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Assessment of physical properties of granules with paracetamol and caffeine

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KEYWORDS

Caffeine; Paracetamol; Granules; Excipients; Binders; Physical properties

1. Introduction

Granules are the drug form very convenient in application compare to drug powders. They are easier to swallow, since they do not atomize nor adhere to the mucous membranes of the oral cavity or throat (Bauer et al., 2012).

The granulation process is carried out to give the powder substances the granular form, with similar particle size, which leads also to reduce the amount of dust (Jachowicz, 2013). Preparation of the granules thus obtaining large particles of the substance and thereby enhancing the properties associated with the flow, convenient and accurate dispensing of the drug form. Granulation also enables the improvement of properties such as surface texture, porosity or wettability. It has a positive influence on the disintegration time and the solubility of the active substance (Bauer et al., 2012).

Changing of these values is important especially in case of hydrophobic substances, and with poor flowing properties like caffeine and paracetamol. Low flowable material not only makes it difficult to correct the dispensing, but also a difficulty in preparing other solid drug forms. The formation of solid drug forms comprising compounds having a low solubility always faces the problem of providing a sufficiently high bioavailability of the active substances. These difficulties can be resolved through the introduction of appropriate excipients for the formulation of the drug (Tkachenko et al., 2003). The formulation of granules with caffeine, paracetamol and suitable excipients can contribute to improving the physical characteristics, bioavailability and more convenient dosing of the drugs.

The excipients used to prepare the granules were: Lactose monohydrate is a sugar used as a diluent in the production of granules which are characterized by high hardness and prolonged disintegration time. Therefore lactose is used in combination with disintegrant. Mannitol is a sugar alcohol used also as a filler in granules. Due to the chemical structure is used as a substitute of sugars in drug forms. Calcium hydrophosphate is used as a diluent and a drying agent in pharmaceutical technology. This substance has good flowability. Good mechanical strength of obtained granules and tablets with calcium hydrophosphate characterized by. Corn starch has a variety of uses: as a diluent, a disintegrant and a binder. Practically it is insoluble in cold water. The most important use of polyethylene glycol 6000 and polyvinylpyrrolidone K30 as binder (Bauer et al., 2012).

There are granules available in the market containing paracetamol and caffeine. However, most of them are effervescent, e.g. Resolve extra, Molfen.

The purpose of this study is to determine the effect of various excipients on the quality of granules with paracetamol and caffeine. In the first step the compositions of granules were prepared, than drug forms were done and tested. The distribution of particle size, compactability, flow properties, moisture content and disintegration time were determined. The evaluation of properties of individual granules helped to indicate formulation with good features, which perhaps will be a good alternative to currently available painkillers with caffeine and acetaminophen that are commonly used.

2. Materials and methods

2.1. Materials

Granules were prepared using the following substances: paracetamol (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), caffeine anhydrous (Fluka Chemie AG, Buchs, Swiss), lactose monohydrate (Pharma Cosmetic, Cracow, Poland), D-mannitol (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), calcium hydrophosphate anhydrous (PPH POCH S.A., Gliwice, Poland), corn starch (Radix-Bis, Rotmanka, Poland), polyethylene glycol 6000 (PEG) (Fluka Chemie AG, Buchs, Swiss), polyvinylpyrrolidone K30 (PVP) (Fluka Chemie AG, Buchs, Szwiss), and ethyl alcohol 96% (v/v) (PPH POCH S.A., Gliwice, Poland).

In the first step the compositions of granules were prepared and done, then tested. Two groups of granules which differ in the type of binder were analyzed. (Table 1) In the first group, the binder was polyethylene glycol 6000 (Granules I-V) and in the second polyvinylpyrrolidone K30 (Granules VI-X). Both groups consisted of five series of granules varying in fillers.

Table 1.

2.2. Methods

All substances were mixed and then solutions of binders were added in small volumes. These were: 50% (w/w) solution of PEG 6000 in water and 25% (w/w) solution of PVP K30 in 96% (v/v) ethanol and water in equal quantities. All granules were made by wet granulation in Wet Granulator FAG Erweka (Frankfurt, Germany). The resulting granules were dried in a dryer (Mettler INB500, Germany) at 45°C for 5 h. After the drying process granules were sieved by 1.6 mm sieve in order to unify the particle size. The dust was sifted through a sieve of 1.2 mm and these particles were granulated again.

All the pharmaceutical technical procedures have been performed in accordance to the requirements of the European Pharmacopoeia 8.0 (The Council of Europe, 2014). The following apparatus were used for testing: moisture analyzer WPS 210S Radwag (Radom, Poland) equipped with halogen lamps for determination of moisture content, sieve shaker AS 200 Retsch (Haan, Germany) with sieves made of stainless steel for particle-size distribution estimation. Furthermore, compactability was measured in Erweka SVM 222 tapped density tester (Heusenstamm, Germany) with 100 mL glass cylinders and flow characteristics were done in Erweka GTB Granulate and Powder Flow Tester (Heusenstamm, Germany). The additional test of disintegration time was carried out in conical flasks according to the Polish Pharmacopoeia 6.0 (The Minister of Health, 2002).

3. Results

3.1. Determination of moisture content of the granules

The assay was performed until a constant weight of the sample has been fixed. Drying process was carried out at 130°C. The sample mass of powdered granules was 3.0 g. The obtained results are shown in Table 2.

Table 2.

3.2. Particle-size distribution estimation by analytical sieving

The analytical sieves with following mesh sizes were used: 2.0 mm, 1.25 mm, 1.0 mm and 0.75 mm. The mass of the sample of tested granules was 25.0 g. The vibration amplitude in sieve shaker was set to 1.0 mm. Results are shown in Table 3.

Table 3.

3.3. Apparent density and tapped density of granules

The settling apparatus produced in 1 min 250 ± 15 taps from height of 3 ± 0.2 mm. The sample of granules having a mass of 40.0 g was carefully poured into the dry cylinder. Apparent volume before settling (V_0) was read then. Apparent volume after settling (V_{1250}) was read after 1250 taps of the cylinder and then tapped density of granules (d_{1250}) was calculated. Results are shown in Table 4.

Table 4.

3.4. Angle of repose

Into a dry funnel with a nozzle having a diameter of 10 mm a test sample of 100 mL was introduced. The measurement of the angle of repose was according to Ph. Eur. 8.0; an integrated driven laser of Flow Tester measured the side wall of the built-up cone and calculated the actual angle. The obtained results are shown in Table 5.

Table 5.

3.5. Flow through an orifice

The Flow Tester in all 'flow through an orifice' tests was equipped in the funnel with nozzle having a diameter of 10 mm.

3.5.1. *The measurement of the time it takes for 100 mL of granules to pass through the orifice*

The results of flow rate-volume test are shown in Table 6.

Table 6.

3.5.2. *The measurement of the time it takes for 100 g of granules to pass through the orifice*

The results of flowability test are shown in Table 7.

Table 7.

3.5.3. *The measurement of the amount of granules passing through the orifice in 10 s*

The results of the flow rate as a function of time are shown in Table 8.

Table 8.

3.6. *Flow angle*

This examination was also performed on the Flow Tester equipped in the funnel with nozzle having a diameter of 10 mm. A suitable volume of tested granules was introduced into a funnel. The end of the measurement was at the moment when 100.0 g of granules was poured out from the funnel. The curve mass (m) versus time (t) during the test was drawn and software of GTB Flow Tester indicated the flow angle (α) of the plotted curve to the time axis. The results are shown in Table 9 and flow diagrams are shown in Fig. 1 and 2.

Table 9.

Fig. 1

Fig. 2

3.7. *Compressibility index and Hausner ratio*

The Compressibility index and Hausner ratio were calculated according pharmacopoeia equations with the use of data obtained during apparent density and tapped density test. Results are shown in Table 10.

Table 10.

3.8. *Disintegration of granules*

A sample of 1.0 g of granules was placed into the conical flask filled with 50.0 mL distilled water at $37 \pm 2^\circ\text{C}$. The disintegration time was measured using a stopwatch and the test was considered completed when no granules was observed. Results are shown in Table 11.

Table 11.

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4. Discussion

The study was conducted to determine the effect of the excipients on the properties of prepared granules.

Determination of moisture content of the granules showed the highest moisture in formulations containing a mixture of lactose and corn starch (X – 6.59%, and V – 6.22%; Table 2). While the time needed to establish a constant weight of the tested samples was the longest for these formulations. These properties are probably due to the presence of hygroscopic maize starch in granules. The lowest moisture content had granules III – 0.58%. These observations are consistent with the results of the study by Szumilo et al. (2012), which found that the addition of starch increases the moisture content of the preparation as well. The presence of mannitol and calcium hydrophosphate contributes in reduction of the moisture level in the granules. Uribarri et al. (2003) pointed out that the diameter of the granules was increased with an increase in the volume of the binder solution added and with an increase in the kneading time and was decreased when the chopper was used. The percent of fine powders, present in granulate, was significantly diminished with an increase of the volume of binder solution and diminished with an increase in the kneading time, the influence of the use of chopper was insignificant in their work.

Particle-size distribution estimation by analytical sieving has revealed the most homogeneous particle size of granules with a mixture of mannitol and calcium hydrophosphate (VIII and III). In this case fraction of the largest size of the granules from 1.25 mm to 2.0 mm was 97.83% for granules VIII and 92.16% for granules III of the mass of tested samples (Table 3). Granules consisting of lactose in combination with corn starch have the largest number of particles of the smallest size, i.e., a fraction of less than 0.75 mm. These observations indicate low strength and a tendency to crushing of these granules which is probably related to the disintegrating properties of the starch and too poor bonding of the mixture of lactose and corn starch by the use of the specific binders. Ax et al. (2008) were found, that the droplet size of the binder liquid has great influence on agglomerate size and binder distribution at short mixing times, with increasing time, the mechanical stresses acting in the mixer becomes more and more dominating in the process. Simple physically based criteria were also evaluated by Rajniak et al. (2007), which employ the morphological properties of excipients (size and surface roughness) together with physical properties of the used binder for prediction of the coating versus agglomeration regime at given flow conditions (collision velocity). As they expected, a preferential coalescence and growth of the mannitol granules from the blend of mannitol + CaHPO₄ was observed.

The highest apparent density was found in preparations containing calcium hydrophosphate as a filler (granules: IV – 0.609 g/mL and IX – 0.577 g/mL; Table 4) and the lowest – containing mannitol (granules: VII – 0.353 g/mL and II – 0.444g/mL). These observations are consistent with the results obtained by Kraciuk and Sznitowska (2011). It should also be noted that the granules with nearly 90% content of mannitol (II and VII) had a lower apparent density than prepared of a mixture of equal amounts of mannitol and calcium hydrophosphate (III – 0.513 g/mL and VIII – 0.471 g/mL). This is due to the presence of

calcium hydrophosphate characterized by a higher bulk density than mannitol. It also follows the properties of the mannitol – in contrast to other fillers, decreasing amount of mannitol in granules leads to increased density of the formulation (Kraciuk and Sznitowska, 2011). Comparing the formulas differing only the type of binder, it was observed that the granules prepared using a solution of PVP have a lower density, than those made with solution of polyethylene glycol (Table 4). These results suggest that PEG solution binds stronger the powder particles compared to polyvinylpyrrolidone. Similar relationships between the composition of granules, and the results of apparent density observed in the case of the tapped density (Table 4). The biggest changes of this parameter were exhibited by granules containing calcium hydrophosphate (granules IV – an increase of 0.062 g/mL and IX – an increase of 0.058 g/mL) and a mixture of lactose and the corn starch (granules: X and V).

The flowability of granules were tested by various methods in order to characterize the formulation for this property as precisely as possible. To evaluate the different characteristics of flow of granules the following tests were performed: the measure of angle of repose and flow angle, the tests of flow through an orifice and determination of compressibility index and Hausner ratio.

The values of the angle of repose were similar for all granules (Table 5). The study showed that all prepared formulations were characterized by a fair flow property because the value of angle of repose of each of them was in the range from 36.0° to 40.0°. The smallest angle was observed in granules VIII – 36.7°, and the cone with the biggest angle of repose was formed by granules IV – 39.88°. It has been found that the formulations containing mixtures of fillers: mannitol with calcium hydrophosphate (III and VIII) and lactose with maize starch (V and X) were characterized by the best flow properties, because their angles of repose were the smallest.

The flow through an orifice was measured in three ways. The measurement of the time it takes for 100 mL of granules to pass through the orifice confirmed that all the prepared formulations have similar flow properties (Table 6). The shortest flow time was observed in granules V, X, VII (7.7 s) and II (7.9 s). This confirmed the findings of the previous study showing that the best flow properties had granules comprising a mixture of corn starch with lactose and that the formulations prepared with mannitol had better flow properties than the preparations with lactose.

A greater diversity of flowability was observed by measuring the time it takes for 100 g of granules to pass through the orifice (Table 7) and the amount of granules passing through the orifice in 10 s (Table 8). Both studies have consistently shown that the most preferred flowability (the shortest period of repose and the largest free-flowing mass within the prescribed time) characterized granules I, IV and IX. The lowest mass flow was determined in formulas VIII and III (respectively 38.5 and 41.0 g/10s), which confirmed the findings of the study time flow rate of 100 mL granules. Analysing the measurement results, it was found that the mannitol granules are characterized by poorer flow capacity compare to formulations containing lactose, which is consistent with the conclusions of Kraciuk and Sznitowska (2011). It was also noted that the granules containing a mixture of lactose with maize starch (V and X) showed the inferior flow compared to those obtained with lactose alone (I and VI). This is probably due to poor flow properties of maize starch, which drew attention of Seppälä

et al. (2010). Additionally, there was a clear impact of binder on the flowability of granules. The use of PEG 6000 during the preparation of granules, resulted in improving their flow properties. This was expressed in reducing flow time and increasing the amount of granules passing through the orifice in specified time. The improvement was clearly evident in the case of formulations containing lactose or mannitol (Tables 7 and 8).

Comparison of the results obtained during the examination of flow of granules through an orifice in different variants, didn't give the clear conclusion regarding this parameter. Follow the instructions given by Ph. Eur. 8.0 determining volume flow rate may be preferable, since during tableting dies are filled volumetric.

The flow angle for granules was determined by plotting the curve of mass from the time (Figures 1 and 2). All the preparations had similar high values of an angle within the range from 76.5° to 82.1° (Table 9). The largest flow angle had the granules IV and IX, (82.1° and 81.9° respectively), and the smallest: VII and II (76.5° and 78.8° respectively). It was found that formulations containing calcium hydrophosphate had best flow, in contrast to formulations with mannitol. Better flow properties had granules with polyethylene glycol (Table 9). The flow angle is a resulting parameter from the relation of the mass as a function of time, this is why this study confirmed almost all conclusions based on the results of measurement of mass flow rate.

An important parameters in assessing the flow of drug forms are also: a compressibility index and Hausner ratio, determined based on the apparent volume or density and tapped volume or density. The Hausner ratio of most prepared granules ranged from 1.05 to 1.11, while the compressibility index ranged from 4.59 to 10.48% (Table 10). These values indicate excellent flow character of the investigated formulations. Only in case of the granules V and X values of these parameters were slightly higher. This shows that the addition of corn starch worsens the flowability of granules, which confirms the reports by Seppälä et al. (2010). The impact of the binder was seen especially for the granules with mannitol, where the replacement of PEG with a solution of PVP contributed to nearly a twofold increase in compressibility index of 5.26% to 10.48%, and therefore to the deterioration of the flow properties.

The test of disintegration time of granules showed that all prepared drug forms comply with the pharmacopoeia with regard to this property. All the prepared granules were disintegrated in less than 10 minutes (Table 11). The longest disintegration time were determined for formulations containing lactose (granules I and VI, 86.20 s and 95.60 s respectively), slightly lower for the formulations with mannitol (granules II and VII). The shortest disintegration time was found for the granules with calcium hydrophosphate (formulations IV and IX; 10.20 s and 9.40 s, respectively). It has been shown that formulations containing polyvinylpyrrolidone disintegrate rapidly. This confirm that the presence of polyethylene glycol promotes the formation of stronger bonds between particles and thereby granules of a higher strength.

5. Conclusion

The effect of fillers on the quality of the granules is greater than the binders. Because of low moisture content, granules with mannitol, calcium hydrophosphate and a mixture of these substances can be used as filling agents during the granulation of active substances sensitive to moisture. Granules comprising lactose in combination with corn starch have the lowest uniformity of grain size and the largest amount of particles of the smallest size, which contributes to the formation of preparation of low strength and resistance to crushing. The density of granules depends both on the type of filler materials and the used binder. A solution of polyethylene glycol stronger binds the powder particles, which showed higher values of apparent density of obtained granules compare to the drug forms with polyvinylpyrrolidone. All the prepared granules fulfill the requirements of Pharmacopoeia for disintegration time – each of them underwent disintegration in less than 10 minutes. Because acetaminophen and caffeine are classified as a poor free-flowing powder, the form of granules had higher flowability. The flowability of granules depends on the components, method of testing and environmental conditions. Granules are a convenient alternative drug form for powders and tablets.

References

- Ax K., Feise H., Sochon R., Hounslow M., Salman A., 2008. Influence of liquid binder dispersion on agglomeration in an intensive mixer. *Pow. Tech.* 179, 3, 190-194.
- Bauer K. H., Frömming K. H., Führer C., 2012. *Pharmazeutische technologie, mit einföhrung in die biopharmazie*, 9th ed. Wissenschaftliche Verlagsgesellschaft, Stuttgart.
- Jachowicz R., 2013. *The drug form. Optimisation of oral and eye medications in modern pharmaceutical technology*, 1st ed. PZWL, Warsaw.
- Kraciuk R., Sznitowska M., 2011. Effect of different excipients on the physical characteristics of granules and tablets with carbamazepine prepared with polyethylene glycol 6000 by Fluidized Hot-Melt Granulation (FHM). *AAPS Pharm Sci Tech.* 12, 4, 1241-1247.
- Rajniak P., Mancinelli C., Chern R. T., Stepanek F., Farber L., Hill B. T., 2007. Experimental study of wet granulation in fluidized bed: Impact of the binder properties on the granule morphology. *Int. J. Pharm.* 334, 1, 92-102.
- Seppälä K., Heinämäki J., Hatara J., Seppälä L., Yliruusi J., 2010. Development of a new method to get a reliable powder flow characteristics using only 1 to 2 g of powder. *AAPS Pharm Sci Tech.* 11, 1, 402-408.
- Szumilo M., Zimmer Ł., Swiader K., Belniak P., Dwornicka D., Paz C., Poleszak E., 2012. The influence of excipients on dissolution of caffeine from granules. *Curr. Iss. Pharm. Med. Sci.* 25, 2, 194-197.
- The Council of Europe, 2014. *The European Pharmacopoeia*, 8th ed. Strasbourg.
- The Minister of Health, 2002. *The Polish Pharmacopeia*, 6th ed. Warsaw.
- Tkachenko M.L., Zhnyakina L.E., Kosmynin A.S., 2003. Physicochemical investigation of paracetamol-caffeine solid mixtures. *Pharm. Chem. J.* 37, 8, 430-432.
- Uribarri E., Laguna A., González M., 2003. Studies of wet granulation in small scale high shear mixer of 20 mg tablets of policosanol. *Boll. Chim. Farm.* 142, 8, 343-346.

TABLES

Table 1. The composition of granules (amounts of the substances are given in parts)

Granules	Paracetamol	Caffeine	Lactose	Mannitol	Calcium hydrophosphate	Corn starch	PEG 6000	PVP K30
I	1.67	0.33	88.00				10.00	
II	1.67	0.33		88.00			10.00	
III	1.67	0.33		44.00	44.00		10.00	
IV	1.67	0.33			88.00		10.00	
V	1.67	0.33	52.80			35.20	10.00	
VI	1.67	0.33	93.00					5.00
VII	1.67	0.33		93.00				5.00
VIII	1.67	0.33		46.50	46.50			5.00
IX	1.67	0.33			93.00			5.00
X	1.67	0.33	55.80			37.20		5.00

Table 2. The moisture measurement time t [min] and the moisture content in the granules M [percent] and the standard deviation of the moisture content SD ($n = 5$)

Granules I			Granules II			Granules III			Granules IV			Granules V		
t [min]	M [%]	SD	t [min]	M [%]	SD	t [min]	M [%]	SD	t [min]	M [%]	SD	t [min]	M [%]	SD
3.23	4.92	0.03	2.56	0.75	0.02	2.26	0.58	0.03	2.32	0.77	0.04	5.46	6.22	0.06
Granules VI			Granules VII			Granules VIII			Granules IX			Granules X		
t [min]	M [%]	SD	t [min]	M [%]	SD	t [min]	M [%]	SD	t [min]	M [%]	SD	t [min]	M [%]	SD
9.66	4.75	0.08	2.03	0.87	0.03	2.53	1.03	0.04	2.26	1.08	0.10	13.49	6.59	0.04

Table 3. Particle-size distribution of granules (n = 3)

Granules	The mass of granules [g]				Granules	The mass of granules [g]			
	fraction 2.0 mm > 1.25 mm	fraction 1.25 mm > 1.0 mm	fraction 1.0 mm > 0.75 mm	fraction < 0.75 mm		fraction 2.0 mm > 1.25 mm	fraction 1.25 mm > 1.0 mm	fraction 1.0 mm > 0.75 mm	fraction < 0.75 mm
I	21.31	2.31	1.28	0.10	VI	21.99	1.95	0.96	0.10
II	21.82	1.97	1.04	0.17	VII	21.38	2.04	1.34	0.24
III	23.05	1.07	0.65	0.24	VIII	24.45	0.33	0.10	0.11
IV	22.87	1.07	0.72	0.34	IX	21.26	1.77	1.34	0.63
V	21.32	1.20	1.04	1.44	X	18.24	2.70	2.11	1.95

Table 4. Apparent density (d_0) and tapped density of granules (d_{1250}) [g/mL] (n=3)

Granules I		Granules II		Granules III		Granules IV		Granules V	
d_0	d_{1250}	d_0	d_{1250}	d_0	d_{1250}	d_0	d_{1250}	d_0	d_{1250}
0.508	0.551	0.444	0.469	0.513	0.546	0.609	0.671	0.450	0.506
Granules VI		Granules VII		Granules VIII		Granules IX		Granules X	
d_0	d_{1250}	d_0	d_{1250}	d_0	d_{1250}	d_0	d_{1250}	d_0	d_{1250}
0.506	0.531	0.353	0.390	0.471	0.502	0.577	0.635	0.450	0.507

Table 5. Angle of repose α [degrees] and flow property of granules (n=5)

Granules I		Granules II		Granules III		Granules IV		Granules V	
α [°]	Flow property	α [°]	Flow property	α [°]	Flow property	α [°]	Flow property	α [°]	Flow property
39.64	Fair	39.02	Fair	37.94	Fair	39.88	Fair	37.76	Fair
Granules VI		Granules VII		Granules VIII		Granules IX		Granules X	
α [°]	Flow property	α [°]	Flow property	α [°]	Flow property	α [°]	Flow property	α [°]	Flow property
39.60	Fair	38.90	Fair	36.70	Fair	39.14	Fair	37.64	Fair

Table 6. The flow time of granules through the orifice t [s/100 mL] and the standard deviation

SD (n=5)

Granules I		Granules II		Granules III		Granules IV		Granules V	
t [s/100mL]	SD	t [s/100mL]	SD	t [s/100mL]	SD	t [s/100mL]	SD	t [s/100mL]	SD
8.3	0.11	7.9	0.47	8.6	0.68	8.1	0.37	7.7	0.55
Granules VI		Granules VII		Granules VIII		Granules IX		Granules X	
t [s/100mL]	SD	t [s/100mL]	SD	t [s/100mL]	SD	t [s/100mL]	SD	t [s/100mL]	SD
8.1	0.22	7.7	0.43	8.0	0.42	8.1	0.63	7.7	0.29

Table 7. The flow time of granules through the orifice t [s/100 g] and the standard deviation

SD (n=3)

Granules I		Granules II		Granules III		Granules IV		Granules V	
t [s/100 g]	SD	t [s/100 g]	SD	t [s/100 g]	SD	t [s/100 g]	SD	t [s/100 g]	SD
16.2	0.12	21.2	0.55	17.4	0.38	16.1	1.07	22.8	1.53
Granules VI		Granules VII		Granules VIII		Granules IX		Granules X	
t [s/100 g]	SD	t [s/100 g]	SD	t [s/100 g]	SD	t [s/100 g]	SD	t [s/100 g]	SD
18.9	0.49	23.0	0.36	19.2	0.80	16.9	0.75	23.5	0.93

Table 8. The amount of granules passing through the orifice m [g/10 s] and the standard deviation SD (n=3)

Granules I		Granules II		Granules III		Granules IV		Granules V	
m [g/10 s]	SD	m [g/10 s]	SD	m [g/10 s]	SD	m [g/10 s]	SD	m [g/10 s]	SD
67.0	0.61	50.2	2.76	41.0	1.46	60.6	0.84	57.6	0.15
Granules VI		Granules VII		Granules VIII		Granules IX		Granules X	
m [g/10 s]	SD	m [g/10 s]	SD	m [g/10 s]	SD	m [g/10 s]	SD	m [g/10 s]	SD
52.4	2.56	44.0	1.57	38.5	0.78	60.3	2.28	50.5	2.19

Table 9. The mean flow angle α [°] (n = 3)

Granules I	Granules II	Granules III	Granules IV	Granules V
81.0	78.8	80.2	82.1	79.1
Granules VI	Granules VII	Granules VIII	Granules IX	Granules X
78.7	76.5	79.6	81.9	78.8

Table 10. Compressibility index – CI (per cent), Flow character – FCh and Hausner ratio - HR

(n=3)

Granules I			Granules II			Granules III			Granules IV			Granules V		
CI	FCh	HR	CI	FCh	HR	CI	FCh	HR	CI	FCh	HR	CI	FCh	HR
7.69	Excellent	1.08	5.26	Excellent	1.06	6.04	Excellent	1.07	9.19	Excellent	1.10	11.19	Good	1.13
Granules VI			Granules VII			Granules VIII			Granules IX			Granules X		
CI	FCh	HR	CI	FCh	HR	CI	FCh	HR	CI	FCh	HR	CI	FCh	HR
4.59	Excellent	1.05	10.48	Excellent	1.11	6.24	Excellent	1.07	9.13	Excellent	1.10	11.21	Good	1.13

Table 11. Disintegration time of granules t [s] and the standard deviation SD (n=5)

Granules I		Granules II		Granules III		Granules IV		Granules V	
t [s]	SD	t [s]	SD	t [s]	SD	t [s]	SD	t [s]	SD
95.60	0.89	58.60	1.52	10.40	0.55	10.20	1.10	13.00	1.22
Granules VI		Granules VII		Granules VIII		Granules IX		Granules X	
t [s]	SD	t [s]	SD	t [s]	SD	t [s]	SD	t [s]	SD
86.20	1.10	56.00	0.71	9.80	0.84	9.40	0.55	12.60	0.89

FIGURES

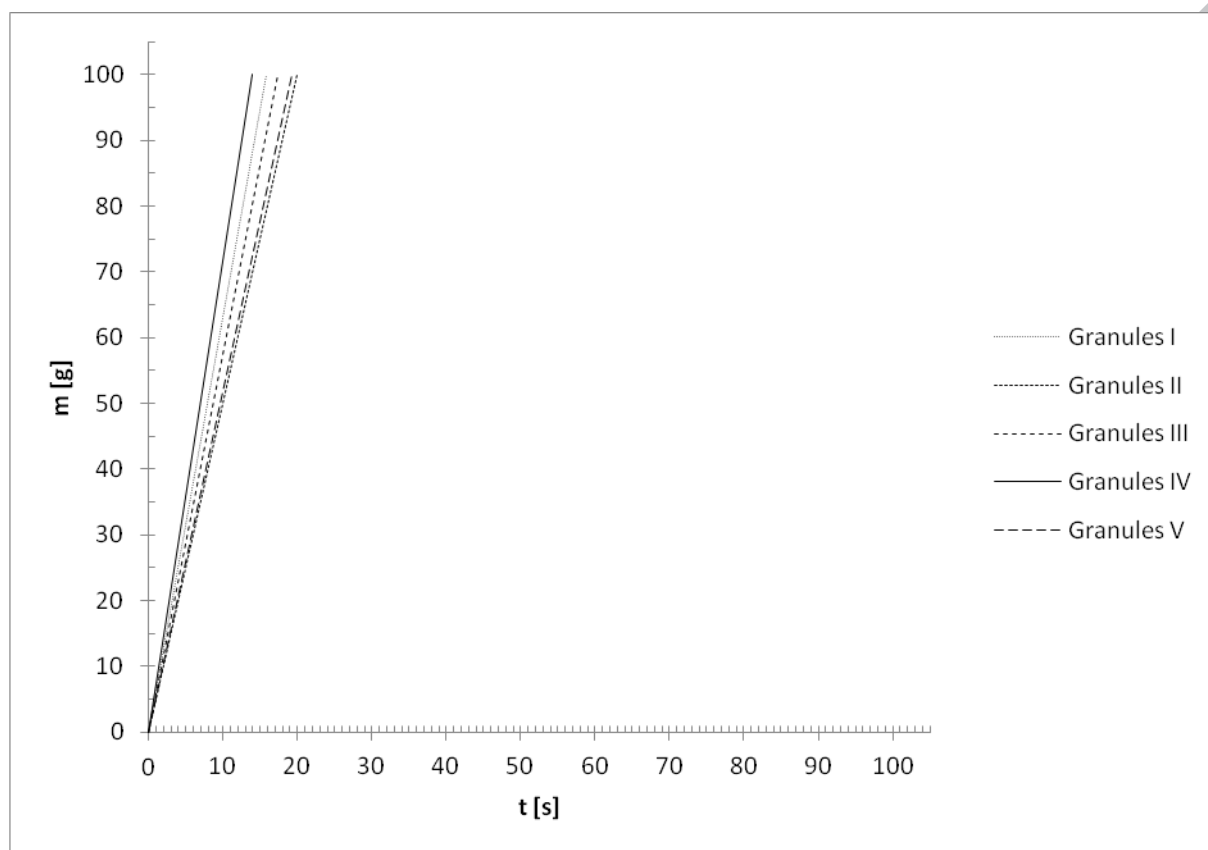


Fig. 1 Flow diagram of granules I-V (n = 3)

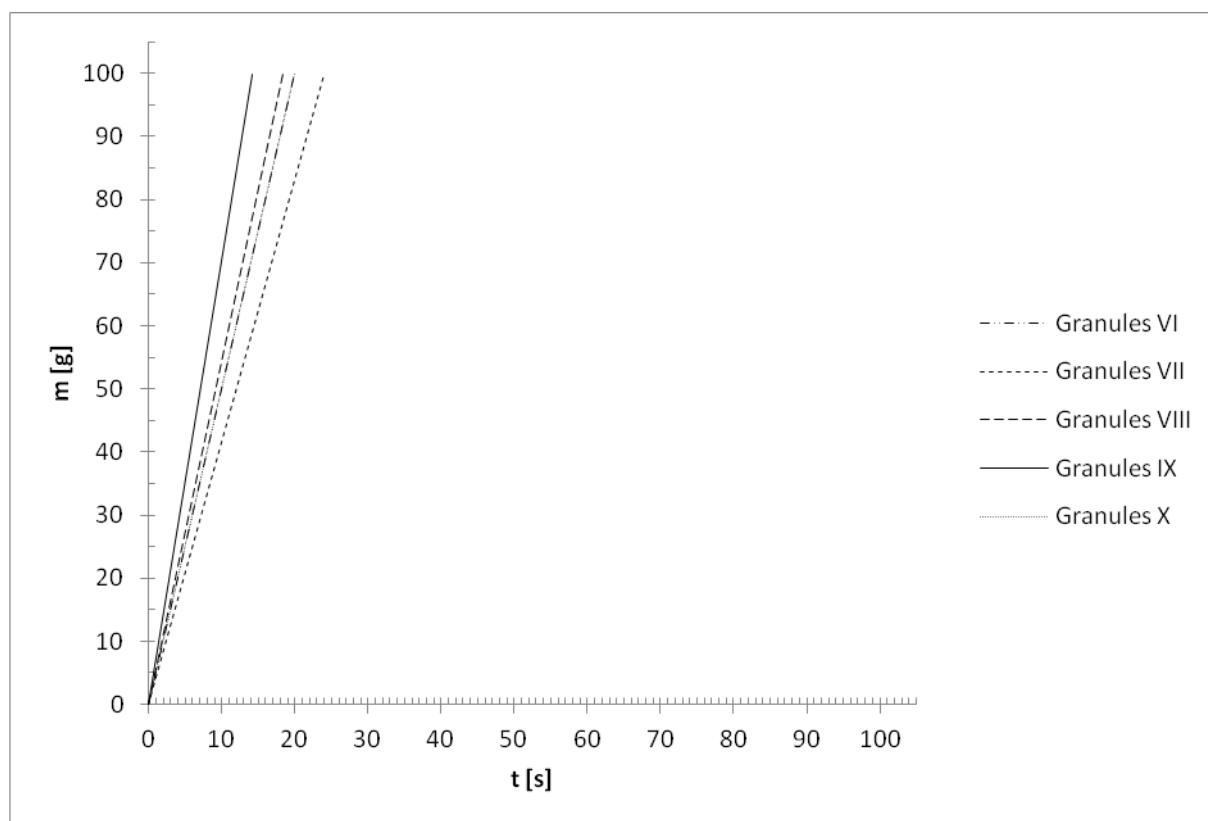


Fig. 2 Flow diagram of granules VI-X ($n = 3$)