniform among them. This test was performed by the WV method for F5T pilot. The AV of the compressed tablet was found to be 10.34, below the limit of acceptance L1 = 15 [20,21,23].

Conclusion

The comparative analysis regarding the evaluation of different formulations for producing 750 mg calcium carbonate tablets by direct compression was proved to be very important for the selection of best adjuvants and their concentrations. These components resulted in tablet formulations with good flow and compression properties, especially F5T formulation. The final product developed, F5T, with a final tablet weight of 1.0 g, was found to meet the requirements from Brazilian, British and the United States pharmacopeias. It also displayed satisfactory quality for further *in vivo* bioavailability studies and production at industrial scale.

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Contribution of the Authors:

I.D.R.P.: analysis and interpretation of data; statistical analyses; drafting of manuscript;
I.C.C.B.: statistical analyses; drafting of manuscript;
G.M.C.P.S.: study conception and design; acquisition of data
G.C.: study conception and design; analysis and interpretation of data; statistical analyses; provision of reagents/resources; drafting of manuscript; critical revision of the intellectual content.

References

1. Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signalling. Nat Rev Mol Cell Biol 2000 Oct 1;1(1):11–21.

2. Orrenius S, Zhivotovsky B, Nicotera P. Calcium: Regulation of cell death: the calcium–apoptosis link. Nat Rev Mol Cell Biol 2003 Jul;4(7):552–565.

3. Buzinaro EF, Almeida RNA De, Mazeto GMFS. Biodisponibilidade do cálcio dietético. Arq Bras Endocrinol Metabol 2006 Oct;50(5):852–861.

4. Premaor MO, Brondani JE. Nutrição e saúde óssea: a importância do cálcio, fósforo, magnésio e proteínas. Rev da AMRIGS. 2016;60(8):253–263.

5. França NAGr, Martini LA. Cálcio. Funções Plenamente Reconhecidas de Nutrientes. Int Life Sci Inst do Bras 2014;1:1–24.

6. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J Clin Endocrinol Metab 2011;96(1):53–58.

7. Straub DA. Calcium Supplementation in Clinical Practice: A Review of Forms, Doses, and Indications. Nutr Clin Pract 2007;22(3):286–296.

8. Wang H, Bua P, Capodice J. A comparative study of calcium absorption following a single serving administration of calcium carbonate powder versus calcium citrate tablets in healthy premenopausal women. Food Nutr Res 2014;22(58):1–6.

9. Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of Calcium as the Carbonate and Citrate Salts, with Some Observations on Method Osteoporos Int 1999 Jan 1;9(1):19–23.

10. Gali JC. Osteoporose. Acta Ortopédica Bras 2001 Jun 29;9(2):53–62.

11. Hanzlik RP. Relative Bioavailability of Calcium from Calcium Formate, Calcium Citrate, and Calcium Carbonate. J Pharmacol Exp Ther 2005 Jan 28;313(3):1217–1222.

12. Pereira GAP, Genaro PS, Pinheiro MM, Szejnfeld VL, Martini LA. Cálcio dietético – estratégias para otimizar o consumo. Rev Bras Reumatol 2009;49(2).

13. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Assistência Farmacêutica e Insumos. Relação Nacional de Medicamentos Essenciais - RENAME 2014. 9. ed. Brasília: Ministério da Saúde, 2015.

14. WHO. World Health Organization. Model List of Essential Medicines. 2017.

15. Ofori-Kwakye K, Mfoafo KA, Kipo SL, Kuntworbe N, Boakye-Gyasi M El. Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. Saudi Pharm J 2016 Jan;24(1):82–91.

16. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline Cellulose, a Direct Compression Binder in a Quality by Design Environment-A Review. Int J Pharm 2014;473:64–72.

17. Rojas J, Buckner I, Kumar V. Co-proccessed excipients with enhanced direct compression functionality for improved tableting performance. Drug Dev Ind Pharm 2012;38(10):1159–1170.

18. Rocha J, Faculdade S, Anápolis A De, Cristina A, Faculdade F, Anápolis A De. Otimização do processo de compressão de comprimidos de hidroclorotiazida. Ens e Ciências Biol Agrárias e da Saúde. 2013;17(5):9–17.

19. Sausen TR, Mayorga P. Excipiente para a produção de comprimidos por compressão direta. Infarma - Ciências Farm 2013 Dec 30;25(4):199.

20. British Pharmacopoeia Commission. British Pharmacopoeia 2014. London: TSO; 2014.

21. United States Pharmacopeia and National Formulary (USP 38-NF 33). Rockville, MD: United States Pharmacopeial Convention; 2015.

22. Prista, L. V. N.; Alves, A. C.; Morgado R. Técnologia Farmacêutica. Lisboa: Fundação Calouste Gulbenkian; 2008.

23. ANVISA. Agência Nacional De Vigilância Sanitária. Farmacopeia Brasileira 5ª edição. Brasília: Editora Fiocruz; 2010.

24. Santana AKM, Nunes LCC, Medeiros FPM, Silva MJ, Lavra ZMM, Rolim-Neto PJ. Otimização e validação do método analítico volumétrico para quantificação do carbonato de cálcio. Rev Ciencias Farm Basica e Apl 2007;28(2):177–183.

25. Bacher C, Olsen PM, Bertelsen P, Kristensen J, Sonnergaard JM. Improving the compaction properties of roller compacted calcium carbonate. Int J Pharm 2007;342(1–2):115–123.

26. Osei-Yeboah F, Sun CC. Validation and applications of an expedited tablet friability method. Int J Pharm 2015;484(1–2):146–155.

27. Caiaffa MC, Martins NG. Desenvolvimento de comprimidos de carbonato de cálcio com base no delineamento estatístico fatorial fracionado. Rev Bras Farm 2004;85(1):19–22.

28. Toller AB, Schmidt CA. Excipientes à base de celulose e lactose para compressão direta. Discip Sci 2005;6(1):61–80.

29. Stirnimann T, Di Maiuta N, Gerard DE, Alles R, Huwyler J, Puchkov M. Functionalized calcium carbonate as a novel pharmaceutical excipient for the preparation of orally dispersible tablets. Pharm Res 2013;30(7):1915–1925.

30. Fausett H, Gayser C, Dash a K. Evaluation of quick disintegrating calcium carbonate tablets. AAPS PharmSciTech 2000;1(3):E20.

31. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment - A review. Int J Pharm 2014;473(1–2):64–72.