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Original Article

EVALUATION OF MECHANICAL STRENGTH AFTER COMPRESSION OF METFORMIN 500MG TABLETS PRODUCED BY DIFFERENT WET ROUTES

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ABSTRACT

Objective: This work evaluated the post-compression hardness gain of Metformin tablets made from two granulates of the same formulation, but with different formation principles, one by the fluidized bed and the other in a V-shaped mixer.

Methods: The base granulate for the production of the tablets was prepared using Metformin HCL as the main active ingredient. After compression, the prepared tablets were tested with different evaluation parameters like relative humidity, apparent and compacted density, granulometric dispersion, hardness, moisture content, and friability for complete characterization.

Results: All prepared samples were within the pre-established humidity ranges (MT1 = 3.31%, MT2 = 2.72%, MT3 = 1.73%, LF1 = 3.25%, LF2 = 2.43% and LF3 = 1.79%). The density determination showed that the granules produced in the fluidized bed are less dense than those of the V mixer. LF2 sample had an apparent density of 0.525 g/ml and a compacted density of 0.546 g/ml, while the MT2 sample had an apparent density of 0.711 g/ml and a compacted density of 0.738 g/ml, corroborating the greater porosity of granules produced in a fluidized bed. It was found that there is a difference in the increase in hardness between the two granulation methods. The tablets manufactured from the granules elaborated in a V-shaped mixer showed a greater gain in comparison with those produced in the fluid bed. The MT1 sample had the highest gain percentage, reaching 99.47%, 48 h after compression. The MT2 sample obtained, for the same time, 76.34%, at a much slower speed than MT1. As for the other samples, all increased between 24 and 42%. These results are justified by the migration of agglutination liquid that occurs during the drying step.

Conclusion: This work demonstrated that the product Metformin 500 mg tablet has increased hardness after compression, with most significance in the first hour after the procedure. It was possible to verify that the tablets made from the granules produced in a V-shaped mixer have a greater increase in hardness than those produced by the fluidized bed, in the same humidity range.

Keywords: Hardness, Post-compression, Povidone, Fluidized bed, V blender

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INTRODUCTION

Wet granulation is widely used in the pharmaceutical industry, to transform powder particles into solid aggregates, giving them greater density, compressibility, and mechanical resistance, better flow properties, as well as better homogeneity of the components, when comparing simple mixtures of powders [1-6].

Among the various technologies applied for the production of granules by the wet method, the fluidized bed is one of the most advantageous, since the mixing, granulation, and drying steps can be performed in a single equipment, continuously [7-10]. In this procedure, the powder particles are suspended by a rising air stream, receiving a jet of the agglutinating solution. The result of this technique is more porous granules since their densification occurs only by the action of capillary forces of the agglutinating solution liquid [11].

It is well known in the practice of industrial routine a granulation technique by using V-shaped mixers, where the dry mixture is mixed with the agglutinating solution and later drying in circulating air drying ovens. This is a much less costly technique than granulation and drying in a fluidized bed, leading to the formation of denser granules, since, besides the action of the capillary forces of the binder solution, the diffusion principle on which the equipment's operation is based, helps in the approximation of solid particles, resulting in greater density [12].

As the name implies, V-shaped mixers were originally designed to be used as mixers for solids and powders through convective movements of the material, producing a gentle and fluid mixture, moving equal portions of particles by gravitational force. The use of this equipment as granulators is still small compared to other granulation methods commonly used by the pharmaceutical industry [13]. This reflects a scarcity of research articles on the use of this equipment as granulators, which justifies our interest in studying this inexpensive method of obtaining granules within the manufacture [14].

During the follow-up of tablet compression processes within the manufacture, it was observed that some formulations that use granulation by the V mixer present the phenomenon of post-compression hardness gain. This phenomenon has already been observed by some authors, who relate this post-compression hardness gain to granules obtained by the wet method with the moisture of the granulate after drying [15]. Besides that, another interfering factor would be the water balance of the tablet with the environment, since losing moisture to the environment would cause an increase in hardness over time [16]. In addition to the granule formation process, it is also known that the moisture in the granules must be in an ideal working range in order to obtain adequate compaction properties [17, 18]. This is one of the major factors that interfere with the compression response parameters, such as hardness and friability.

The tests of mechanical resistance of hardness and friability are official within the legal context of the Brazilian Pharmacopeia, being these parameters for evaluation of the integral quality of the tablets. The hardness test determines the tablet's resistance to crushing or rupture under radial pressure. The hardness of a tablet is proportional to the compressive strength and inversely proportional to its porosity. The friability, on the other hand, allows determining the resistance of the tablets to abrasion when subjected to the action of specific equipment [19].

The formulation used in this work was Metformin 500 mg, which uses Polyvinylpyrrolidone (PVP) as a binder. This polymer is very soluble and can make weak bonds and hydrogen bridges with several substances that have hydrogen acceptor groups [20]. Also, because of its solubility, povidone may undergo migration along with the solvent during drying, which may be intergranular or intragranular migration [21].

Intergranular migration usually occurs in static bed drying, in which the solute passes from granule to granule until it reaches the top of the bed. Thus, part of the granules would have the binder on its surface and part would not. In compression, these granules with different amounts of binder on the surface, resulting in different interactions (binder-drug, drug-drug, drug-excipient), and from a binder-drug bond, solid bridges will be formed. This results in an increase in hardness even after the compression force has been applied [22].

Intragranular migration, in turn, occurs in fluidized bed drying processes, where the granule formation takes place more individually. Here, the migration of the solute results in a granule with the binder on the surface, making it more rigid and resistant to deformation, resulting in little or no variation in hardness [21]. Therefore, this paper aims to evaluate the influence of the granulation process, comparing fluidized bed and V-shaped mixer, and the influence of the moisture of the granulate itself in the increase of post-compression hardness in Metformin 500 mg tablets.

MATERIALS AND METHODS

Granules production–formulation

The internal formulation phase comprises the active ingredient, Metformin Hydrochloride (Alcon Biosciences), cornstarch (Ingredion Brasil), colloidal silicon dioxide (Cabot GmbH), and povidone-PVP K30 (BASF SE). Purified water was used as a solvent in the granulation. In the external phase, magnesium stearate (Peter Greven Asia Sdn Bhd) and sodium starch glycolate (Itacel Farmoquimica Ltda) were used. As it is a formulation used by a commercial company, quantities cannot be reported in this work to respect confidentiality contracts.

Fluidized bed granulation

The production of the granules was carried out in a Comasa fluidized bed (SK developer) in sufficient quantity for the production of 1.5 kg of granules, which followed the steps of sieving, in 1.0 mm sieve, dry mixture followed by granulation and drying. In all stages, an average flow rate was used, with a high application rate in the granulation stage. The inlet temperature used for mixing and granulation was 40 ˚C and for drying it was 50 ˚C. The granulate was divided into 3 parts, forming the samples LF1, LF2, and LF3; each one was dried to the following humidity ranges:

a) LF1: 2.9–3.3% b) LF2: 2.2–2.6% c) LF3 1.5–1.8%

After reaching the humidity ranges, the granules were calibrated in a granulator (Comil), at 350 RPM, in a 2.0 mm sieve, mixed manually with the external phase ingredients, and taken for compression.

Granulation by V mixer

The production of the granules in the V-mixer (Lawes) used enough supplies to produce 5 kg of granules, which followed the steps: sieving, in 1.0 mm sieve, dry mix followed by wet mix. The dry mixture was carried out at the speed of 8 RPM, for 5 min. The binder solution was divided into parts and the mixture was added sequentially, at 8 RPM, for 5 min. After wet mixing the granulate was divided into 3 equal parts, forming the samples MT1, MT2, and MT3. Each part was dried in a forced-air circulation oven at a temperature of 50 ˚C until the following humidity ranges were reached:

a) MT1: 2.9–3.3% b) MT2: 2.2–2.6% c) MT3: 1.5–1.8%

After reaching the humidity ranges, the granules were calibrated in a granulator (Comil), at 350 RPM, in a 2.0 mm sieve, mixed manually with the external phase ingredients, and taken for compression.

Determination of the relative humidity of the granulate

Relative humidity was determined by a halogen lamp moisture analyzer (Mettler-Toledo HB43-S), using 5.000 g for the analysis, at 60 ˚C [23].

Apparent and compacted density test

After calibration, approximately 10 g of the granulate was weighed in a 50 ml graduated cylinder and the apparent volume was measured. After tapping the bottom of the graduated cylinder 100 times against a soft, solid surface, the compacted volume was also measured following the standards preconized by the Brazilian Pharmacopoeia [19]. In both cases, the weight value was divided by the volumes obtained to determine the apparent and compacted densities (g/ml). The granules of the MT2 and LF2 samples were used, as they have moisture in the intermediate range (2.2–2.6%), being evaluated with the best ones for the analysis.

Particle size dispersion test

The used sieves (Mesh 12, 25, 45, 60, 80, and 120), were weighed and stacked in a decreasing way, from the smallest to the largest mesh, and were coupled to the vibrating table. [24] Approximately 100 g of sample was deposited in the system and the equipment was activated, at intensity 10, for 20 min. After 20 min, the sieves were weighed to obtain the mass retained in each sieve. For the test, the granules of samples MT2 and LF2 were also used, as they have humidity in the intermediate range, between 2.2 to 2.6%.

Compression

The compression was effected in a Fette 102i rotary tablet press, with 8 stations, using a 12 mm circular punch and a speed of 37 RPM. The tablets should reach an average weight of 596 mg (±5%), with an initial hardness between 5.5 and 6.5 kp. All samples were stored in plastic bags and kept in an environment of controlled temperature and humidity at 25±5 ˚C and humidity<60%, following the same specifications of the production area.

Hardness analysis

The analyzes were performed by determining the average hardness of 10 tablets at 0h, 1h, 12h, 24h, and 48h after compression to assess the product's increased hardness profile. These analyzes were carried out with the tablets obtained with the granules, both from the fluidized bed (LF1, LF2, and LF3) and from the V mixer (MT1, MT2, and MT3), in all established moisture ranges, following the analysis standards established by the Brazilian Pharmacopoeia [19]. A durometer (Erweka THB 125) was used for the essays.

Friability analysis

Friability was measured at 0h, 1h, 12h, 24h, and 48h after compression. The tests were carried out with the tablets obtained with the granules, both from the fluidized bed (LF1, LF2, and LF3), and from the V mixer (MT1, MT2, and MT3), in all established humidity ranges, following the analysis standards established by the Brazilian Pharmacopoeia [19]. An Erweka TAR 120/220 friabilometer was used and a precision scale (Mettler-Toledo AL204) was used for the analyzes.

Moisture evaluation

For this test, 10 units were macerated with the aid of mortar and pestle, and the humidity of the powder was determined by a halogen lamp moisture analyzer, using 5.000 g, at 60 ˚C, at 0 h, 1 h, 12 h, 24 h, and 48 h after compression, to check the relationship between the final humidity of the tablet and the increase in post-compression hardness. All humidity was determined by a halogen lamp moisture analyzer (Mettler-Toledo HB43-S) [23].

RESULTS AND DISCUSSION

All samples (MT1, MT2, MT3, LF1, LF2 and LF3) were within the pre-established humidity ranges, being: MT1=3.31%, MT2=2.72%, MT3=1.73%, LF1=3.25%, LF2=2.43% and LF3=1.79%. Thus, after reaching the determined humidity, the granules were calibrated in a 2.0 mm sieve and the external phase was added. Then, the granulometric distribution analysis was performed, and the result is shown in fig. 1.

The granulometric profiles of both granules are similar, with a slight difference in the 25 mesh sieve, in which the granules produced in V mixer obtained a higher percentage of retention in comparison with the granules produced in the fluidized bed. Besides, the collecting

pan, which keeps fine particles with a diameter of less than 120 mesh, showed a higher percentage of retention in the fluidized bed granules. Such results indicate that the fluidized bed produces finer granules than the V mixer. The density determination showed that the granules produced in the fluidized bed are less dense than those of the V mixer, since the LF2 sample had an apparent density of 0.525 g/ml and compacted density of 0.546 g/ml, while the MT2 sample had an apparent density of 0.711 g/ml and compacted density of 0.738 g/ml. As already mentioned, this result corroborates the greater porosity of the granules produced in the fluidized bed.

After the compression step, all the resulting tablets had an average weight between 594.14 mg and 616.00 mg, being within the pre-established range of 596.00±5%. Also, all tests had an initial hardness between 5.5 and 6.5 kp. The hardness gain tests revealed that all tests obtained the highest percentage of gain in the first hour after compression, as shown in table 1.

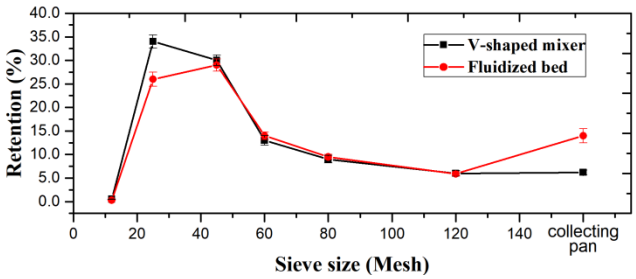

Fig. 1: Comparison between the granulometric profiles of the granules produced by V-shaped mixer and Fluidized bed. Maximum SD V-shaped mixer (±1.40, n=3); Fluidized bed (±1.51, n=3)

Table 1: Comparative data between hardnesses at time 0 h, 1 h, 12 h, 24 h, and 48 h. Comparison of hardness gain percentage in comparison with 0 h time

Sample	Hardness								
	0 h	1 h		12 h		24 h		48 h	
	kp	kp	%	kp	%	kp	%	kp	%
MT 1	5.70±0.36	10.12±1.03	77.54	10.10±0.97	77.19	10.27±0.69	80.18	11.37±0.89	99.47
MT 2	6.55±0.25	9.13±0.67	39.39	9.79±0.23	49.01	10.07±1.12	53.34	11.55±1.23	76.34
MT 3	6.04±0.46	7.90±0.45	30.79	8.84±0.34	46.36	8.78±0.23	45.36	8.35±0,48	38.25
LF 1	5.73±0.23	7.34±0.14	28.10	8.15±0.61	42.26	8.52±0.74	48.69	8.15±0.58	42.23
LF 2	6.29±0.34	8.22±0.87	30.68	8.07±0.89	28.30	8.47±0.99	34.66	8.87±0,23	41.02
LF 3	6.55±0.20	7.62±0.23	16.34	8.82±0.91	34.66	8.47±0.56	29.31	8.16±0.40	24.58

Number of experiments; n=10, results are expressed as mean±SD

The MT1 sample had the highest gain percentage, reaching 99.47%, 48 h after compression. The MT2 sample got, after 48 h, 76.34%, at a much slower speed than MT1, which obtained this value in the first hour of analysis. As for the other samples, all increased between 24 and 42%. These results are justified by the migration of agglutination liquid that occurs during drying. As previously mentioned, the samples produced in V mixer and dried in the oven generate granules with unequal amounts of agglutination that, first, promote the formation of the tablet by agglutination-drug bonds. From this approximation of the granules, solid bridges are formed, giving more rigidity and resistance to the pill. Meanwhile, samples from the fluidized bed generate granules that have a large amount of agglutinating-agglutinating bonds, with little space for forming solid bridges. The MT3 sample, despite being produced in the same condition as MT1 and MT2, did not have a similar gain percentage as the other two because they have very low humidity, which gives more stiffness to the granules. For the same reason, LF3 also got a lower increase when compared to LF1 and LF2, as can be seen in fig. 2. Analyzes performed after 48 h did not obtain significant results of increased hardness, therefore, they were disregarded in this work.

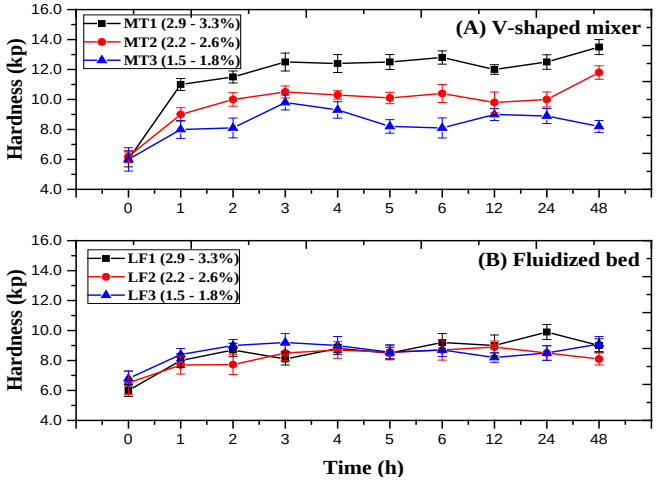

Fig. 2: Comparison of post-compression hardness increase of granules obtained by V-shaped mixer (A) and fluidized bed (B). Maximum SD (A) V-shaped mixer (±0.78, n=10); (B) Fluidized bed (±0.67, n=10)

In fig. 3 we can see that in the same humidity ranges, the granules produced in a V mixer have a more evident hardness increase than those of the fluidized bed, according to the phenomena previously explained.

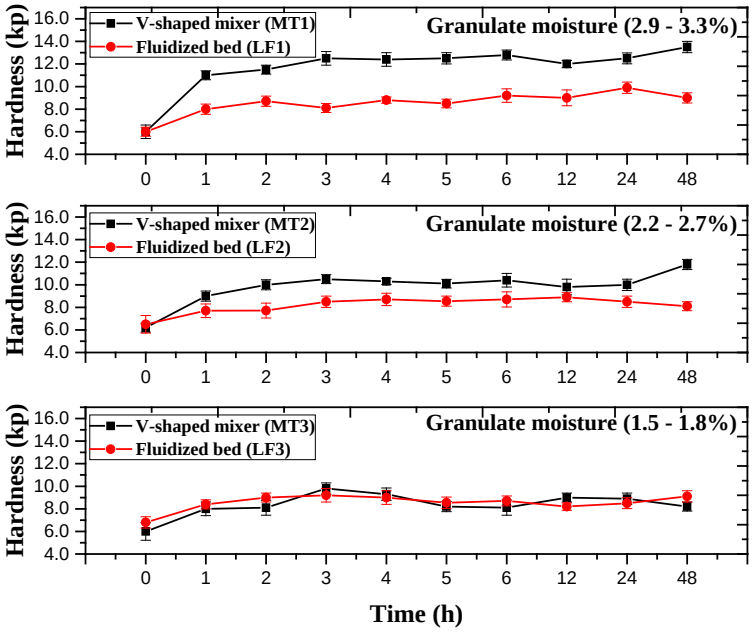

Fig. 3: Comparison of the post-compression hardness increase between V-shaped mixer and fluidized bed with the same humidity range. Maximum SD V-shaped mixer (±0.78, n=10); Fluidized bed (±0.67, n=10)

In the friability assessments, as seen in table 2, we found that MT1 has the lowest friability among all samples, both initially and throughout the analysis times. The MT3 and LF3 samples, which had granular moisture in the lower range, between 1.5 to 1.8%, obtained the highest friability values, being even outside the specification of the Brazilian Pharmacopeia [19], which defines that the values should not be greater than 1.5%. In the analyzes, these samples presented tablets with a high incidence of chipped edges, in addition to units with capping and broken tablets. The cause of these events is related to the mass moisture itself since a very low humidity tends to form porous and friable tablets, with low mechanical resistance [25, 26].

Table 2: Comparative data between friability at time 0h, 1 h, 12 h, 24 h, and 48 h

Sample	Friability (%)				
	0 h	1 h	12 h	24 h	48 h
MT 1	0.338±0.076	0.216±0.055	0.369±0.044	0.299±0.012	0.132±0.060
MT 2	0.430±0.089	0.146±0.041	0.302±0.051	0.352±0.039	0.218±0.034
MT 3	3.736±0.239	3.376±0.359	0.825±0.038	0.805±0.067	0.534±0.065
LF 1	0.557±0.062	0.413±0.067	0.208±0.085	0.232±0.041	0.226±0.092
LF 2	1.155±0.588	0.979±0.107	0.667±0.088	0.701±0.048	0.542±0.085
LF 3	6.146±0.827	1.983±0.588	0.815±0.067	1.070±0.075	0.794±0.057

Number of experiments; n=20, results are expressed as mean±SD

When comparing samples from the same humidity range, such as MT1 and LF1, we find that samples produced in the V-shaped mixer have lower friability than samples produced in the fluidized bed. This is due to the principle of the formation of granules. The granules produced in a fluidized bed rely only on the cohesive forces of the agglutination solution, forming less dense and consequently more friable granules. While the granules produced by the V mixer, besides the cohesion forces, have a greater approximation of the particles because of the diffusion promoted by the equipment, resulting in denser granules [27]. In the MT3 and LF3 samples, the 1 h analyzes do not respond to this pattern, with the mixer friability being greater than that of the fluidized bed. However, the final values remained in the standard of the other tests.

According to the moisture analysis carried out, the humidity variation during the 48 h verified was between 0.10 and 0.23%, for all samples. However, the uncertainty of the humidity balance used in this work is 0.20% [23]. Therefore, we verified that the granular humidity was not an interfering factor in the increase of post-compression hardness.

CONCLUSION

This work demonstrated that the product Metformin 500 mg tablets have increased post-compression hardness, with greater significance in the first hour after the process. It was possible to verify that the tablets made from the granules produced in a V-shaped mixer have a greater increase in hardness than those produced by the fluidized bed, in the same humidity range. This occurs because of the mechanisms of agglutination liquid migration induced by drying, which are intergranular migration and intragranular migration, respectively. It was also observed that in the lowest humidity range, between 1.5 to 1.8%, the MT3 and LF3 samples had similar results of hardness and friability, because in this humidity range the granules become rigid, suffering little deformation, producing porous and friable tablets. Regarding the

humidity of the tablets, we found that it did not change during the analysis time, so it did not influence the increase in hardness.

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Nil

AUTHORS CONTRIBUTIONS

Natália do Nascimento performed experiments, analyzed data, and co-wrote the paper. Emerson Boldo supervised the research and co-wrote the paper.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of the paper.

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