COMPARATIVE STUDY AMONG DIFFERENT TECHNIQUES TO IMPROVE THE PHYSICAL AND TECHNICAL PROPERTIES PREVAILING TO COMPRESSION OF POORLY FLOWING AND HIGHLY COHESIVE DRUG

Khalid M. El-Say[1*], Tamer A. Refaey[2], Ahmed M. Samy[1], Alia A. Badawy[3]
[1] Department of Pharmaceutics and Industrial pharmacy, Faculty of pharmacy, Al-Azhar University, Egypt.
[2] Production supervisor in Egyptian International Pharmaceutical Industries Co. (EIPICO), A.R.E. Egypt.
[3] Department of Pharmaceutics and Industrial pharmacy, Faculty of pharmacy, Cairo University Egypt.
***Email:** elsaykhalid@yahoo.com

ABSTRACT

The objective of this study was directed to improve the physical and technical properties of poorly flowing and highly cohesive drugs to solve the most important problem that affects tablet manufacture. Bezafibrate is a typical member of drugs which exhibit drawbacks or problems under handling. It has very poor flowability, mixing, and compression characteristics due to its highly cohesive behavior. The physical and technical properties of the bezafibrate powder alone during pre-formulation processing were evaluated through particle size analysis and flow properties. Also, in attempt to improve the flowability, bezafibrate was dry coated by different percentages of excipients such as Avicel PH 101, maize starch, lactose monohydrate, starch 1500, lactose monohydrate D.C, Aerosil 200, talc and magnesium stearate. However, the high values of Hausner ratio, Carr's index, angle of repose and absence of flow of powder from a hopper indicated poor flowability of the coated powder. Thermal analysis by differential scanning calorimetery (DSC) indicated that no interaction exists between bezafibrate and any of the tested excipients of the suggested formula. Alternatively, the flow and compression properties of bezafibrate were improved by wet granulation either manually or using high-shear mixer granulator. The prepared granules were evaluated for flow characteristics and then compressed into tablets that were characterized for tablets parameters. Interestingly, manual granulation technique of bezafibrate yielded spheroid granules with better micromeritic parameters including suitable mean size, narrow size distribution, low percentage of lumps, low percentage of fines, and no sticking to the wall of bowl. Finally, the tabletting process showed low values of ejection forces, good tablet properties (weight uniformity, hardness, thickness, friability, and disintegration) and no sticking to machinery tools, indicating good compressibility of the prepared formula.

Keywords: poorly flowing drug, compression, highly cohesive drug.

1. INTRODUCTION

Bezafibrate (BZ), a fibric acid derivative, is a lipid regulating drug. It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias, including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias.[1] The usual dose is 200 mg three times daily by mouth taken with or after food. BZ and other fibrates reduce triglycerides by lowering the concentration of very-low-density lipoprotein (VLDL). They reduce low-density lipoprotein (LDL)-cholesterol to a lesser extent, although the effect is variable, and may also increase high-density lipoprotein (HDL)-cholesterol. [2]

Powder flowability is one of the key parameters in the pharmaceutical tabletting process. The flowability is affected by both the particles properties and the tabletting equipment characteristics. Of the most important problems which affect the tablet manufacture specially BZ are the cohesive and adhesive properties that lead to poor flow, de-mixing and stickiness of material to the machinery parts of compression machine causing friction during the compression process, and producing undesirable tablet properties. These undesirable properties should be avoided by ensuring that the powder possesses adequate physical and technical properties needed for the production of smooth and strong tablets. Recently, several formulation approaches have been used to enhance the flow properties of highly cohesive drugs.

Of such trials, the effect of particle properties on the flowability of ibuprofen which has a needle shaped morphology. The flowability of ibuprofen size fractions was studied in detail using two flow measurement methods[3]. The separated fractions were also compared to magnesium stearate lubricated ibuprofen and its size fractions. The flowability of ibuprofen was significantly affected by both the particle size and size distribution. The flowability increases significantly with the increase in particle size for ibuprofen powders with narrow size distributions. In addition, admixing magnesium stearate to ibuprofen not only increases the flow function of the powder, but also reduces the internal friction angle.

Also, reported improvement of the flowability of three different drug powders namely micronized acetaminophen, levalbuterol tartarate, and didesmethylsibutramine tartarate using small amounts of lubricants, glidants, and other additives, both individually and in combination. Such additives are intimately mixed using a laboratory-scale V-blender with an intensifier bar.[4]

In addition, spherical crystallization (SC) was carried out for preparation of carbamazepine (CBZ) agglomerates to improve micrometric properties as well as dissolution behavior in comparison to conventional drug crystals[5]. Also, a cohesive lactose monohydrate powder was processed in either a tumbling blender or an intensive mechanical processor with either magnesium stearate or fumed silica. The untreated lactose sample exhibited very poor powder flow. Only limited improvements in powder flowability were indicated after the tumbling blending, intensive mechanical processing with the fumed silica or without additives. However, the intensive mechanical processing of the lactose sample with magnesium stearate demonstrated exceptionally large increases in both poured and tapped density as well as notable improvements in all powder flowability indicators examined[6].

One of the most applicable approaches to improve powder flowability is granulation. The general reasons of granulation are to prepare uniform mixtures that do not separate, improve the compression characteristics of the drug, control the drug release, reduce dust, and improve the appearance of the tablet[7]. In particular, wet granulation is a process in which the solid fine particles are bound together into agglomerates by agitation, kneading and laying in the presence of binding liquid to produce wet strength granules that have good tendency to compressibility[8]. Nevertheless, the wet granulation process offers several advantages particularly improving the cohesiveness and compressibility of powders and obtaining suitable flow and compression of drugs having high dosage, poor flow and/or compressibility[9].

Fibrates especially BZ are the drugs of choice for treating hyperlipidemic subjects with type III hyperlipoproteinemia as well as subjects with severe hypertriglyceridemia who are at risk for pancreatitis. Moreover, fibrates appear to have an important role in subjects with high triglycerides and low HDL-C levels associated with the metabolic syndrome or type 2 diabetes mellitus[10]. However, BZ is a typical member of drugs which exhibit drawbacks or problems under handling. It has very poor flowability, mixing, and compression characteristics due to its high cohesive behavior. So, the objective of this study was concerned with the improvement of the flowability and compressibility of BZ powder prevailing to direct compression process. This would also enhance its therapeutic usefulness.

2. MATERIALS AND METHODS

2.1. Materials:

BZ (BP07), from Dolder, (Swizerland); lactose monohydrate, 200 Mesh, (BP07), DMV, (Newzeland); microcrystalline cellulose (Avicel PH 101) (NF22), FMC, (Ireland); lactose D.C., from DMV international, (Germany); maize starch, from Roquette, (France); starch 1500, from Colorcon, (Italy); talc powder purified, from Tardy, (France); hydroxypropylmethylcellulose 2910 (Methocel E5) (USP27), from Colorcon, (England); polyvinylpyrrolidone (plasdone XL) (NF22) (ISP, USP); colloidal silicon dioxide (Aerosil 200) (USP27), from Evonik, (Germany); magnesium stearate (NF22), from Mollink Covidier, (England); methanol, from Brentagg, (Newzeland); sodium phosphate monobasic, and sodium phosphate dibasic from El-Nasr pharmaceutical chemicals (Egypt).

All the above materials were in analytical grade and were used without further purification.

2.2. Methods:

2.2.1. Thermal analysis of BZ and tablet excipients using DSC:

In thermal methods of analysis, a property of an analyte is studied as function of externally applied temperature[11]. From the most common thermal methods applied in pharmaceutical sciences is differential scanning calorimetry (DSC). DSC records the heat flow in and out the sample. Thus, it can be used to analyse endothermic (melting, boiling, sublimation, vaporization, desolvation, glass transitions, chemical degradation, etc.) and exothermic (crystallization, oxidative decomposition) events[12, 13].

The possible interaction between BZ and the selected excipients was tested by utilization of differential scanning calorimetry (DSC, Perkin-Elmer, USA). Aliquot samples of pure BZ and each of the tested excipients were placed in the instrument and analyzed. When melting occured, the temperature difference between the sample and reference was transformed into a heat flow (dq/dt) which was translated to peak shown in chart. The possible interaction could be indicated by comparing difference between the programmed and the actual temperature of the sample.

2.2.2. Micromeretic evaluation of BZ alone and BZ dry coated with different excipients:

Suitable amount of sieved BZ powder alone as well as dry coated known amount of BZ powder, with different excipients in different percentages, were evaluated for the following:

2.2.2.1. Particle size analysis:

The size distribution of BZ powder was performed using sieve analyzer. Series of 6 standard sieves in the range of 1000 - 100 µm were used. A sample of about 100 g was vibrated by a vibratory test sieve shaker at high amplitude for 10 minutes, after that, the fraction retained on each sieve was weighed[14]. Lumps (> 500 µm), fines (< 100 µm), the mean particles (500 - 100 µm), geometric mean diameter (d_{geo}), and geometric standard deviation (S_{geo}) were determined and the results were interpreted.

2.2.2.2. Determination of flow properties:

The flow properties were described through the following methods:

2.2.2.2.1. Direct flow rate method (g/s):

Flow rate was determined using an Erweka GDT flow rate tester with a funnel of the following dimensions: internal diameter at the top equals 6.5 cm and internal diameter of the efflux tube equals 9 mm. A sample of 20 g was used and the time of flow was recorded starting from inlet to outlet of powder.

2.2.2.2.2. Indirect methods:

2.2.2.2.2.1. Bulk density and tapped density method:

The bulk (D_B) and tapped (D_T) densities were determined using measuring cylinder tapping procedure. A sample of about 50 g of BZ powder was weighed and introduced into a 100 ml-graduated cylinder, tapping was performed till a constant volume was reached and the final volume of the sample was measured. Initial (fluff) and tapped densities of each sample were determined by dividing the weight of the sample in grams by the initial and final volume, respectively according to USP[15] as the bulk density (D_B) = Weight / Volume (W/V) before tapping and the tapped density (D_T) = Weight / Volume (W/V) after tapping. From the obtained results, both Hausner ratio and Carr's index were calculated as follows: Hausner ratio (H) = D_T / D_B, and Carr's index = (D_T – D_B) / D_T × 100.

2.2.2.2.2.2. Angle of repose method:

Angle of repose is one of the measures[16] of flow properties of powders and it is measured through a "free flowing method"[17] by Erweka Flowmeter. The angle of repose was calculated by a simple geometry from the base and height of the conical heap formed. The diameter of base (D) and the height of the formed conical heap (h) were measured and utilized in calculation of the angle of repose according to the following equation: $\tan \theta = 2h / D$.

2.2.3. Preparation of BZ tablets by direct compression

The suggested formula for BZ tablets is displayed in table (1). BZ tablets were prepared by direct compression technique using HPMC as a dry binder. The basic experiment was carried out by dry coating of sieved BZ powder with Aerosil 200 in a plastic bag for 3 minutes, after that, lactose D.C., HPMC, Plasdone, and magnesium stearate were added with mixing after each addition. HPMC percentage was used in 1, 3, and 5, and compensated by a corresponding variation in lactose D.C. percentage to keep the total formula weight of 97.5 g (300 tablets). The prepared formula was evaluated for micromeretics as described before and the obtained results were displayed in tables (2 and 3). The prepared powder was directly compressed into tablets using a rotary tablet machine (Korsch XL 100, Germany), equipped with sensors for measuring pre-compression force, main compression force for upper punches, lower punches and ejection forces, with an 11mm concave punch. The machine speed was set to 20 rpm, pre-compression 5 KN and main compression force 10 KN. The produced tablets were evaluated for compression characteristics and the results were interpreted. Tools (upper and lower punches) and tablets were visually inspected for presence of sticking, picking or filming.

Table 1: Formulation ingredients of BZ tablets

Ingredient	Weight per one tablet (mg)	Weight per 1000 tablets (g)	Weight per 3000 tablets (g)	Percent
BZ	200	200	600	61.530
Aerosil 200	1.950	1.950	5.850	0.600
Lactose monohydrate	4.387	4.387	13.162	1.350
HPMC E5	9.750	9.750	29.250	3.000
Plasdone K30	16.250	16.250	48.750	5.000
Magnesium stearate	4.875	4.875	14.625	1.500
Avicel PH 101	87.815	87.815	263.445	27.020
Total weight	325	325	975	100.000

2.2.4. Preparation and evaluation of BZ granules:

The basic experiment for wet granulation of BZ powder was carried out by dry coating of BZ with Aerosil 200 in a plastic bag for 3 minutes. After that, lactose monohydrate, Avicel PH 101, Plasdone were added and the mixing was performed for 3 minutes. The powder blend, batch size for 1000 tablets, was granulated by hand while batch size for 3000 tablets, was granulated mechanically using high shear-mixer granulator, both with HPMC (20% solution) to produce a wet mass which was passed through sieve 800 µm – USP, the mass was dried in hot air oven till moisture content; 0.5 – 1.0%. The prepared granules were homogenized through 500 µm sieve and evaluated for micromeretics and flow properties. The frequency distribution data for the size of BZ granules are represented in table (4) and the flow properties are represented in table (5).

2.2.5. Preparation of BZ tablets after granulation:

Magnesium stearate was added to the sieved granules and mixed. The finished formula was compressed using a compaction machine (Korsch XL 100, with an 11mm concave punch). The tablets were prepared under different compression forces (5, 10, 15, and 20 KN), and

evaluated for compression characteristics (ejection force, weight variation, thickness, hardness, friability %, and disintegration time). The pre-compression and main compression were recorded and the results were interpreted (tables 6, 7).

2.2.6. Evaluation of BZ tablets

The following tests were performed to evaluate the tablets:

2.2.6.1. Visual inspection

The machinery tools (punches and dies) were inspected for sticking, picking or filming and also tablets were inspected for tablet drawbacks.

2.2.6.2. Ejection force

Ejection force of prepared BZ tablets was determined through the values shown by the computerized program of the compression machine under a wide range of compression forces.

2.2.6.3. Uniformity of dosage unites (weight variation)

Twenty tablets were individually weighed, the average weight was determined and then the relative standard deviation (RSD) was calculated. The limit is 325 mg ± 5 %. No more than two tablets deviate from this range and non deviates by more than double this limit[18].

2.2.6.4. Tablet thickness

Tablet thickness was measured using dial thickness gauge, (Mitutoyo, Japan). Thickness measurement was performed directly after compression process (thickness at zero time) and 48 hours after compression.

2.2.6.5. Hardness of tablets

The hardness of tablets was determined using 4M tablet hardness tester (Schleuniger, Switzerland). The average of 12 determinations for tablets prepared at each compression force and the relation between hardness and compression force is graphically represented in figure (11).

2.2.6.6. Friability of tablets

Friability of the tablets prepared by wet granulation at different compression forces was determined using an Erweka Friabilator, type PTF1 (Pharmatest, Hainburg, Germany). In each run 20 tablets were carefully dedusted, weighed and rotated in the tester 100 times at 25 rpm, then the tablets were dedusted and weighed again. The friability of tablets was determined as percentage loss in weight according to the following equation: Friability % (% loss in weight) = $(W_1 - W_2) / W_1 \times 100$

2.2.6.7. Disintegration time

Disintegration time for BZ tablets compressed at different compression forces was determined by disintegration apparatus (Pharmatest, Germany). Six tablets were placed in six tubes of the basket and the apparatus was operated using water as the immersion fluid maintained at 37 ± 2°C. The tablets were observed and the time taken for complete disintegration of all tablets was determined. The test was performed three times and was met if not less than 16 of the total of 18 tablets tested were disintegrated[19].

3. RESULTS AND DISCUSSION

3.1. Thermal analysis of BZ and excipients using DSC:

The unchanged peak and melting point of BZ shown in figures (1- 6) indicate no interaction exists between BZ and any of the tested excipients (lactose monohydrate, HPMC E5, Avicel PH 101, Plasdone K30, and magnesium stearate) indicating the compatibility of the drug with its excipients.

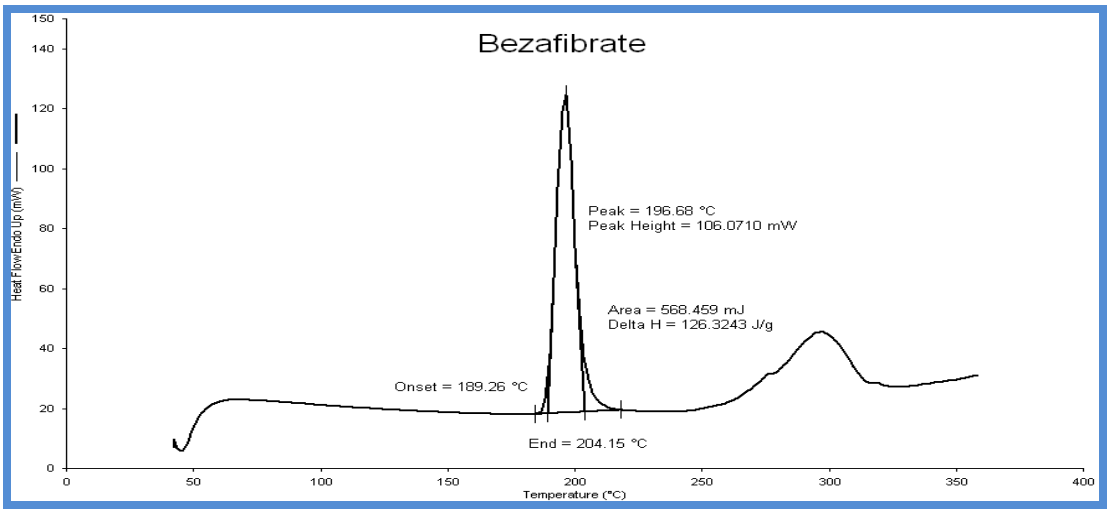

Figure 1: Thermal investigation of a pure BZ

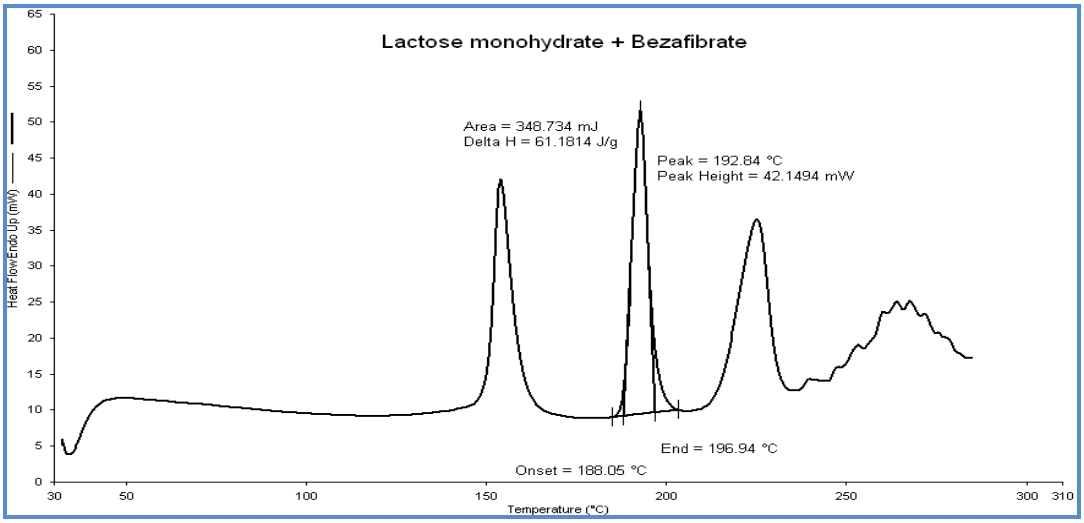

Figure 2: Thermal investigation of BZ with lactose monohydrate

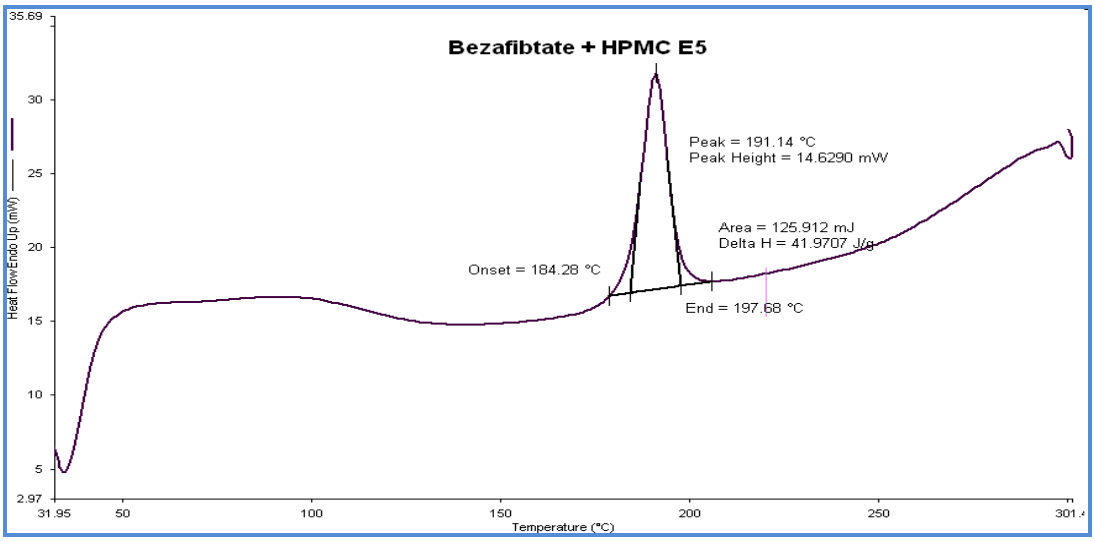

Figure 3: Thermal investigation of BZ with HPMC

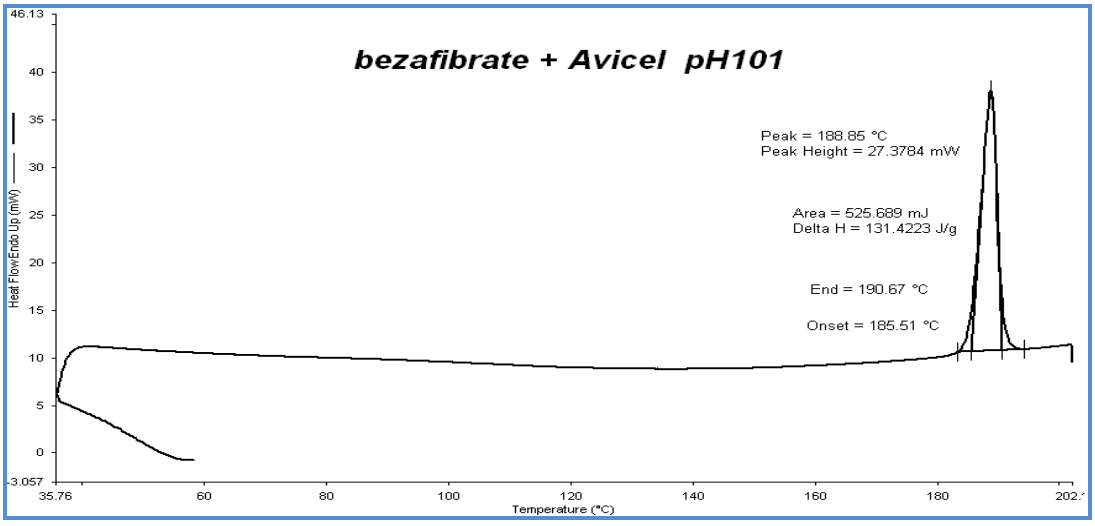

Figure 4: Thermal investigation of BZ with Avicel PH 101

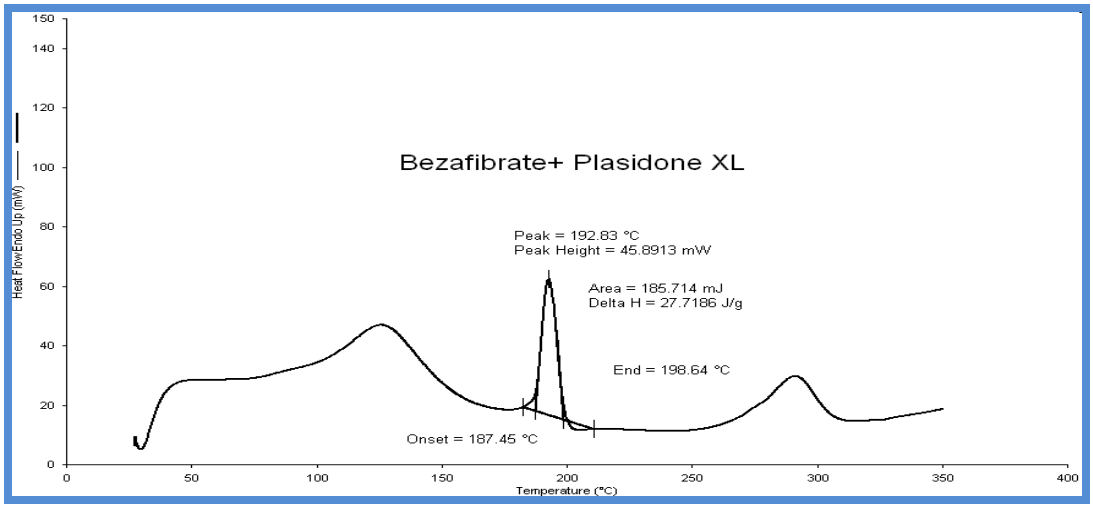

Figure 5: Thermal investigation of BZ with Plasdone XL

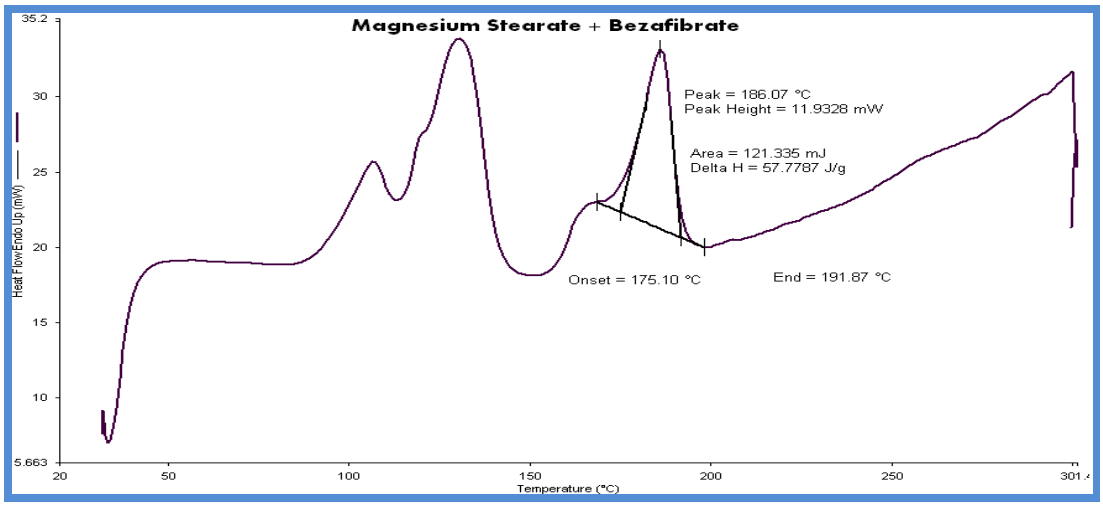

Figure 6: Thermal investigation of BZ with magnesium stearate

Table 2: Frequency distribution data for particle size of pure BZ powder and prepared formula for direct compression with different % of HPMC

Particle size range (µm)	Particle size mean (µm)	Frequency %			
		BZ alone	Formula with 1% HPMC	Formula with 3% HPMC	Formula with 5% HPMC
1000 - 800	900	0	0	0	0
800 - 500	650	0	0	0	0
500 - 425	462.5	2.6	3	2.04	2
425 - 325	370	12	12.7	11.7	13
315 - 200	257.5	14.3	15.4	14.2	17.3
200 - 100	150	27.1	25.1	26.4	22.4
100 - 0	50	44	44.1	45.6	45.3
% Lumps (> 500 µm)		0	0	0	0
% Mean (500-100 µm)		56	56.1	54.4	54.7
% Fines (< 100 µm)		44	44.1	45.6	45.3
(d_{geo})		315 µm	325 µm	311 µm	298 µm
(S_{geo})		16.315	16.047	16.796	16.316

3.2. Characterization of BZ powder and suggested formula for direct compression

Table (2) shows the frequency distribution data of pure BZ powder as the following: The size distribution can be specified simply by just two values; the geometric mean diameter (d_{geo}) equal 315 µm and the geometric standard deviation (S_{geo}) equal 16.315. From the observed data, wide particle size distribution in irregular agreement indicated from the high value of S_{geo}, as prescribed with Kinget and Kemel[20], 56 % mean particles (500 - 100 µm), and 44 % fines (< 100 µm) are shown, as well as adhesion of powder to sieves indicating the cohesive properties of BZ powder.

Also, Table (2) illustrates the frequency distribution data for the prepared formula for direct compression of BZ using 1, 3, and 5 % HPMC. The resulted data show high percent of fines, low geometric mean diameter (d_{geo}), high geometric standard deviation (S_{geo}), and wide particle size distribution in irregular agreement, as well as adhesion of powder to sieves indicating the cohesive properties of the prepared formula.

The flow properties of BZ powder are illustrated in table (3). As observed in the table, the powder has low bulk density, high difference between bulk and tapped density as indicated by Hausner ratio which equal 1.69, (cohesive powders show Hausner ratio values greater than 1.6)[21], high Carr's index value (40 %). It has been reported that it must not be more than 21%[9]. In addition the powder does not flow from flowmeter, this may be related to the cohesive properties of the powder[22]. So, BZ powder has extremely poor flowing characteristics (very cohesive powder).

Also, the flow properties of the powder of the suggested formula for direct compression has high Hausner ratio, high Carr's index values, and does not flow from flowmeter, so the prepared powder could be described as have poor flowability and cohesive properties. So, sticking in the upper/lower punches and dies was shown. The prepared powder is highly adhesive to machinery tools. The compressed tablets show high ejection force, indicating its cohesive nature of the prepared formula and show weight variation, indicating the poor flowability of the prepared formula.

Table 3: Flow properties of BZ powder and prepared formula for direct compression with different % of HPMC

Parameter	BZ alone	Formula with 1% HPMC	Formula with 3% HPMC	Formula with 5% HPMC
Bulk density (g/ml)	0.422	0.425	0.439	0.460
Tapped density (g/ml)	0.715	0.695	0.702	0.720
Carr's index (%)	40.959	38	37	36
Hausner ratio	1.694	1.635	1.599	1.565

Table 4: Frequency distribution data for the size of BZ granules prepared by wet granulation using manual and mechanical methods

Particle size range (µm)	Particle size mean (µm)	Frequency %	
		Manual granules	Mechanical granules
1000 – 800	900	1.41	0
800 – 500	650	8.75	0
500 – 425	462.5	12.07	4
425 – 325	370	15.49	10
315 – 200	257.5	18.42	14
200 – 100	150	18.71	28
100 – 0	50	25.15	44
% Lumps (> 500 µm)		10.16	0
% Mean (500-100 µm)		64.69	56
% Fines (< 100 µm)		25.15	44
(d_{geo})		527 µm	390 µm
(S_{geo})		7.67	16.3

3.3. Micromeretic evaluation of BZ granules

Table (4) and figures (7 and 8) show the frequency distribution data of the BZ granules prepared manually and mechanically. From observed data, the percentage of lumps, fines, and mean granules size is 10.16, 25.15, and 64.69, respectively, the geometric mean diameter (d_{geo}) is 527 µm, and the geometric standard deviation (S_{geo}) is 7.67. The resulted data indicates a narrow granule size distribution in a good agreement with the previous finding being the flowability increases significantly with the increase in particle size specially for powders with narrow size distributions. On the contrary, the frequency

distribution data of the BZ granules prepared with high-shear mixer granulator observed that, lumps are absent, the percentage of fines and mean granules is 44 and 56, respectively, led to decreases in the geometric mean diameter (d_{geo}) is 390 µm and the geometric standard deviation (S_{geo}) is 16.3 that deteriorate the flowability of the granules.

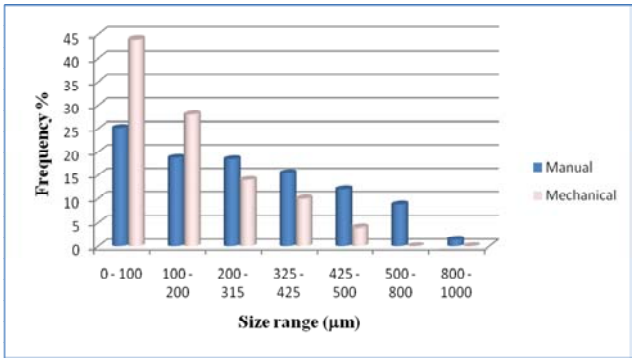

Figure 7: Particle size distribution of the prepared manual and mechanical granules

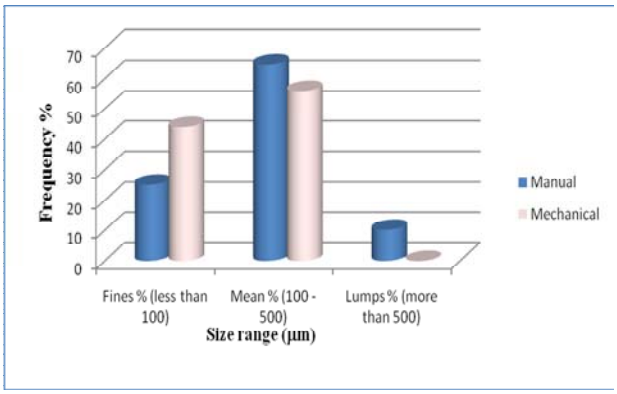

Figure 8: Percentage of the fines, mean, and lumps of the prepared manual and mechanical granules

The flow properties of the BZ granules are illustrated in table (5) and figures (9 and 10). From observed data, Hausner ratio was 1.32, Carr's index was 24.4 %, angle of repose was 16° and the granules flow freely from a hopper (7 g/sec) for granules prepared manually. On the other hand, the flow parameters of granules prepared by high shear-mixer granulator were Hausner ratio was 1.44, Carr's index was 30 %, angle of repose was 27°, and the flow rate is 3.5 g/sec indicating lower flowability of the prepared granules by this technique than the manual one. In general, powders with angles greater than 60° would have unsatisfactory flow properties, while powders with minimum angle of repose up to 25° would have excellent flowability[23]. Our findings support the use of intensive manual kneading technique as an effective method to coat cohesive powders with selected additives, modify the surface nature of the particles, reduce the interparticle cohesive forces, decrease the pore volume occupied by air and hence improve the flowability in a good agreement with[6].

Table 5: Flow properties of BZ granules prepared by wet granulation using manual and mechanical methods

Parameter	Mean Value	
	Manual granules	Mechanical granules
Flow rate (g/s)	7	3.5
Angle of repose (degree)	16	27
Bulk density (g/ml)	0.465	0.5
Tapped density (g/ml)	0.615	0.72
Carr's index (%)	24.4	30
Hausner ratio	1.32	1.44

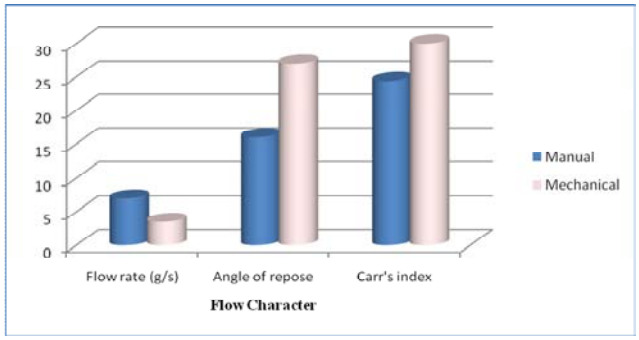

Figure 9: Comparison between flow characters of the prepared manual and mechanical granules

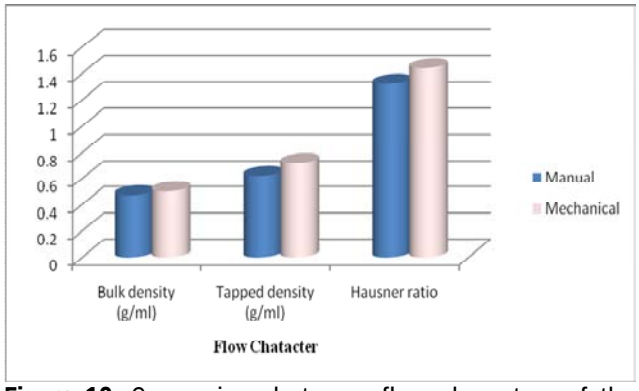

Figure 10: Comparison between flow characters of the prepared manual and mechanical granules

3.4. Evaluation of BZ tablets

3.4.1. Visual inspection

No presence of sticking, picking, filming or any of tablet drawbacks in tabletting of granules prepared by both methods.

3.4.2. Ejection force

As shown in tables (6 and 7), both methods showed low values of ejection forces not more than 1.5 KN, so the prepared BZ granules have a good compressibility under a wide range of compression forces.

3.4.3. Uniformity of dosage unit (weight variation)

Tables (6 and 7) show the RSD of average weight of 4 sets (each of 20 tablets) prepared under different compression forces. The values of RSD range from 0.621

to 1.096 for tablets from granules prepared manually, and from 0.701 to 1.033 for tablets from granules prepared mechanically, so the data could be described as conforming to BP specifications for weight variation test *(BP, 2007).*

Table 6: Evaluation of BZ tablets from manually prepared granules under different compression forces

Main compression force (KN)	Ejection force (KN)	Average weight (mg)	Average thickness (mm)	Average hardness (N)	Friability %	Disintegration time (min)
5	0.23	330	1.64	40	0.36	3
10	0.24	334	1.58	60	0.18	7
15	0.24	332	1.50	75	0.12	17
20	0.27	332	1.46	100	0.06	30

Table 7: Evaluation of BZ tablets from mechanically prepared granules under different compression forces

Main compression force (KN)	Ejection force (KN)	Average weight (mg)	Average thickness (mm)	Average hardness (N)	Friability %	Disintegration time (min)
5	1.5	329	1.55	40	0.23	1.5
10	1.5	331	1.53	55	0.20	5
15	1.4	330	1.56	70	0.18	12
20	1.3	327	1.50	90	0.18	23

3.4.4. Tablet thickness

Tables (6 and 7) show tablet thickness at zero time and after 48 hr. The RSD values of average thickness range from 0.712 to 1.106 for tablets from granules prepared manually, and from 0.429 to 0.867 for tablets from granules prepared mechanically.

3.4.5. Hardness of tablets

Tables (6 and 7) illustrate the relationship between the compression force and tablet hardness, it is approximately linear (R^2 = 1.0 for tablets from manually prepared granules) and (R^2 = 0.994 for tablets from mechanically prepared granules) related to the compression force till a maximum value is obtained (100 N at compression force of 20 KN). In general, the granules have good compressibility indicated by the relatively good hardness at low compression forces (e.g. the hardness is 60 N at a compression force of 10 KN). The relation between hardness and compression force was graphically represented in figure (11).

3.4.6. Friability of tablets

Tables (6 and 7) explain the effect of main compression force on the tablet friability, the friability decreases by increasing of the main compression force. The friability of the tested tablets ranges from 0.06 to 0.36 % that conform the pharmacopoeial limits (not more than 1.0 % is considered acceptable for most products) *(USP, 2008).*

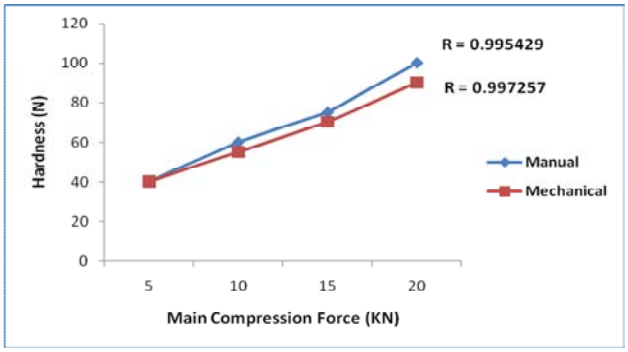

Figure 11: Effect of main compression forces on the hardness of tablet prepared from different granulation techniques

3.4.7. Disintegration time of tablets

Table (6 and 7) illustrate the relation between the compression force and disintegration time of BZ tablets. From observed data, the tablets from mechanically prepared granules disintegrated faster than those from manually prepared granules which compressed at the same compression force. The faster disintegration of tablets may be attributed to the high porosity of these tablets allowing water to penetrate into the inside of the tablet to facilitate erosion. In general, the disintegration time increases by increasing the compression force i.e. tablets which compressed at low compression force show short disintegration time (3 min), while those compressed at high compression force show higher disintegration time (30 min). In general the disintegration time for prepared BZ tablets is conforming to the pharmacopoeial limits *(USP, 2008).*

CONCLUSION

From the obtained results, it has been concluded that dry coating of BZ with different excipients are not sufficient to improve the flowability and the compressibility of BZ. On the other hand, wet granulation with both techniques (either manually or using high-shear mixer granulator) can be successfully employed. The utilization of different techniques of granulation has strong impact on the particle size distribution of the granules and on their flowability, while the effect on other physical and technical properties was little and insignificant, as all tablets possess uniformity of weight, low friability, good hardness, and reasonable disintegration time at all compression forces used. In addition to the produced tablets free from any drawbacks or problems and low ejection force are required.

Acknowledgment: The authors gratefully acknowledge the support of Prof. Dr. Omar El-Ahmady Director of R&D and quality sector of Egyptian International Pharmaceutical Industries Co. A.R.E.

REFERENCES

1. Martindale, The Complete Drug Reference, S.C. Sweetman (Ed.), 35th ed, London, Pharmaceutical Press, Electronic version, (2005).
2. Goodman & Gilman's " Pharmacological Basis of therapeutics " 11th edition, edited by Goodman Gilman A., Hardman J.G., and limbird L.E., Graw-Hill M.C., (eds.); 36, pp. 892-894, (2006).
3. Liu LX, Marziano I, Bentham AC, Litster JD, White ET, Howes T. **"**Effect of particle properties on the flowability of ibuprofen powders**"**. Int. J. Pharm. Oct 1;362 (1-2):109-17, (2008).
4. Pingali KC, Saranteas K, Foroughi R, Muzzio FJ. "Practical methods for improving flow properties of active pharmaceutical ingredients". Drug Dev. Ind. Pharm. Dec;35(12):1460-9, (2009).
5. Maghsoodi M, Tajalli Bakhsh AS. **"**Evaluation of physico-mechanical properties of drug-excipients agglomerates obtained by crystallization**"**. Pharm. Dev. Technol. Feb 22, (2010).
6. Zhou Q, Armstrong B, Larson I, Stewart PJ, Morton DA. "Improving powder flow properties of a cohesive lactose monohydrate powder by intensive mechanical dry coating". J. Pharm. Sci. Feb;99(2):969-81, (2010).
7. Swarbrick J. & Boylan J. C., (eds.), "Encyclopedia of Pharmaceutical technology" Marcel Dekker, Inc.; New York, vol. 7, pp. 121-122, (1998).
8. Ansel H.C., Allen L.V., and Popovich N. G. (eds.), "Pharmaceutical Dosage forms and Drug Delivery systems" 8th edition, Lippincott Williams, and Wilkins, Philadelphia, pp. 209-218, (2005).
9. Aulton M.E. (ed.), in "Pharmaceutics; The design and manufacture of medicines" 3rd edition, Churchill Livingstone, London, pp. 177, 242-245, (2007).
10. Robins, S.J. Targeting low high-density lipoprotein cholesterol for therapy: lessons from the Veterans Affairs High-Density Lipoprotein Intervention Trial. Am. J. Cardiol., 88:19N-23N, (2001).
11. Giron, D., Applications of thermal analysis in the pharmaceutical industry. J.Pharm. Biomed. Anal. **4** (6) 755-770, (1986).
12. Brittain, H.G., Methods for the characterization of polymorphs and solvates. In Polymorphism in Pharmaceutical Solids, Brittain, H.G. (Ed.), Marcel Dekker, Inc., New York, pp. 227-278, (1999).
13. Clas, S.D., Dalton, C.R., and Hancock, B.C., Differential scanning calorimetry: applications in drug development. Pharm. Sci. Technol. Today 2 (8) 311-320, (1999).
14. Martin A., Bustamant P., and Chun A.H.C., (eds.) "Physical Pharmacy" 4th Edition, Micromeritics, Lippincot, Williams & Wilkins., pp. 423-445, (2006).
15. United State pharmacopoeia 27th, United State pharmacopoeia convention Inc., Twin brook Parkway, Rockville, and MD pp. 2271-2272, (2008).
16. Fernandes M., Vela M.T., Rabasco A.M.; "Reological study of lactose coated with acrylic resins", Drug Dev. Ind. Pharm., 16 (2), pp. 295-313 (1990).
17. Neumann B. S., "Advances in Pharmaceutical Sciences" Vol. 2, edited by Bean H. S., Carless J. E., and Beckett A. H., (eds.) Academic Press, London, p. 181, (1967).
18. British pharmacopoeia, vol. (4), p. A 304, (2007).
19. United State pharmacopoeia 31th, Vol. 1, United State pharmacopoeia convention Inc., Twin brook Parkway, Rockville, and MD pp. 266-276, (2008).
20. Kinget R., and Kemel R.; "Preparation and properties of granules" Acta Pharm., Technol., 31, 57-62, (1985).
21. Lieberman H. A., and Lachman L. (eds.), "Pharmaceutical Dosage forms: Tablets" volume 2, 2nd ed., Marcel Dekker, New-York, pp. 325-336, (2005).
22. Hiestand E.N., "powders; Particle-Particle Interactions" J. Pharm. Sci., 35, pp. 1325-1344, (1966).
23. Carr, R. L., "Classifying flow properties of solids" Chem. Eng., 69-72, Feb. 1 (1965).

****