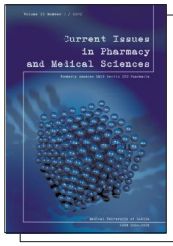

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Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy

The influence of excipients on dissolution of caffeine from granules

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ABSTRACT

Four formulas of granules with caffeine were chosen to examine the influence of excipients on dissolution profiles of active substance from this drug form. The formula I: caffeine 1.0 parts, potato starch 69,3 parts, lactose 29,7 parts, glycerol 86% 2.0 parts, gelatin mucilage 4% (w/w) 98.0 parts; the formula II: caffeine 1.0 parts, Avicel 49,5 parts, lactose 49,5 parts, glycerol 86% 2.0 parts, gelatin mucilage 4% (w/w) 98.0 parts; the formula III: caffeine 1.0 parts, D-Mannitol 99,0 parts, glycerol 86% 2.0 parts, gelatin mucilage 4% (w/w) 98.0 parts and the formula IV: caffeine 1.0 parts, Avicel 49,5 parts, lactose 49,5 parts, and 0.5% solution of PVP 100.0 parts. This solution was prepared by dissolution of 0.5 parts PVP in 95.5 parts of mixture of ethanol 96° and water 1:1 (w/w). The granules were obtained in wet granulator. Their flow properties, moisture content, disintegration time and dissolution of active substance were tested. All granules passed the pharmacopoeial dissolution test because 80% of caffeine dissolved in 10 minutes time.

Keywords: caffeine, granules, excipients, wet granulation, dissolution

INTRODUCTION

The caffeine is a popular active substance frequently included in oral analgesic preparations together with aspirin, paracetamol, or codeine. As a stimulant of the central nervous system, it can produce a condition of wakefulness and increased mental activity [1]. The substance is sparingly soluble in water and has very poor flow properties (a flow rate below 10 mg/s) [9]. Application of caffeine as granules with suitable excipients may contribute to improvement of its physical properties. The granule can be taken easily and the active substance can be dosed more precisely.

The aim of this paper is to analyze the influence of excipients on technological parameters of granules with caffeine. First, formulas of granules were elaborated, than all of them were tested. Their flow properties, moisture content, disintegration time and dissolution profile of active substance were tested.

MATERIAL AND METHODS

Reagents and instrumentation

The following substances were used to prepare granules: anhydrous caffeine (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), potato starch (Melvit S.A., Ostroleka, Poland), lactose (PPH Galfarm Cracow, Poland), gelatin from bovine skin (Loba Feinchemie GmbH, Fischamend, Austria), glycerol (PPH POCH SA Gliwice, Poland), Avicel – microcrystalline cellulose (FMC BioPolymer, Brussels, Belgium), D-mannitol (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), polyvinylopyrrolidone K30 (PVP) (Fluka Chemie AG, Buchs, Swiss) and ethanol (PPH POCH S.A., Gliwice, Poland). Hydrochloric acid 0.1 mol/l (PPH POCH SA Gliwice, Poland) was used to prepare solutions of caffeine for spectrophotometric examinations and as a dissolution media in *in vitro* dissolution test.

The granules were obtained in wet granulator Erweka FAG (Germany). The measurement of moisture content was performed with a moisture analyzer WPS 210S manufactured by RADWAG (Radom, Poland). The patent apparatus for the measurement of repose of powders and granules [3] consistent with requirements of Polish Pharmacopoeia IX [8] was applied to measure mechanical qualities of granules. A dissolution test was conducted using a paddle dissolution tester Erweka DT 600 (Germany). The amount of caffeine in solutions obtained from granules was examined in spectrophotometer UV-Vis (Helios Omega Thermo Scientific, USA) with Vision Pro software.

Preparation of granules

Four formulas of granules with caffeine were obtained. *The **formula I***: caffeine 1.0 parts, potato starch *69.3* parts, lactose *29.7* parts, glycerol 86% 2.0 parts, gelatin mucilage 4% (w/w) 98.0 parts.

*The **formula II***: caffeine 1.0 parts, *Avicel 49.5* parts, lactose *49.5* parts, glycerol 86% 2.0 parts, gelatin mucilage 4% (w/w) 98.0 parts.

*The **formula III***: caffeine 1.0 parts, *D-Mannitol 99.0* parts, glycerol 86% 2.0 parts, gelatin mucilage 4% (w/w) 98.0 parts.

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*The **formula IV***: caffeine 1.0 parts, *Avicel 49.5* parts, lactose *49.5* parts, and 0.5% solution of *PVP* 100.0 parts. This solution was prepared by dissolution of 0.5 parts PVP in 95.5 parts of mixture of ethanol *96*° and water 1:1 (w/w).

Preparation: The substances were weighed out. Powdered substances were added in portions to a mortar and then they were mixed. Solutions of binding substances were added in small portions to powders, until the plastic mass was obtained. This mass was granulated in wet granulator through a shield of 2.2 mm. The granule was dried in dryer at temperature of 45°C for 63 h. Then, it was sifted through a sieve of 1.6 mm to obtain uniform granule. The dust was sifted through a sieve of 1.2 mm and these particles were granulated again [6, 10].

MEASUREMENTS OF PROPERTIES OF GRANULES

Measurement of the moisture content in the granules

This measurement was based on determination of dry mass. The tests were performed with a moisture analyzer. The analyzer determined start mass of a sample, and performed continuous measurement during intensive heating process with a halogen lamp at 130°C. The measurement was finished when the mass of tested sample of granules was not changed during 10 seconds [2].

Sieve test

The degree of fineness of granules was determined by sieving them through sieves of 1.20 mm, 1.02 mm and 0.75 mm placed one on another on a laboratory shaker. The mass of granules was controlled in every 5 minutes. The test lasted 15 minutes. A percentage m/m passing the sieves was calculated after that [8].

Measurement of the flow time

The measurement was performed in accordance to requirements of Polish Pharmacopoeia IX [8]. During measurement, the definite volume of granules (100 ml) was deposited in the funnel of the apparatus and the time of monotonous flow of the whole quantity of granules was measured with a stopwatch. The nozzle under a funnel of the apparatus had a diameter of 10.0 mm.

Measurement of the angle of repose

The measurement of the angle of repose was done in the same apparatus as the above test [3]. The measured volume of granules (100 ml) was placed in the funnel of the apparatus with a closed nozzle. After opening of the nozzle the granule was piling up the cone. The height of the cone was measured at constant diameter (100 mm) of its basis, which was marked with the external edge of the apparatus. Based on the height of the cone and its diameter, tangent of the angle created by freely flowing granule was counted using trigonometric functions. The measurement was made at constant distance among the funnel and the basis of the apparatus (600 mm), size of the nozzle of the funnel (10 mm), and constant volume of tested granule [8, 10].

Measurement of the apparent volume and poured density

The graduated cylinder of 250 ml was used for measurement of apparent volume of granules. The 250 ml of examined granules that is regarded as the unsettled apparent volume was placed into the dry cylinder without compacting. Such measurement is recommended by Polish Pharmacopoeia IX [8]. The results of poured density or apparent density before settling could be expressed in grams per milliliter.

Disintegration test

One dose of granules (1 g) was placed in a conical flask containing 50 ml of water at 37°C±2°C. The flask had to be moved with round movements every 30 s. Granules had to be dissolved or dispersed in water within 10 minutes [7].

Determination of absorption spectrum and standardization curve for caffeine solution

The solution of caffeine in hydrochloric acid (0.1 mol/l) with the concentration of 0.01 mg/ml was prepared in accordance to Polish Pharmacopoeia VI. It was measured spectrophotometrically over the range 230 to 360 nm [7, 10]. The absorption spectrum of solution reached the maximum at 272 nm. Then the absorbance of caffeine solutions in hydrochloric acid (0.1 mol/l) with the concentrations from 0.005 mg/ml to 0.05 mg/ml was measured at maximum λ = 272 nm and the standardization curve was made. The standardization curve can be described by the equation: A = 45.4613 x C (A – absorbance, C – concentration). Coefficient was 0.999422.

Dissolution test. A dissolution test of caffeine from granules was conducted using a paddle tester in compliance with method 2 (paddle apparatus) in Polish Pharmacopoeia IX [8]. The dissolution medium was 900 ml of hydrochloric acid (0.1 mol/l). Other parameters included paddle speed of 75 rpm and temperature of 37±0,5°C [4]. Granules equivalent to 150 mg caffeine were added directly into the dissolution medium. Samples were taken at 1, 2, 5, 10, 15, 30, 45 and 60 min, and replaced with an equal volume of the same medium. An aliquot of 2.0 ml was filtered through a 0.22 mm filter. The sample solutions were diluted and the concentration of dissolved caffeine was determined using the UV-VIS method at 272 nm. In this study, the dissolution percentage after 10 min was used to evaluate the dissolution properties of granules in accordance to Pharmacopoeia [8]. All experiments were performed six times.

RESULTS AND DISCUSSION

The analysis of the data from the examination of granules allowed for defining the influence of excipients on the physical properties of granules and the active substance, like dissolution or flow properties.

The moisture content was the highest in granule I. It was caused by large amount of potato starch (70%) which is hygroscopic. The lowest moisture was in granule III with mannitol. The type of binding solution did not influence moisture content, which proved similar moisture content in granule II and IV.

The sieve test showed that the most uniform particles were in granule I. The granule II and III had similar particles' size, but differences between fractions were greater.

The granule IV revealed the largest variations of sizes between fractions of particles and this feature distinguished it from the other granules. It is caused by binding solution used in production of this granule. Gelatin mucilage bounded particles stronger than PVP solution and it was the reason the granules I, II and III were more uniform than the granule IV.

Table 1. The mean moisture content in the granules and standard deviation (n=10)

Granule I		Granule II		Granule III		Granule IV	
M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
7.04	4.66	3.92	4.52	0.95	7.79	3.16	4.93

M [%] – mean moisture content, *SD* [%] – standard deviation

Table 2. The fineness of granule particles (n=3)

Granule	A percentage m/m passing the sieves [%]			
	fraction 1.6 mm >1.2 mm	fraction 1.2 mm >1.02 mm	fraction 1.02 mm >0.75 mm	fraction <0.75 mm
I	94.84	4.00	1.12	0.04
II	91.76	6.52	1.64	0.08
III	92.60	6.36	0.96	0.08
IV	79.60	15.04	4.84	0.52

Granules I and II had the shortest and similar flow time. The flow time was the longest for granule IV. Granule II and IV had the same ingredients but different binding solutions. This was a cause of their worse flow properties.

Table 3. The mean flow time and standard deviation (n=10)

Granule I		Granule II		Granule III		Granule IV	
t	*SD*	*t*	*SD*	*T*	*SD*	*t*	*SD*
16.94	1.07	15.98	1.74	18.60	0.99	28.91	1.03

t [seconds] – mean flow time, *SD* [%] – standard deviation

All granules exhibited similar angle of repose. The granule III had the lowest and the granule IV the highest angle. These results referred to good and in granule III – very good flow ability. Seppälä et al. [9] confirmed that mannitol had a better flow ability than lactose. Application of caffeine in the form of granule improved its flow ability, because as pure substance it had only fair flow ability [9].

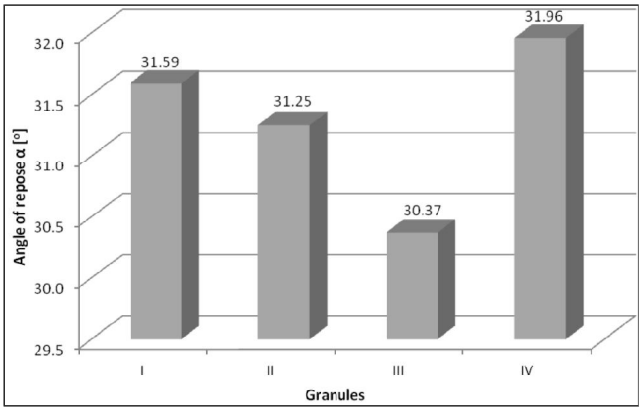

Fig. 1. The mean angle of repose á (n=10)

The granule I and III had identical poured density. Poured density of granule II was almost two times higher than granule IV. This granule had the lowest poured density. It was the consequence of strongly bounding of particles by gelatin mucilage in granules I, II and III.

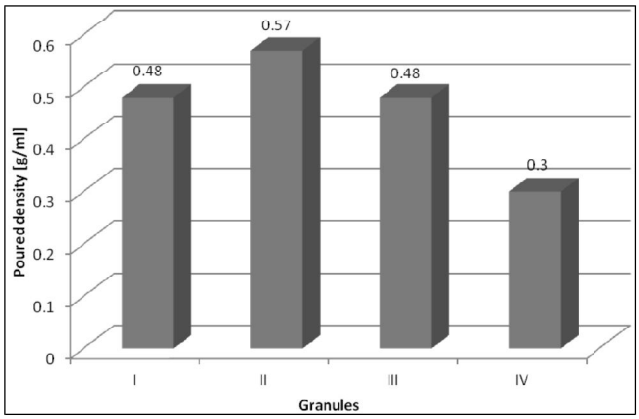

Fig. 2. The mean poured density of the granules (n=3)

After disintegration test it was obvious that the granule III did not meet the pharmacopoeial standards, because it was dispersed in water after 60 minutes. This was the result of the reaction between microcrystalline cellulose and gelatin mucilage. The change of binding solution reduced the disintegration time seven times. The other granules dispersed in water during 10 minutes, which was in accordance to pharmacopoeial standards. The granule IV had the optimal disintegration time. This proved that combination of lactose and microcrystalline cellulose increased the resistance of granule [5].

Table 4. The mean disintegration time and standard deviation (n=10)

Granule I		Granule II		Granule III		Granule IV	
t	*SD*	*t*	*SD*	*t*	*SD*	*t*	*SD*
1.84	11.30	60.00	0.00	2.60	8.96	8.75	3.62

t [minutes] – mean disintegration time, *SD* [%] – standard deviation

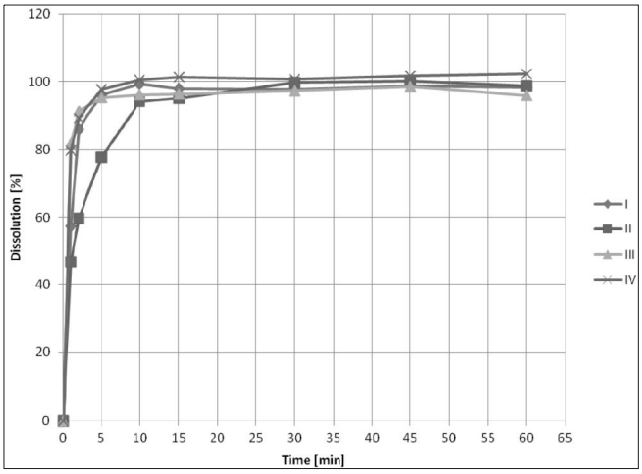

Fig. 3. Dissolution profiles of caffeine from granules in time (n=6)

Dissolution test revealed the fastest release of caffeine from the granule III and IV with 81.80% and 79.89% of active substance released after 1 minute respectively. From granule I, 57.25% of caffeine was released and 46.69% from

granule II at the same time. Although the granule III did not meet the pharmacopoeial standards in disintegration test, it dissolved active substance in accordance to standards [8]. It was probable that caffeine dissolved quickly from granules even though excipients (microcrystalline cellulose and lactose) were strongly bounded with gelatin mucilage. All granules passed the dissolution test, because more than 90% of caffeine was dissolved from the drug form in 10 minutes. It was: 99.26%, 94.05%, 96.12%, 100.47% from I, II, III, IV granule respectively. Pharmacopoeial standards required 80% dissolution of active substance in 10 minutes [8].

CONCLUSIONS

The result of the study indicated that excipients influenced moisture content of granules. The lowest one had the granule with mannitol. The binding solution did not influence this feature. Granules made with gelatin mucilage had more homogenous particles in contrast to particles of granule made with PVP solution. The binding solution influenced flow properties of granules and PVP significantly extended their flow time. The caffeine in the form of granules had better flow properties. The best one was the granule with mannitol, which had the smallest angle of repose. This granule is suitable for patients with lactose intolerance. Gelatin mucilage cannot be used in granules with microcrystalline cellulose, because such a granule did not meet the pharmacopoeial standards in disintegration test. All of prepared granules passed the pharmacopoeial dissolution test because 80% of active substance dissolved in 10 minutes.

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