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THE INFLUENCE OF EXCIPIENTS ON PHYSICAL PROPERTIES OF TABLETS AND DISSOLUTION OF CAFFEINE

MICHAŁ SZUMIŁO*, KATARZYNA ŚWIĄDER, PIOTR BELNIAK, JESSICA WOJCIECHOWSKA and EWA POLESZAK

Chair and Department of Applied Pharmacy, Medical University of Lublin, 20-093 Lublin, 1 Chodzki St., Poland

Abstract: Caffeine is a common component of everyday diet but also a popular ingredient of some analgesics. Before it is administered to a patient, it has to be properly prepared using appropriate procedures to get the suitable drug form with various excipients. The tablets with caffeine were obtained using a wet granulation method. Three groups with four series of tablets were obtained with the constant concentration of caffeine but with different combinations of excipients, including potato starch and lactose, microcrystalline cellulose and lactose and D-mannitol alone. The binder solution of polyvinylpyrrolidone was added in all series of granules used in tabletting but in different quantities. A number of pharmacopoeial tests were conducted to determine the properties of the obtained tablets. All series of tablets positively passed physical tests. More than 80% of caffeine dissolved after 45 min from most series. Only two of 12 series of tablets did not meet pharmacopoeial requirements in a dissolution test. The results of the study indicated that proposed compositions of the tablets are suitable for administration of caffeine in that drug form.

Keywords: caffeine, tablets, excipients, binder, dissolution

Tablets are one of the most prevalent and frequently used drug forms. They are characterized by number of advantages including convenient form to use, ensure dosing accuracy, stability of the drug substance and modification of its release. Moreover, the process of compression is profitable and used on large industrial scale (1).

The basis of modern technology of solid oral drug form is preparation of optimal form that allows suitable concentration of the active substances in the human tissues, taking into consideration the physicochemical properties of both, the active ingredients and excipients. Additionally, the drug form has to be easy used as a medicament (2).

Caffeine is a well-known psychoactive substance that is present mainly in coffee, tea, soft and energy drinks, but it can be also used as an active ingredient of medicaments (3). Caffeine is applied in patients with hypotension, orthostatic hypotension, syncope or circulatory collapse. Together with paracetamol, aspirin or codeine, it is an ingredient of some analgesic preparations (Apap Extra, Coffepirine, Solpadeine) (4). Caffeine increases their analgesic effects by nearly 40%. Caffeine with ergotamine is applied in treatment of migraine and vasomotor headaches. It can replace conventional non-steroidal anti-inflammatory drugs (NSAIDs) in analgesic preparations, since it has fewer side effects mostly associated with inhibition of cyclooxygenase isoforms, e.g., it does not affect platelet aggregation and coagulation (5, 6).

The aim of this study was to obtain and compare the tablets with caffeine using the wet granulation method. A series of tests were conducted to determine the effect of different types and quantities of excipients on the properties of tablets.

EXPERIMENTAL

Materials

The following substances were used in preparation of tablets and in further study: anhydrous caffeine (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), lactose monohydrate (Pharma Cosmetic, Kraków, Poland), potato starch, ethanol 96 percent v/v, the analytical sample with hydrochloric acid 0.1 mol/L (Avantor Performance Materials, Poland

* Corresponding author: e-mail: michal.szumilo@umlub.pl

S.A., Gliwice, Poland), microcrystalline cellulose Avicel PH-101 (FCM BioPolymer, Brussels, Belgium), D-mannitol (Pharma-Zentrale GmbH, Herdecke, Germany), polyvinylpyrrolidone K 30 (PVP) (Fluka Chemie AG, Buchs, Switzerland), corn starch (Radix – Bis, Rotmanka, Poland) and magnesium stearate (PPH ''Standard'' Sp. z o. o. Lublin, Poland). All the reagents and chemicals used were of analytical grade.

Granulation and tabletting

Granules were prepared by wet granulation method. The binder solution of polyvinylpyrrolidone (PVP) in ethanol 96 percent and water (1 : 1, v/v) was added to the mixture of caffeine and excipients. The wet mass was granulated in rotary granulator (Erweka, Germany) using a disc with a mesh size of 1.6 mm. Then, the granules were dried in a dryer (Memmert INB500, Germany) at 50^{o}C for 5 h and unified.

Table 1. The composition of tablets with different excipients (concentration – % w/w)

Group	Tablets	Caffeine	Potato starch	Lactose	Avicel	D-Mannitol	PVP	Corn starch	Magnesium stearate
1	I	40.00	33.95	14.55			1.00	10.00	0.50
	II	40.00	32.90	14.10			2.50	10.00	0.50
	III	40.00	31.15	13.35			5.00	10.00	0.50
	IV	40.00	27.65	11.85			10.00	10.00	0.50
2	V	40.00		24.25	24.25		1.00	10.00	0.50
	VI	40.00		23.50	23.50		2.50	10.00	0.50
	VII	40.00		22.25	22.25		5.00	10.00	0.50
	VIII	40.00		19.75	19.75		10.00	10.00	0.50
3	IX	40.00				48.50	1.00	10.00	0.50
	X	40.00				47.00	2.50	10.00	0.50
	XI	40.00				44.50	5.00	10.00	0.50
	XII	40.00				39.50	10.00	10.00	0.50

Table 2. The average results of measuring the uniformity of the thickness, diameter and mass of the tablets (n = 20).

Series	Thickness [mm]	Diameter [mm]	Mass [mg]	SD [%]
Group 1				
Tablets I	3.02	9.02	248.35	3.93
Tablets II	3.04	9.05	249.59	4.56
Tablets III	3.01	9.04	249.83	4.47
Tablets IV	2.96	9.02	246.46	3.75
Group 2				
Tablets V	3.13	9.02	251.13	3.78
Tablets VI	3.19	9.04	248.54	4.81
Tablets VII	3.29	9.02	250.87	4.09
Tablets VIII	3.26	9.03	248.93	4.85
Group 3				
Tablets IX	3.07	9.03	247.44	4.02
Tablets X	3.14	9.02	248.76	4.31
Tablets XI	3.27	9.06	245.13	4.30
Tablets XII	3.28	9.03	248.48	3.83

SD - standard deviation of the mass

Table 3. Mass of tablets before and after the friability test.

Series	Mass before the test [g]	Mass after the test [g]	Mass loss [g]	Mass loss [%]
Group 1				
Tablets I	6.488	6.434	0.054	0.83
Tablets II	6.489	6.442	0.047	0.72
Tablets III	6.535	6.513	0.022	0.34
Tablets IV	6.594	6.573	0.021	0.32
Group 2				
Tablets V	6.578	6.542	0.036	0.55
Tablets VI	6.490	6.464	0.026	0.40
Tablets VII	6.600	6.561	0.039	0.59
Tablets VIII	6.495	6.463	0.032	0.49
Group 3				
Tablets IX	6.402	6.356	0.046	0.72
Tablets X	6.486	6.448	0.038	0.59
Tablets XI	6.560	6.530	0.030	0.46
Tablets XII	6.508	6.470	0.038	0.58

Table 4. The average values of mass of the tablets before and after drying process, the time of the test and the moisture content (n = 10).

Series	Mass before the test [mg]	Mass after the test [mg]	Time [min]	Moisture [%]	SD [%]
Group 1					
Tablets I	245.44	224.13	2.02	6.44	0.96
Tablets II	246.98	228.76	1.58	7.38	1.05
Tablets III	248.32	230.87	2.08	7.78	1.05
Tablets IV	242.86	225.03	2.16	6.84	1.71
Group 2					
Tablets V	250.89	239.14	1.54	5.56	1.09
Tablets VI	251.26	237.62	2.01	4.80	1.70
Tablets VII	254.47	242.41	1.46	6.01	0.84
Tablets VIII	247.83	237.80	1.47	4.81	0.74
Group 3					
Tablets IX	237.05	234.75	1.51	4.64	0.70
Tablets X	248.33	241.33	1.38	3.89	0.78
Tablets XI	240.48	225.27	2.08	6.60	1.54
Tablets XII	243.55	226.12	2.28	8.29	0.92

SD - standard deviation of the moisture content.

The three groups of granules with different excipients were prepared (Table 1). In each group four series of granules containing an increasing amount of binding solution were made. The granules were mixed with the calculated proportional amounts of the lubricant i.e., 10.00% w/w of corn starch and 0.50% w/w of magnesium stearate. Their quantity in each series was identical. The mixture was then tabletted using punch tablet press (Erweka, Germany). Each tablet contained 100.00 mg of caffeine.

Uniformity of mass and size

Uniformity of mass was checked on 20 randomly selected tablets according to European Pharmacopoeia 7.0 (7). They were individually weighed using a precision balance (Mettler Toledo AT 201 Fact, Switzerland). Diameter and thickness (height) of tablets were measured by electronic caliper (Limit, Sweden) with an accuracy of 0.1 mm.

Friability of tablets

The pharmacopoeia test of friability was conducted in friability tester (Erweka TAR 120, Germany) on randomly selected tablets with total weight as close as possible to 6.5 g (7). The drum speed was set at 25 rpm. Test time was 4 min.

Thermal analysis

Measurement of the moisture content of 10 randomly selected tablets was performed by direct thermogravimetric method in a moisture analyzer (WPS 210S Radwag, Poland) at 130^{o}C (7, 8). The samples were dried to a constant mass. Moisture was determined relatively to the initial mass of the sample, as the loss of mass as per cent m/m.

Disintegration

The study required by the European Pharmacopoeia 7.0 (7) was made in disintegration tester (Erweka ZT 222, Germany) on six randomly selected tablets. The disintegration time was measured in water at 37 ± 2^{o}C.

Table 5. The average tablet disintegration time.

Time [min]			
Group 1	Group 2		Group 3
Tablets I 3:00	Tablets V 18:02	Tablets V 15:00 *	Tablets IX 8:19
Tablets II 5:32	Tablets VI 16:40	Tablets VI 15:00 *	Tablets X 10:12
Tablets III 7:37	Tablets VII 15:00		Tablets XI 10:18
Tablets IV 11:10	Tablets VIII 14:07		Tablets XII 10:35

* The disintegration time of 12 more tablets. The 16 units from the group of 18 tablets met the requirements of the pharmacopoeia.

Table 6. The average content of caffeine in tablet (n = 10).

Series	The average content [%]	SD [%]
Group 1		
Tablets I	102.74	2.74
Tablets II	100.49	0.49
Tablets III	101.81	1.81
Tablets IV	102.42	2.42
Group 2		
Tablets V	103.07	3.07
Tablets VI	99.87	0.13
Tablets VII	107.12	7.12
Tablets VIII	96.31	3.96
Group 3		
Tablets IX	99.73	0.27
Tablets X	109.20	9.20
Tablets XI	100.18	0.18
Tablets XII	100.41	0.41

SD - standard deviation.

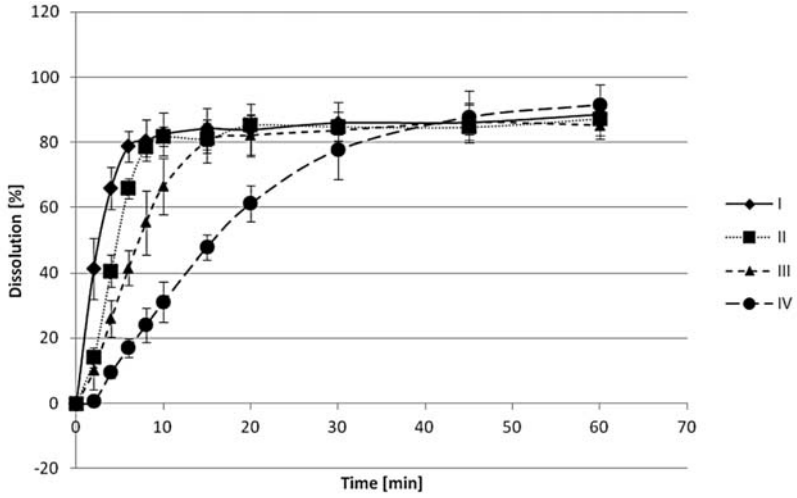

Figure 1. Dissolution profiles of caffeine from tablets of Group 1 in time (n = 6)

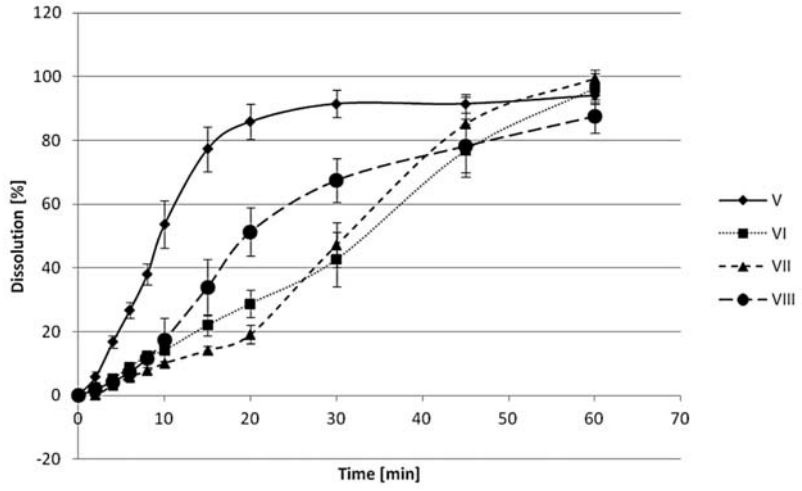

Figure 2. Dissolution profiles of caffeine from tablets of Group 2 in time (n = 6)

Uniformity of content

The test was performed according to the Ph. Eur. (7). Randomly taken 10 tablets were powdered and dissolved in 0.1 mol/L hydrochloric acid. The absorbance was measured at a wavelength of 272 nm (9). The amount of caffeine in solutions was determined in UV-Vis spectrophotometer (Helios Omega Thermo Scientific, USA) with Vision Pro software.

Dissolution test for tablets

The pharmacopoeia test was conducted in stirrer type dissolution tester with paddles (Erweka DT 600, Germany) using 6 randomly taken tablets from each series (7). Conditions were set as: 900 mL of 0.1 mol/L hydrochloric acid solution at 37 ± 0.5°C, stirrer speed 50 rpm. Samples were taken at the following times: 2, 4, 6, 8, 10, 15, 20, 30, 45 and 60 min. The absorbance of the solutions was measured at a wavelength of 272 nm (9). The solution of 0.1 mol/L hydrochloric acid was used as reference.

RESULTS AND DISCUSSION

A technology of tablets with caffeine using the wet granulation method was presented. Physical

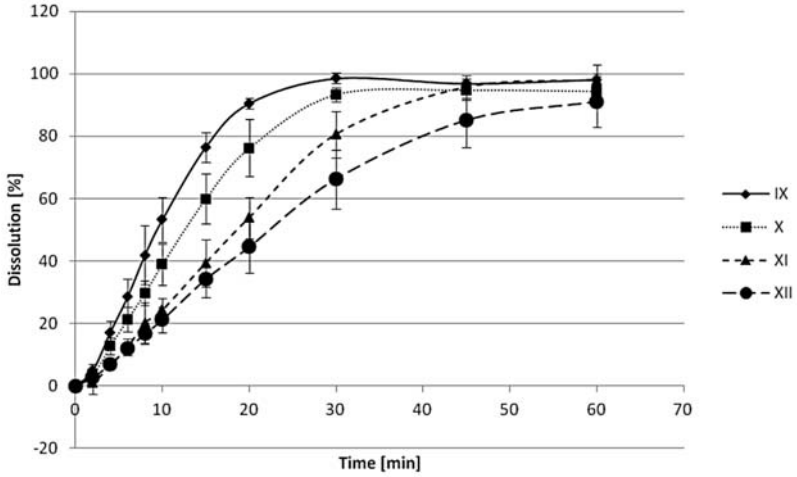

Figure 3. Dissolution profiles of caffeine from tablets of Group 3 in time (n = 6)

properties of obtained tablets were evaluated using various, mostly pharmacopoeial tests. Three groups of tablets were made with 4 series in each group. They contained different amounts of various excipients. In Group 1 potato starch and lactose in a ratio of 7 : 3 were applied. Group 2 contained microcrystalline cellulose and lactose in a ratio 1 : 1, whereas tablets from Group 3 were obtained using mannitol alone. In each group, a subsequent series of increasing binder content was applied as follows: 1.00, 2.50, 5.00 and 10.00% w/w of PVP. All series contained one active ingredient - caffeine in constant amount of 100.00 mg (40% w/w) in each tablet. The same lubricants in constant quantities were added just before the tableting process in all series. These were: corn starch (10.00% w/w) and magnesium stearate (0.50% w/w).

The uniformity of mass of single-dose preparations test showed that masses of tablets were included in the range from 237.50 to 262.50 mg and did not exceeded ± 5% deviation from the declared mass of tablets that was 250.00 mg (Table 2), so they met the criteria set by the Ph. Eur. (7). The diameter of the tablets was also measured and for each series it did not differ by more than 0.1 mm (Table 2). The difference in the thickness of tablets did not exceed deviation of ± 5% (Table 2). The external appearance of tablets was assessed as well. They were characterized by a uniform and smooth surface without any mechanical defects.

Mechanical strength of the tablets were evaluated; it was carried out by friability test. None of the series exceed 1.0% the mass loss (Table 3) and it was consistent with requirements of Ph. Eur. (7). The largest loss of mass was noted for Group 1 compared to other groups. Furthermore, in this group, the loss of mass was parallel with amount of PVP and was the highest in tablets with lower amount of PVP. Generally, the mechanical strength of tablets increased with binder content, what was also observed by the others (10).

The moisture and water content in the tablets was also examined (Table 4). The highest moisture content was in tablets containing starch and lactose (Group 1) while the lowest in tablets with microcrystalline cellulose and lactose (Group 2). It is clear that increased moisture content is the consequence of hygroscopic properties of potato starch (11).

An important physical feature of tablets affecting the pharmaceutical availability of the active substance is a disintegration time. This feature greatly affects the rate of dissolution of active ingredient from the drug form, and thereby provides the desired therapeutic effect. Disintegration time was longer for series V and VI from Group 2 (Table 5) than that recommended by Ph. Eur. i.e., 15 min (7). After repeating the study on the next 12 tablets of these series, the obtained results were acceptable. In most series disintegration time of tablets was prolonged with increasing amount of binder - PVP. It is well seen in Groups 1 and 3. Such relationship was not observed for Group 2 with mixture of excipients, i.e., microcrystalline cellulose and lactose. As reported by Kolodziejczyk and Zgoda (10) as well as Szumiło et al. (11), the combination of these two components in the suitable ratio results in increased stability and durability of tablets or granules.

It can be concluded that increased disintegration time of the tablets is associated with higher content of the binding components. That in turn, leads

to longer release time of the active substance and prolonged action of the drug.

Uniformity of content test revealed that caffeine content in obtained tablets ranged from 96.31 to 109.20% (Table 6). The tablets meet the pharmacopoeial criteria (85-115% of active substance content in one unit) (7).

In the final part of the study the dissolution of caffeine from tablets test was conducted. It allows specifying the pharmaceutical availability that is the rate of active substance released from the drug form, which determines, among others, the rate of absorption of the drug in the organism (7).

The results are shown in figures as relation of the quantity of caffeine dissolution over time. The results of dissolution of tablets from Group 1 containing lactose and potato starch are shown in Figure 1. These tablets are characterized by rapid release of the active substance. The presented results showed that the rate of drug dissolution decreased with increasing amount of binder (PVP) and decreasing amount of the disintegrant component - potato starch. The largest amount of caffeine (91%) dissolved from series IV of this group.

The dissolution curves of caffeine from tablets of Group 2 shown in Figure 2 are very diverse. The fastest dissolution of the drug was observed from series V tablets. More than 85% of the active ingredient was dissolved after 20 min. In contrast, series VI tablets were characterized by a slow dissolution process. After 45 min only 75% of active ingredient was dissolved. The final result was 96%.

The dissolution profiles of tablets from Group 3 showed a similar relationship as Group 1, except slower dissolution of caffeine. As shown in Figure 3, the amount of active ingredient dissolved was getting smaller in each successive series. Comparing the results of dissolution and compositions of drug forms, it can be concluded that the dissolution rate of drug decreased with increasing amount of PVP in the tablet.

Dissolution of caffeine from tablets did not meet pharmacopoeial requirements only in two series i.e., VI and VIII. More than 80% of the active ingredient dissolved after 45 min from other series of this group.

CONCLUSION

Uniformity of mass of the obtained tablets was consistent with pharmacopoeial standards. Although mannitol reduced the mechanical strength, the tablets met their requirements for friability. An increase in the amount of binder (PVP) caused prolonged disintegration of tablets, which resulted in slower dissolution rate of active substance from the drug form. Mixture of microcrystalline cellulose and lactose (1 : 1) was associated with an increase in the durability and prolonged tablet disintegration time from 4 to 12 min; thereby the dissolution rate of the active substance was reduced. However, two series of this group did not meet the requirements of the dissolution test.

Analysis of relationship between the received dissolution profiles and the content of the binder indicated that the fastest dissolution of the active substance took place with the least amount of PVP (1% w/w) in the tablet. The proposed compositions of the tablets are suitable for administration of caffeine in this drug form, however, a combination of microcrystalline cellulose and lactose with PVP may cause inappropriately long dissolution of the active ingredient from conventional release tablet.

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