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Original article

Assessment of physical properties of granules with paracetamol and caffeine

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ABSTRACT

Caffeine increases the analgesic properties of acetaminophen and therefore it is reasonable to use both substances together in one drug form in stronger pain. Currently, there are no commercially available pharmaceutical combination products containing acetaminophen and caffeine, which is present as granules. The aim of the study was to obtain twelve different granules with these therapeutic substances and determine the effect of various excipients on the quality of the drug form. All the granules were made by wet granulation. Two types of binders were used: polyethylene glycol 6000 (PEG) and polyvinylpyrrolidone K30 (PVP) as well as different types of fillers. The physical properties of granules were assessed in accordance to the requirements of the European Pharmacopoeia 8th ed. The highest apparent density was found in preparations containing calcium hydrophosphate (0.609 g/mL) and the lowest – containing mannitol (0.353 g/mL) as a filler. 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%. 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.

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).

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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–Aidrich 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.

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 (Memmert 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.

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.

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

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