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Developing and evaluation of orodispersible tablets containing caffeine

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Abstract

Starting from the premise that a reduced number of active pharmaceutical ingredients (APIs) are used to treat hypotension, the aim of this study consisted of developing new formulations of caffeine-orodispersible tablets (CAF-ODTs). The formulation variables were the type of disintegrant and its concentration. The CAF-ODTs were prepared by direct compression, (CAF1, CAF2 and, CAF3) each of them containing 100 mg of CAF / tablet. The proposed formulations were analyzed from a pharmacotechnical point of view. For the formulations developed the tablets' physical appearance, resistance to crushing, friability, disintegration behaviour, and the in vitro caffeine release were evaluated. White tablets, with a resistance to crushing decreasing in the following order CAF1 > CAF2 > CAF3 were obtained. The friability test showed that all the formulations are respecting the in-force European Pharmacopoeia (Ph. Eur. 10) requirements with values less than 1 %. The disintegration time for all three formulations was less than 180 seconds, the smallest time being registered in the case of CAF2 formulation, where Sodium Starch Glycolate (SSG) was used as a disintegrant (24-30 s, as a result of the different methods used. Through the in vitro releasing study, it was observed that over 99.9 % caffeine was released from all three analyzed formulations. By investigating the amount of caffeine released after 1 minute, it can be noticed that the largest amount released was recorded in CAF2 formulations, where SSG was used as a disintegrant. Compared to CAF2, the amount of CAF released was reduced to half, after the first five minutes for CAF1 formulation, where sodium croscarmellose was used, and ten times lower in the case of CAF3 where no disintegrant was used. Based on the results obtained we can conclude that all three formulations are respecting the pharmacotechnical in-force officinal requirements. The presence of SSG in the CAF2 formulation led to obtaining tablets with a reduced disintegration time in comparison to the other two formulations proposed in this study.

Keywords: orodispersible tablets (ODTs), caffeine, dissolution test, pharmacotechnical properties

INTRODUCTION

Caffeine (1,3,7-trimethylpurine-2,6-dione) (CAF) represents a drug that might be used for multiple therapeutic effects. Its chemical structure is presented in Figure 1 [1].

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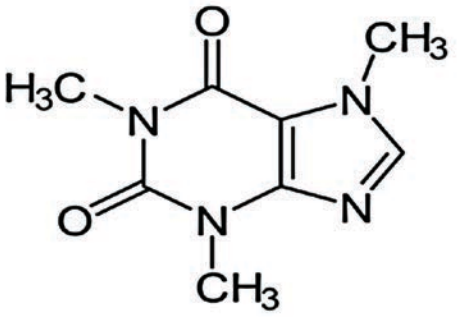

FIGURE 1. Chemical structure of caffeine the model active pharmaceutical ingredient (API) in the proposed ODTs

The therapeutic effects that can be attributed to caffeine: analgesic effect based on the vasoconstrictor effect and on its capacity of prohibiting the prostaglandins synthesis, favours the dopaminergic neuronal protection with good effects on Parkinson disease, conducts to a decrease of β-amyloid production decreasing the risk of Alzheimer disease, also, has the property of increasing the arterial tension and produces bronchodilatation [2,3,4,5,6]. Caffeine is a drug usually presented in medicines in combinations with other active pharmaceutical ingredients such as acetaminophen, aspirin and, codeine [7,8]. Caffeine is a well-known used drug to treat hypotension associated with various pathologies, but on the pharmaceutical market, no caffeine-containing (over-the-counter) OTCs are found. Taking into account this aspect, our objective is to develop and evaluate CAF orodispersible tablets (CAF-ODTs) for patients with diseases associated with hypotension. This category of patients is not taken into consideration as a result of the fact that numerous patients are developing hypertension, so a new pharmaceutical formulation that addresses this category might represent an advantage, also, the fast occurrence of the therapeutic effect in the case of CAF-ODTs represents a huge advantage in comparison with the traditional tablets where the pharmaceutical effect occurs slower [9,10,11]. ODTs represent pharmaceutical formulations where the critical parameters are represented by the taste, the disintegration time and, resistance to crushing [12,13,14]. If these three parameters are accomplished the most important characteristics are fulfilled. The ODTs are present the following advantages in comparison with conventional tablets: the possibility of using them for patients that are experiencing dysphagia or deglutition problems, better compliance for the geriatric and paediatric patients. Also, other advantages are represented by the fact that for the administration we do not need water, as well as they are easy to handle and transported [15,16,17]. Regarding the API, an advantage is represented by the fast occurrence of the therapeutic effect owed to the bypassing first-pass effect [18]. The fast disintegration time can be a result of the presence of the superdisintegrants [19]. The superdisintegrants that presented the best properties regarding the disintegration times are sodium croscarmellose usually used in concentrations between 2-8 %, sodium starch glycolate used in orodispersible tablets in concentrations between 4-8 % and, Crospovidone (2-5 %) [20,21]. Sodium croscarmellose and sodium starch glycolate rely on swelling for disintegration while Crospovidone disintegration mechanism includes both swelling and wicking. Besides these superdisintegrants, new natural disintegrants are developed such as soy polysaccharides, banana starch, and mango peel pectin [22,23,24].

In this study, two different superdisintegrants were used, represented by sodium croscarmellose in the first formulation and sodium starch glycolate in the second formulation, whilst in the third formulation, no disintegrant was used to highlight the importance of using a superdisintegrant when developing ODTs. [25,26]. This study aimed to obtain CAF-ODTs containing 100 mg of caffeine and to evaluate the superdisintegrant effect and compression force role.

MATERIALS AND METHODS

Developing orodispersible tablets with caffeine

To obtain orodispersible tablets the following pharmaceutical ingredients were used: API - caffeine - (CAF - Rochem, United States of America - USA), lactose, Lactopress® (LCT - DFE Pharma, Germany), sodium croscarmellose, Vivasol® (CCS - JRS Pharma, Austria), sodium starch glycolate, Primojel® (SSG - DFE Pharma, Germany), Aerosil® 200 (Degussa, Japan), Magnesium stearate (Alfa Aesar, USA), mannitol, (MNT - VWR Chemicals, USA) and banana flavour (BFL - JinTai, China). The proposed formulations were obtained using an eccentric press (Korsch, Germany), using 10 mm punches. The powders were mixed using a V Blender (YM-4, United Kingdom) in reverse order of their densities, the last powders added being the lubricants. Three formulations of caffeine orodispersible tablets (CAF-ODTs) were produced noted as CAF1, CAF2 and, CAF3, their composition is presented in Table 1.

TABLE 1. The composition of the CAF-ODTs

Ingredient's role	Used substance	Amount (mg)		
		Formulations		
		CAF1	CAF2	CAF3
Active subsstance	CAF	100	100	100
Filler	LCT	274	274	274
Superdisintegrant	LCT	274	274	274
	CCS	8	-	-
	SSG	-	8	-
Lubricant	Aerosil®	5	5	5
	Magnesium stearate	1	1	1
Sweetener	MNT	9	9	9
Flavour agent	BFL	1	1	1
Total amount		398	398	390

CAF - caffeine; CCS - sodium croscarmellose; SSG - sodium starch glycolate; MNT - mannitol; BFL - banana flavour

The physical appearance of ODTs

The tablets must present a uniform aspect, intact margins, and the smell, taste, and, colour should be following the properties of the excipients and API used.

Uniformity of mass

It was calculated using a four-decimal balance (KERN, Germany). For each formulation, 20 tablets were weighed and the uniformity of mass was calculated. According to the 10th European Pharmacopoeia (Ph. Eur. 10), for 18 of the tablets, the standard deviation of ± 5% is accepted while for two a ± 10% deviation from the declared mass is accepted [27].

Resistance to crushing

To obtain the values belonging to the CAF-ODTs, the force (N) needed to break the tablet was measured using the Pharmatest 441E apparatus (Erweka, Germany). Ten CAF-ODTs for each formulation were used and their average breaking force was calculated.

Friability

To accomplish the friability, the Pharmatest PTF 10ER apparatus (Erweka, Germany) was used. For this test, 20 tablets were weighed. The tablets were tested using 25 rotations per minute (rpm) for four minutes. The operation was followed by dedusting and weighing process. The accepted value is less than 1 % for the calculated friability after 100 rotations as presented in the Ph. Eur. 10 [27].

Disintegration test

Two methods were used to determine the disintegration time through two different tests. In the first case (method A), a Pharmatest PTZ Auto 1E apparatus (Erweka, Germany) was used. The disintegration time was achieved at a constant temperature of 37±0.3°C. The disintegration time was established using disks. The second method (method B) was a much easier one using a Berzelius glass of 100 ml, and 50 ml of water as a disintegration media, thermostated at 37±1°C in which a tablet was introduced and its disintegration time was noticed. The disintegration time for orodispersible tablets has to be less than 180 seconds according to Ph. Eur. 10 [27].

Dissolution test

To evaluate the amount of API dissolved the following apparatus were used: dissolution test Erweka type I (Erweka, Germany), and a UV-VIS spectrophotometer Shimadzu 1800 (Agilent, USA), the path length of the cuvette was 1 cm. The dissolution media used was phosphate buffer, pH = 6.8. The dissolution media volume was 900 ml, thermostated at 37 ± 0.5°C using 50 rpm. 5 ml of dissolution media were sampled at 1, 2, 5, 10, 15, 20 and, 30 minutes. The volume taken out of the dissolution apparatus was replaced by the same volume of 5 ml dissolution media, kept at 37 ± 0.5°C. The solution was filtered using a Millipore filter with a diameter of 0.45 µm. To assess the caffeine concentration a spectrophotometric method was used where the specific wavelength was 273 nm.
Standard calibration curve of CAF: a stock solution of 100 µg/ml CAF was prepared in phosphate buffer with pH = 6.8. From this solution five dilutions were made resulting the following concentrations 50 µg/ml, 40 µg/ml, 20 µg/ml, 10 µg/ml, and 2 µg/ml [27,28].

RESULTS AND DISCUSSION

Physical appearance

White tablets with a uniform white colour, intact margins, shaped as flattened cylinders with a convex surface were obtained with a characteristic banana odour. No differences regarding the physical appearance of the three formulations were observed.

Uniformity of mass

As it can be seen in Table 2, the obtained SDs are respecting the limit value, none of the values obtained exceeding the permitted values. The largest deviation in the case of CAF1 was +3.4123 %, whilst the minimum was -3.244 %. For CAF 2 the SD ranges from -3.0596 % to +2.4342 % whilst for the CAF3 the SD

FIGURE 2. The physical appearance of the CAF-ODTs

ranged between -4.2686 % up to +3.0972 %. All the tablets respected the admitted SDs of ± 5 %.

Determination of the tablet's hardness

As presented in Table 3 the resistance to crushing of the CAF-ODT is different, the first formulation presenting the highest values, a fact that represents an advantage because obtaining ODTs with good mechanical properties represents a challenge. Usually, this parameter, together with the disintegration ability represents critical factors. The CAF2 and CAF 3 presented good mechanical properties, while the first CAF-ODT presented the best mechanical properties.

Friability test

Taking into consideration the results found in Table 4, the friability and resistance to crushing results can be related because the formulation that presented the highest mechanical force needed to produce the breaking of the tablet presented also the lowest values regarding the friability test. All the developed formulations are respecting the limit value admitted of maximum 1 % friability.

TABLE 2. The uniformity of mass of the CAF-ODT (n = 20)

CAF1	CAF2	CAF3	Admitted deviations by the Ph. Eur. 10
Uniformity of mass (g)±SD %	Uniformity of mass (g)±SD %	Uniformity of mass (g)±SD %	
0.3981±1.9156	0.3949±1.5283	0.3909±1.8982	±5 % for 18 tablets ±10 % for the remained two tablets

CAF - caffeine; CCS - sodium croscarmellose; SSG - sodium starch glycolate; MNT - mannitol; BFL - banana flavour

TABLE 3. Resistance to crushing of the CAF-ODTs

Formulation	Resistance to crushingF2
	Average values (N)
CAF1	146.38 ± 23.3
CAF2	44.35 ± 7.14
CAF3	43.03 ± 8.23

TABLE 4. Friability test results

Formulation	Friability (%)
CAF1	0.32
CAF2	0.98
CAF3	0.94

Evaluation of disintegration behaviour using two different methods

In the first formulation (CAF1), a higher compression force was used while in the case of the second and third formulation (CAF2 and CAF3) the same compression force was used. If we compare the first

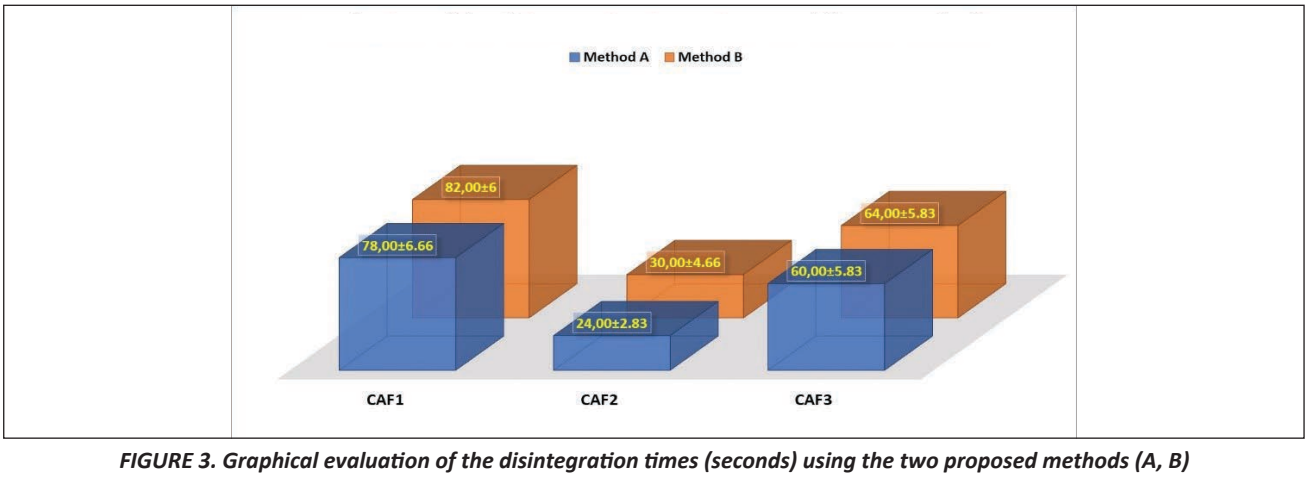

FIGURE 3. Graphical evaluation of the disintegration times (seconds) using the two proposed methods (A, B)

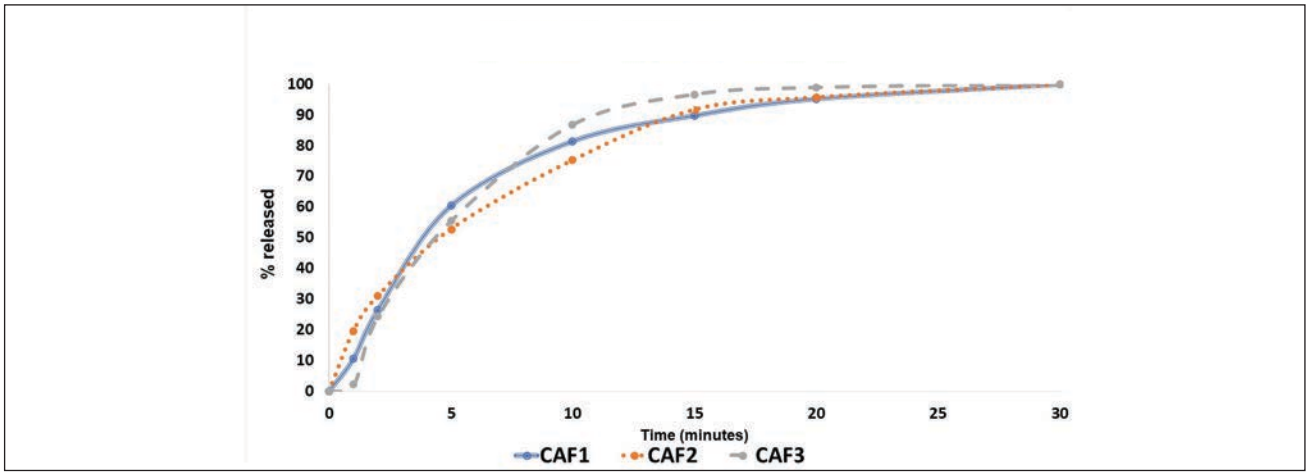

FIGURE 4. The dissolution profile of the CAF-ODTs

two formulations (CAF1 and CAF 2), where the main difference consists of the compression force used and the type of disintegrant we can conclude that the compression force has a high impact on the disintegration time. Also, in the third case (CAF3) where no disintegrant was used, smaller values of the disintegration time were obtained compared to CAF1. We can conclude that the compression force and the presence of the disintegrant influence the disintegration time, all of them being critical parameters that influence the disintegration ability. The proposed formulations respected the in-force regulations of the Ph. Eur. 10 where the disintegration time admitted has to be less than 180 seconds as shown in Figure 3.

The releasing profiles of the CAF from the three CAF-ODTs

After 30 minutes, 99.99 % CAF was released from CAF1 and CAF 3 whilst from CAF2 99.91 % of CAF was released, differences in the case of the release rate occurring in the first five minutes of the determinations. As it can be seen in Figure 4 after five minutes the amounts released from all the formulations tend to be equal. An increased tableting pressure conducts to a slower release of the CAF from the CAF1. If we compare the first two formulations in the case of CAF1 only 10.63 % of the API was released while in the case of the second formulation almost double was noticed to be released (19.7 %), results presented in Figure 4 and Table 5.

Taking into consideration the superdisintegrant used, its presence favours the disintegration and the fast release of the API, in the case of CAF2 almost 20 %

TABLE 5. Amount of CAF released from the CAF-ODTs

Prelevation time (minutes)	Amount of CAF released from the CAF-ODTs (%)		
	CAF1	CAF2	CAF3
0	0	0	0
1	10.62	19.70	2.21
2	26.48	31.12	24.47
5	60.46	52.90	55.53
10	81.45	75.26	86.80
15	89.84	91.71	96.64
20	95.26	95.72	98.89
30	99.99	99.91	99.99

being released after one minute while in the case of CAF3, 2.21 % being released. Also, the amount of released API is influenced by the presence of the superdisintegrant as in the CAF1 and CAF2 after the first two minutes, more API was released where the superdisintegrants were used. A possible enlargement of the concentration of the disintegrant might conduct to better release rates, in this study small concentrations of 2 % were used, while in other studies higher concentration of disintegrant were used, this representing an opportunity in the future studies for improving two critical parameters represented by the dissolution profile and the disintegration time [29]. Also using a natural disintegrant might represent an advantage. Usually, concentrations between 4-8 % of CCS and SSG are being used. Many studies attest the fact that a concentration at the upper limit permitted increases the disintegration time, but if the upper limit is deprecated, the disintegration time might be affected in a negative way increasing the disintegration time,

and decreasing the amount of the API released [30,31,32,33].

For CAF1 and CAF3 formulations after 10 minutes, it can be noticed that over 80 % of the total amount of the API was released whilst in the case of the CAF2, this amount was exceeded after ten minutes. After 15 minutes in two of the three formulations (CAF2 and CAF3), the amount of API released exceeded 90 % while in the CAF3 formulation it was almost 90 %. In all of the formulations, the amount of the API released after 30 minutes was more than 99.9 % fact which is in accordance with the in-force pharmacopeia.

In the study conducted by Desai and his collaborators, three types of rapid dissolving tablets were developed using ascorbic acid, ibuprofen and aspirin (three formulations for each API). In all the formulations developed the disintegration times were very small. The disintegration times in the case of aspirin and ascorbic acid were less than 15 seconds whilst in the case of ibuprofen the disintegration times could be found in the range of 20-35 seconds. Different amounts of disintegrants or a mixture of disintegrants was used. In the future studies where CAF-ODT will be developed a mixture of superdisintegrants or a higher amount of superdisintegrants might be used to improve the disintegration time. In this study the best value regarding the disintegration was recorded in the case of CAF2 where the disintegration time was between 24-30 s depending on the disintegration test used. The tablets resistance to rupture in the case of CAF2 and CAF3 is in the same range with the rapid dissolving tablets obtained by Desai and his collaborators where values between 20-45 N were noticed. In the CAF1 formulation a better resistance to rupture was noticed compared to all the formulations developed by Desai and his collaborators of 146.38 N.

CONCLUSIONS

Three CAF-ODTs formulation were successfully obtained. For the CAF1 formulation, CCS was used, in the case of CAF2, SSG was used, while in CAF3 no disintegrant was used. The tablets were obtained by direct compression. The tablets correspond to the requirements of friability, uniformity of mass, resistance to crushing, and disintegration times. The first formulation presented good mechanical properties as a result of the increased tabletting pressure and also a good release profile, the only parameter that was affected negatively was the disintegration time which was the lowest of all the three proposed formulations. In the case of the in vitro release studies, after 30 minutes over 99.9% of the API was released, larger amounts of released API being registered in the formulations where the disintegrant was used.

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