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Preparation and Characterization of Low Dosage Omeprazole Tablets

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Abstract

Five different mixtures of seven components were prepared for tableting. Saccharose, a basic ingredient in each mixture for tableting, was pretreated by top-spray fluid-bed granulation process using polyvinylpyrrolidone as a binder. Microcrystalline cellulose (MCC), mannitol, lactose and PanExcea MC200G, original and granulated, were used as fillers in prepared mixtures. Magnesium stearate was added in each mixture as a glidant. Each component and mixtures for tableting were characterized by particle size distribution, bulk and tapped density, angle of repose, as well as calculated compressibility index and Hausner ratio. Tablets were characterized using standard tests on disintegration, hardness, dimensions and friability. Omeprazole was added to the mixture using the process of simple powder blending in a tumbling bed unit and by wet fluid-bed granulation process. Additionally, omeprazole content was determined in 10 randomly selected tablets. The results revealed a significant effect of particle size distribution on the properties of a mixture, and thus the characteristics of tablets. It was shown that granulated materials own suitable particle size distribution, better flowability, greater hardness of tablets and more uniform composition of omeprazole in tablets thus ensuring the targeted dosage content of the active ingredient in each tablet produced.

Keywords

Omeprazole, Tableting, Fluid-Bed Granulation, Particle Size Distribution, Uniformity of Content

1. Introduction

Omeprazole is a substituted benzimidazole, widely used as a gastric acid secretion blocker that selectively inhibits the proton pump in the gastric mucosa. Omeprazole is poorly soluble in water but it degrades rapidly in aqueous solutions at low pH values as the negatively charged ion. A conventional oral dosage form and an enteric-coated dosage form are the most common solid dosage forms of omeprazole [1, 2].

Tablets are one of the most frequently used dosage forms for delivering active ingredients making more than 50% of all dosage forms [3]. Tablet contains several ingredients but the most important one is active ingredient due to its therapeutic acting ability. Excipients, such as fillers, binders, disintegrants, glidants, lubricants and others are highly necessary too because the suitable tablet cannot be composed of active ingredient only. Tablet usually requires combinations of excipients that will provide properties such as additional bulk volume, improved flow behavior, better compressibility, flavoring, improved disintegration characteristics or enhanced appearance [4]. Tablets must fulfill many physical specifications and high quality standards. These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration and dissolution profile. Those factors must be controlled during the process (in-process controls) and verified after the production of each batch to ensure that established product quality standards are fulfilled [5].

Compressibility of powders can be expressed by two indicators: the compressibility index and Hausner ratio. In the pharmaceutical industry, the optimal value of angle of repose is between 40 and 50°. If the value is greater than 50°, the powder is rarely accepted in further production [6]. Bulk and tapped density, and angle of repose are simple, fast and popular methods for characterizing powder flow [7]. Powder

flow of active ingredients and excipients is highly important when charging the matrix of the tablet machine. The materials required for the production of tablets fulfill the matrix during a certain period of time. If the composition has poor rheological properties and does not fulfill the matrix in a desired way, variations of composition are expected, which naturally, will reduce the therapeutic value of the drug [8].

In the majority of published studies about omeprazole formulations, focus is made on the investigation of the stability [2] and quality of the enteric coating [2, 9]. S. Bozdag et al. [2] and C. O. Migoha et al. [9] prepared a formulation for the tablets containing 20 mg of omeprazole. The active ingredient, omeprazole, was added to the formulation during simple blending process. Although the content of omeprazole in tablets was previously reported, many improvements can be done to reach high uniformity of omeprazole substance in tablet dosage forms.

In some cases, blending the ingredients is not sufficient to achieve uniform distribution of drug. The ingredients may be incompatible because of the particle size, particle density, flow characteristics, compressibility and moisture content. These incompatibilities can cause segregation during blending or during transfer of the mixture to the tableting press, as well as separation of the active ingredient during tableting process. Therefore, active ingredient could easily segregate from other ingredients in the blending process. In contrast to the mixing process, granulation process can significantly improve flow and compression characteristics, reduce segregation, improve uniformity of content and eliminate excessive amounts of fine particles. In the cases where the active ingredient in a formulation represents a very small portion of the overall tablet, it is quite difficult and challenging to ensure that each tablet has the same amount of active ingredient. The granulation process can provide it. There are two possible paths: 1. granulation of individual ingredients and subsequent blending with other excipients, and 2. granulation of all ingredients together.

The best way to ensure that each tablet contains the proper amount of active ingredient, especially if the content of active ingredient is very small, is to blend the active ingredient thoroughly with other ingredients and then granulate the mixture with appropriate binder. After granulation in a suitable stochastic environment, each granule would contain a proportional amount of all ingredients, and the active ingredient would be uniformly distributed in tablets [10].

As already emphasized, development process of dosage forms that contain small proportion of drug must be thoroughly accessed. The quality standards must be assured, including mechanical properties of the tablets as well as uniformity of content. This research aims to those quality standards for 10 mg omeprazole tablets. In this, we are using premixing and granulation process to produce tablets from excipients of different size distributions. Our primary goal is to reach the uniform distribution of omeprazole in tablets produced.

2. Experimental

2.1. Materials

Pure omeprazole ($C_{17}H_{19}N_3O_3S$), microcrystalline cellulose (MCC) and mannitol were supplied by Pliva Croatia Ltd. Saccharose and lactose (Lach-Ner, Croatia), polyvinylpyrrolidone (PVP) Kollidon® 30 (BASF, Germany), PanExcea MC200G (Avantor Performance Materials, Poland), magnesium stearate (abcr GmbH, Germany) and other chemicals used were of analytical grade and procured from commercial sources. List of used ingredients and their role in the tablet are shown in Table 1.

Table 1. *List of used ingredients and their role in the tablets.*

Ingredient	Role in tablet
Saccharose	Basic component
Polyvinylpyrrolidone (PVP)	Binder
Microcrystalline cellulose (MCC)	Filler
Mannitol	Filler
Lactose	Filler
PanExcea	Filler
Mg stearate	Glidant
Omeprazole	Active ingredient

2.2. Methods

The study was conducted in two steps. The first objective was to find the most suitable mixture for tableting and to produce placebo tablets with the best characteristics (hardness and friability). Second stage of the research comprised selection of the mixture that will result in tablets of best performance and addition of the active substance, omeprazole. Omeprazole was embedded into the mixture using two methods: classic blending of components using tumbling bed unit and by granulation process. Produced omeprazole tablets were tested on mechanical resistance and uniformity of the API content. Experimental procedure was run according to Figure 1.

2.2.1. Comminution of Saccharose

Comminution of saccharose was performed in a laboratory ball mill at 105 rpm using 95 ceramic grinding balls for 15 minutes.

2.2.2. Granulation of Saccharose and PanExcea

Granulation was performed in a stochastic fluid-bed environment provided using Uni-Glatt lab unit (Glatt GmbH, Binzen, Germany). 200 g of feed material was granulated in a top-spray mode with 32 mL of binder, 30 wt.% aqueous solution of PVP. Granulation at ambient temperature was conducted in alternating cycles: 30 seconds of spraying the binder followed by a period of fluidization only (30 seconds). Binder was delivered to the powder bed using peristaltic pump with a flow rate of 10 g min^{-1} and by spray nozzle. Afterwards, the obtained granules were dried for 20 minutes in a fluidized bed at a temperature of 40°C. Furthermore, overlarge lumps have been efficiently separated from granulated substance using the sieve of 800 m.

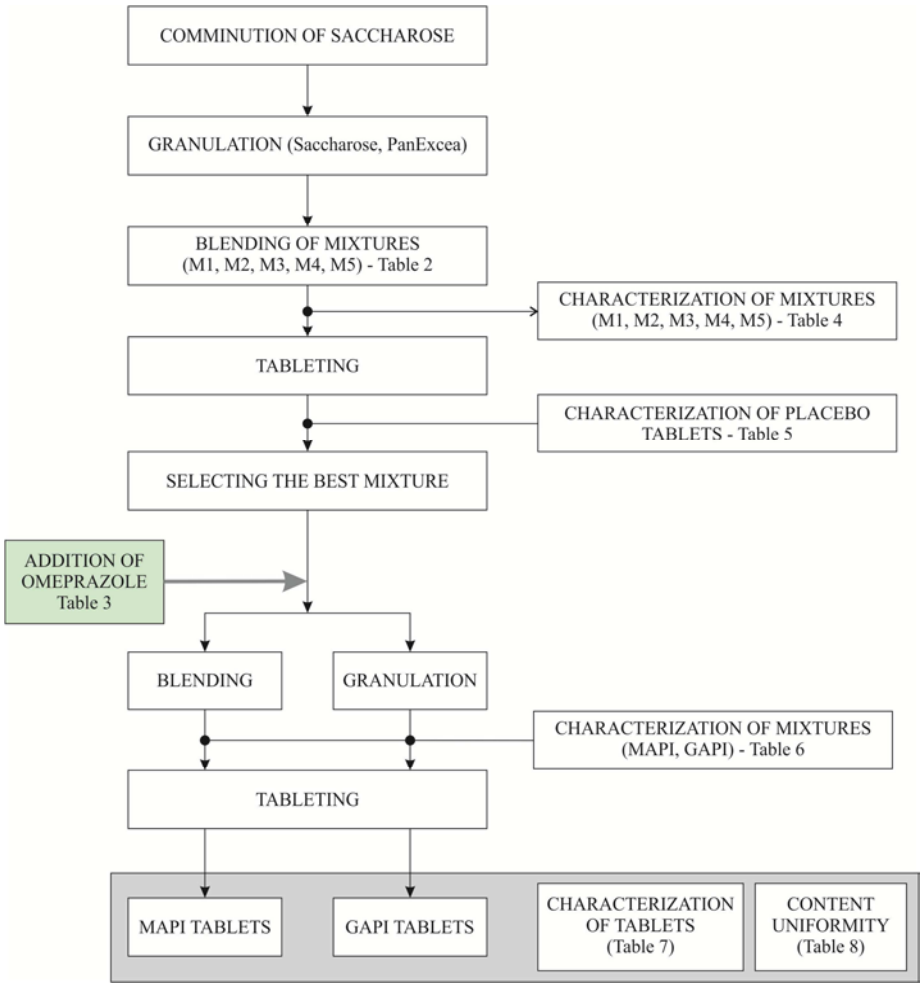

Figure 1. *Diagram of the experimental procedure.*

2.2.3. Preparation of Mixtures

Five different mixtures were prepared for tableting as shown in Table 2.

Table 2. *The mass fraction of individual components in prepared mixtures.*

Ingredient	Mass fraction, %				
	M1	M2	M3	M4	M5
Saccharose granulated	77	77	77	77	77
PanExcea	20	–	–	–	–
Mannitol	–	20	–	–	–
Microcrystalline cellulose (MCC)	–	–	20	–	–
Lactose	–	–	–	20	–
PanExcea granulated	–	–	–	–	20
Mg stearate	3	3	3	3	3

2.2.4. Blending

Powder components were blended in a horizontal drum for 3 minutes. Magnesium stearate was added to the mixer in the last minute.

2.2.5. Characterization of Mixtures

Particle size distribution, bulk and tapped density and angle of repose were determined for all prepared mixtures. Particle distribution was measured using laser diffraction (SALD-3101, Shimadzu, Japan) with measuring range from 0.4 to 3000 μm. Dry measuring unit was used and the samples were dispersed at 0.4 MPa. Presented particle size distribution is a mean value of three measurements. Bulk density and tapped density were determined using Erweka SVM TDT 101/201 (Erweka GmbH, Heusenstamm, Germany). The compressibility index and Hausner ratio were calculated from tapped and bulk density. Measurement of the angle of repose was carried out on the device (Erweka GmbH, Heusenstamm, Germany).

2.2.6. Tableting

40 g of prepared mixtures (M1, M2, M3, M4 and M5) were compressed using an eccentric single punch tableting machine TDP-5T (Zhejiang Wisely Machinery Co. Ltd., Zhejiang, China) equipped with 6 mm round punches and 5 mm depth charging.

2.3. Characterization of Tablets

2.3.1. Friability

Friability of the tablets was determined using J. Engelsmann AG friability tester at 25 rpm for 4 minutes. 6.5 g of tablets were weighed and friability was expressed as weight loss in %.

2.3.2. Tablet Dimensions and Hardness

Tablet thickness, hardness, and diameter were determined with Erweka TBH 30 tester (Erweka GmbH, Heusenstamm, Germany). Testing was conducted on 10 randomly selected tablets. Hardness, diameter, and thickness are expressed as the mean value of all measurements (Table 5).

2.3.3. Weight Uniformity

The average tablet weight was determined on the basis of 20 randomly selected tablets. The mean value and standard deviation for each formulation are shown in Table 5.

2.3.4. Disintegration Test

Tests were carried out using Erweka ZT 303 unit (Erweka GmbH, Heusenstamm, Germany) with 6 tablets at the same time. The tablets are placed in a basket with the appropriate liquid (distilled water or 0.1 M HCl) held at temperature 37±2°C preferably in 1 liter beaker. The rack moves up and down in the liquid at the specific rate. The end point of the test is indicated when all 6 tablets are dissolved representing final disintegration time, shown in Table 7 for MAPI and GAPI tablets.

2.3.5. Nitrogen Adsorption/Desorption Porosimetry

ASAP2000 (Micromeritics, USA) gas sorption analyzer was used to determine the adsorption/desorption isotherm, specific surface area and pore size distribution of tablets tested. Pre-weighed tablets were firstly degassed at 300°C to a residual pressure of 6.67 Pa. The analysis was performed using N_2 as the adsorbate at 77 K. Specific surface areas were estimated using Brunauer-Emmet-Teller (BET) adsorption model from a linear part of BET plot. Pore size distribution was calculated from the adsorption branch of isotherm using Barret-Joyner-Halenda (BJH) model. Porosimetry results in terms of specific surface area, pore volume and average pore size are reported in Table 5.

2.4. Addition of the Active Ingredient, Omeprazole

The objective of this study was to achieve uniformity of content as high as possible in prepared omeprazole tablets. The targeted value was 10 mg of omeprazole per tablet. The appropriate amount of omeprazole has been calculated according to the mean values of the weight of M5 tablets (0.0789 g). The active ingredient was added in two ways, by blending and granulation. Blending was conducted as described in Section 2.2.4. Omeprazole, saccharose, and PanExcea were granulated simultaneously in a lab scale fluid-bed unit with a top-spray arrangement and with a binder solution, 30 wt. % aqueous solution of PVP. The amount of PVP was calculated to ensure the same ratio of components as in the blended mixtures. Granulation conditions were the same as in previous experiments.

Table 3. *The mass fractions of individual components.*

Ingredient	Mass fraction, %	
	Blending (MAPI)	Granulating (GAPI)
Saccharose granulated with PVP	67.35	–
PanExcea granulated with PVP	17.50	–
Mg stearate	2.65	2.65
Saccharose + PanExcea + Omeprazole granulated with PVP	–	97.35
Omeprazole	12.50	

UV/Vis spectrophotometer Lambda 35 (PerkinElmer, Waltham, USA) was used to determine the content uniformity of omeprazole in tablets. Procedure for UV spectrophotometric measurements is as follows: 10 tablets were randomly selected from each batch and triturated in a mortar. Each tablet was then dissolved in 25 mL of deionized water. Before the tests, the solution was filtered using Chromafil Xtra PET-120/25 of 1.2 µm filters. Measurements were performed at the wavelength of 280 nm which corresponds to the maximum of absorption of omeprazole. The amount of omeprazole in each tablet was calculated from previously constructed calibration lines.

3. Results and Discussion

3.1. Characteristics of Mixtures and Placebo Tablets

The values obtained by methods for testing powder flow are shown in Table 4. Flowability of powders can be considered excellent to very poor and according to the values of compressibility index and Hausner ratio it can be divided into seven categories [6].

Accordingly, mixtures M1, M2, M3 and M4 are of passable and fair flowability while the mixture M5 has good flowability. In pharmaceutical industry powders that have the angle of repose up to 50 ° have satisfactory properties of flowability [6]. The values of the angle of repose show that all mixtures have satisfactory flowability. The best flowability was noticed for mixture M5. Mixture M4 has poor flowability according to the values of the compressibility index and Hausner ratio.

Table 4. *Flowability of prepared mixtures.*

Mixture	Bulk density, kg m^{-3}	Tapped density, kg m^{-3}	Compressibility index, %	Hausner ratio	Angle of repose, °
M1	806.5	1000.0	19.35	1.240	37.14
M2	757.6	961.5	21.21	1.269	43.29
M3	735.3	892.9	17.65	1.214	44.24
M4	714.3	925.9	22.86	1.296	49.21
M5	625.0	714.3	12.50	1.143	36.71

Figure 2 shows particle size distribution for all mixtures. From particle size distribution it can be observed that the addition of

various fillers differs the distribution of particle sizes in the medium size range 2-300 μm. It also shows that mixture M5 has a negligible portion of particles between 2 and 300 μm. This was expected because the mixture M5 is composed of granulated saccharose and granulated filler PanExcea and therefore has mostly particles of larger size. The particle size distribution obtained by granulation gave the best flowability for the mixture M5.

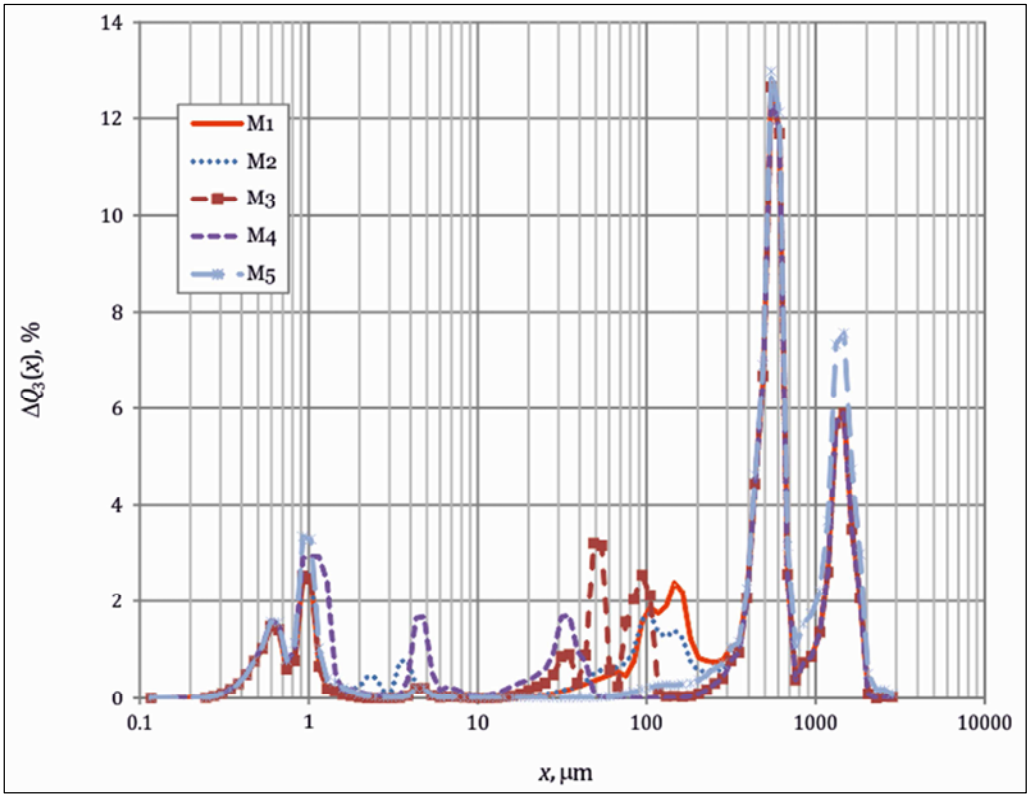

Figure 2. *Particle size distribution for all mixtures.*

From the results shown in Table 5 it is evident that tablets M2 and M5 have the highest value of hardness. The greater hardness of tablets M2 is attributed to a greater degree of mannitol polydispersity resulting in a better packing of particles. M5 tablets also showed high value of hardness which is the outcome of granulation process. The mixture for M5 tablets contains granulated saccharose and granulated filler PanExcea. Both components are granulated with polyvinylpyrrolidone (PVP) as a binder that own high binding properties. During the formation of granules, PVP creates liquid bridges between particles but it is also deposited on the surface of granules. During compression of granules, PVP binder can be easily squeezed onto the surface of granules. This will form an additional binding of granules in tablet matrix thus resulting in a higher hardness of tablets produced in spite of lower granule polydispersity. This fact points to the advantages of the process of wet granulation process in modifying excipients for tablet production.

Table 5. *Mean values of tablet properties.*

	Hardness, N	Diameter, mm	Thickness, mm	Weight of tablets, g	Friability, %	Disintegration time, s		S_{BET}, $m^2\ g^{-1}$	V_p, $cm^3\ g^{-1}$	$d_{av.}$, nm
						H_2O	0.1 M HCl			
M1	22.2	6.187	2.748	0.0978	0.61	356	–	1.70	0.0039	8.73
M2	27.3	6.192	2.720	0.0970	0.76	361	/	1.67	0.0036	8.30
M3	24.2	6.294	2.644	0.0931	0.62	551	723	1.73	0.0023	5.32
M4	26.9	6.380	2.677	0.0944	1.24	265	325	1.85	0.0027	5.77
M5	27.3	6.318	2.333	0.0789	0.46	360	383	2.06	0.0039	7.32

The thickness and weight of the tablet can be associated with the bulk density of the mixture. All tablets were produced using equal compression force and charging depth (5 mm). Materials with smaller bulk density that contain plenty of cavities between the particles are more compressible resulting in a reduced thickness and weight of tablets. The most noticeable difference can be observed for tablets M5 that own the smallest value of thickness and weight, which is a consequence of considerably lower bulk density of this mixture (625 kg m^{-3}), compared to the others.

Friability test is considered successful if the maximum weight loss is no more than 1.00% [11]. From the obtained results for friability (Table 5), it is evident that only tablets M4, whose mass loss is 1.24%, do not meet the aforementioned criterion. The

lowest friability was obtained for tablets M5 (0.46%).

Disintegration test is provided to determine whether tablets disintegrate within the prescribed time [12]. When not otherwise specified, the disintegration test is satisfactory if all tablets dissolve in a suitable medium within 15 minutes. From the results presented in Table 5 it can be seen that tablets disintegrate in less than ten minutes, which means that disintegration time for all tablets is satisfactorily. Maximum time of disintegration was observed for tablets M3 which are containing microcrystalline cellulose that is insoluble in water and hydrochloric acid [13].

Considering the particle size distribution of the components used in mixtures, it is obvious that the mixtures containing filler with smaller particles (M3 - MCC particles up to 200 μm and M4 – lactose particles up to 100 μm) resulted in tablets with smaller pore volume, and thus lower average pore diameter. The value of specific surface area is distinguished for tablets M5 as a consequence of a larger portion of granulated components. The granules are porous in structure, which contributes to a greater proportion of pores and specific surface are respectively.

The best mixture was chosen on the criteria of best powder flowability and on the appearance of tablets that will meet all quality standards. Deviation in weight of the tablets was selected as the most important criterion leading to the fact that the smallest variation of mass indicates relatively precise dosing of the active substance in the tablet (3). From Figure 3 it is evident that tablets M4 and M5 have the lowest standard deviation of weight. However, reviewing the results of other tests revealed that the friability of M4 tablets is beyond the required limits [11]. From the results, it can be seen that the mixture M5 has the best flowability and tablets M5 fulfill all quality criteria, therefore, M5 mixture was selected for the preparation of tablets with the active ingredient, omeprazole.

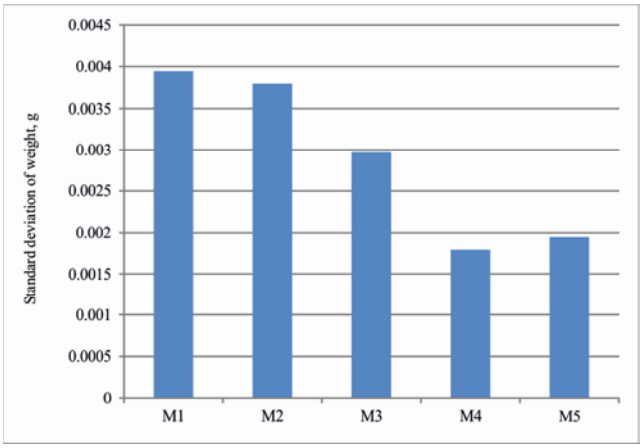

Figure 3. *Standard deviation of weight for tablets.*

3.2. Addition of Omeprazole

Omeprazole was added to the mixture in two ways: blending using tumbling powder blender and granulation process as already mentioned in experimental part (2.4.). Mixture and tablets in which omeprazole was added by blending were named MAPI and those obtained by granulation of GAPI.

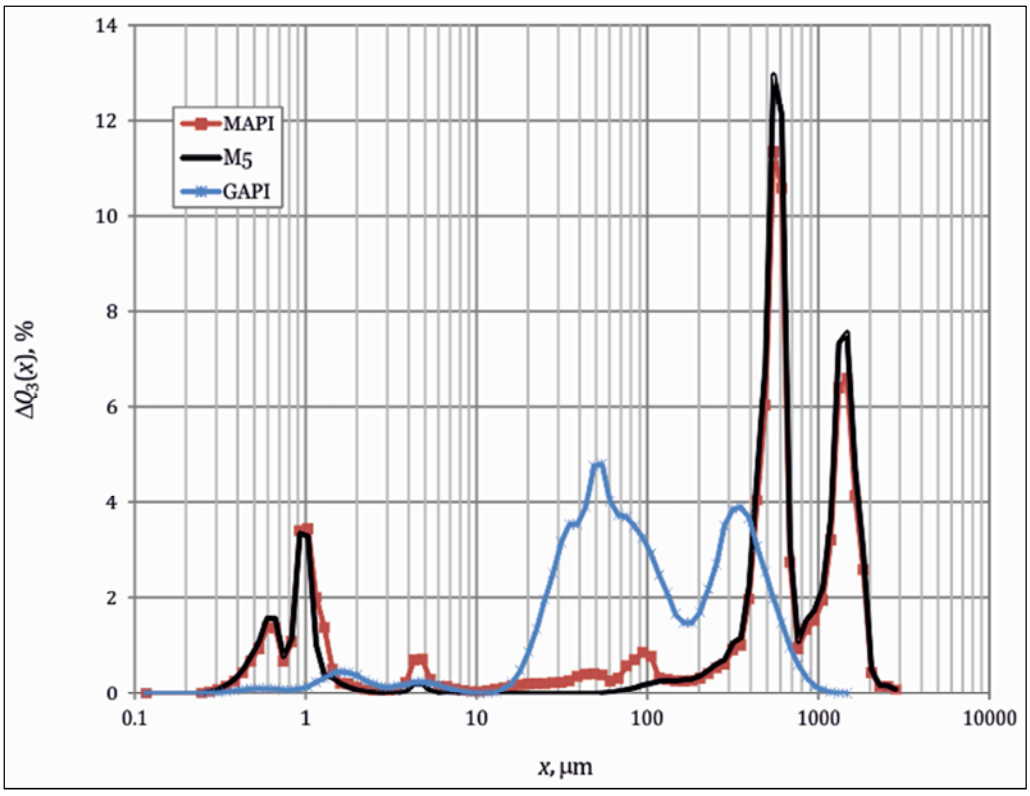

Figure 4. *Particle size distribution for mixtures M5, MAPI and GAPI.*

Table 6. *Flowability of prepared mixtures MAPI and GAPI.*

	Bulk density, kg m^{-3}	Tapped density, kg m^{-3}	Compressibility index, %	Hausner ratio	Angle of repose, °
MAPI	645.2	769.2	16.13	1.192	39.49
GAPI	555.6	625.0	11.11	1.125	42.90

Figure 4 shows comparison of the particle size distribution for mixtures M5, MAPI and GAPI. It can be seen that the addition of omeprazole into MAPI mixture resulted in an alteration in size distribution in the medium size range, 3-100 µm which contributes to the better particle packaging. Flowability of mixtures MAPI and GAPI (Table 6) was reduced with addition of omeprazole compared to the mixture M5. However, the values of angle of repose make both, MAPI and GAPI mixture, highly suitable for tableting. Particle size distribution of GAPI mixture shows that granulation of components reduced the width of distribution in comparison to MAPI. The largest fraction of particles is in the size range between 20 and 800 µm. The resulting distribution shows good flowability (Table 6). Reduced bulk density of GAPI mixture (555.6 kg m^{-3}) is the result of a higher content of granulated material, and increased porosity of the granules. From the values of compressibility index, Hausner ratio and angle of repose, it is evident that a GAPI mixture is of good flowability [6].

Table 7. *Mean values of tablet properties MAPI and GAPI.*

		MAPI	GAPI
Hardness, N		28.0	38.3
Diameter, mm		6.187	6.519
Thickness, mm		2.403	2.322
Weight of tablets, g		0.0848	0.0835
Friability, %		0.61	0.46
Disintegration time, min	H_2O	402	630
	0.1 M HCl	319	419

The results in Table 7 show that MAPI and GAPI fulfilled all quality parameters defined for tablets. The hardness of GAPI tablets is higher by 10 N compared to MAPI tablets, which confirms the better compression of the granulated components. Also, increased hardness of tablets GAPI could be related to the influence of the PVP binder. During granulation of GAPI mixture in a fluidized bed, PVP was sprayed on the powder bed and retained in the granules and onto their surface too. Such addition of PVP contributed to the tablet hardness during compression [10]. Better compressibility and smaller values of bulk density of granulated mixture (GAPI) resulted in a smaller thickness and weight of the tablets, as expected. GAPI tablets, with higher values of the hardness, retained the same friability as M5 tablets. Due to the hardness of GAPI tablets, disintegration period in water is longer comparing to MAPI. Shorter disintegration time in 0.1 M HCl is a consequence of fast degradation of omeprazole in solutions with low pH values [1].

Table 8 shows the results of determination of omeprazole content in 10 randomly selected tablets. The mean value of weight (MV) and standard deviation (SD) was calculated. Standard deviation for GAPI tablet is significantly lower compared to MAPI, which indicates a minor deviation of omeprazole content from the targeted value (10 mg).

Table 8. *The omeprazole content in MAPI and GAPI tablets.*

	MAPI	GAPI
	m **(omeprazole), mg/tablets**	***m*** **(omeprazole), mg/tablets**
1	10.07	10.53
2	9.53	9.73
3	9.15	10.67
4	8.72	10.76
5	7.95	10.98
6	8.79	10.01
7	8.66	10.63
8	10.07	10.77
9	10.28	11.61
10	9.60	10.58
MV	9.28	10.63
SD	1.032	0.625

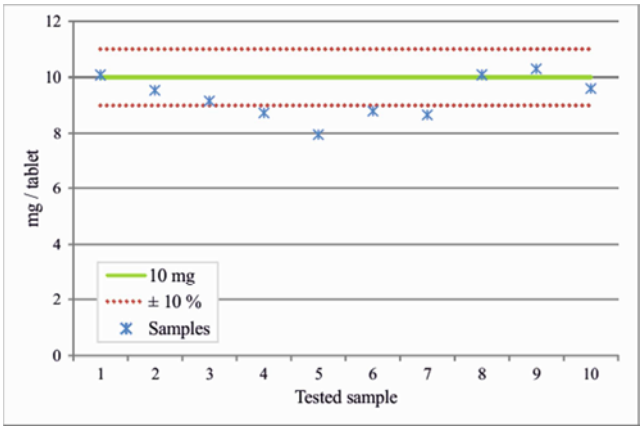

Figure 5. *Variation of omeprazole content in MAPI tablets.*

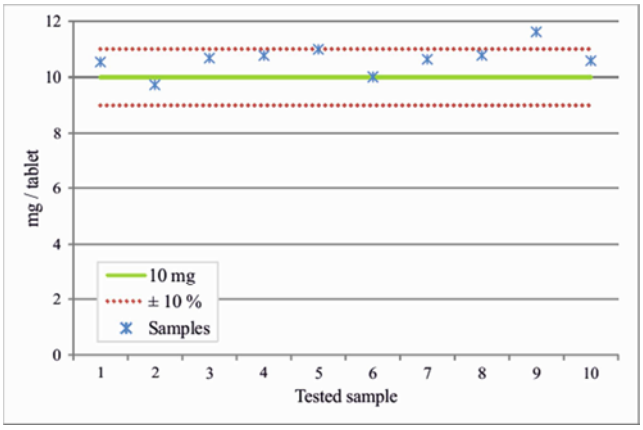

Figure 6. *Variation of omeprazole content in GAPI tablets.*

Figure 5 shows the deviation of omeprazole mass in MAPI tablets. It is evident that the omeprazole content in some tablets significantly deviates from the required value of 10 mg. Reason for this deviation are found in an insufficient homogenization of the mixture and segregation of the mixture

due to the differences in particle size of components. The segregation may occur during the mixing or during the dosing phase in tableting process. According to the pharmacopeia, allowed aberration of omeprazole content is ± 10%. Figure 5 shows that 40% of the tablets does not meet the required standard. Figure 6 shows the deviation of the omeprazole content in GAPI tablets. It is obvious that only one sample has a higher content of omeprazole (11.61 mg). According to the presented results, granulation of the active ingredient with comminuted saccharose and filler PanExcea results in a uniform distribution of the active ingredient in the tablets. Granulation has efficiently solved the problem of segregation that frequently occurs during the blending of the ingredients.

4. Conclusions

Particle size distribution of the filler in the mixture significantly affects its flowability and the end-use properties of the tablets. Increasing the width of particle size distribution and the content of coarser particles leads to the better flowability of powders and better tablet properties, respectively. The best properties of flowability showed a mixture M5 with the filler PanExcea granulated with PVP, containing the largest portion of granular components.

Tablets containing 10 mg of the omeprazole were prepared using process paths for achieving required functionality of a mixture for tableting; blending of components and granulation. The mean content value of omeprazole in GAPI tablets is 10.63 mg and for MAPI tablets is 9.28 mg.

In contrast to the mixing, granulation of the active substance and the excipients is demonstrated to be a better process path for addition of the active substance in the tablets. Due to the much better flowability of mixtures tablets own better end-use properties and more uniform content of active substance.

Nomenclature

$Q_3(x)$	[–]	cumulative size distribution
S_{BET}	[m^2 g^{-1}]	specific surface area
V_p	[cm^3 g^{-1}]	specific pore volume
$d_{av.}$	[nm]	average pore size

Abbreviations

av	average

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