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FORMULATION AND MANUFACTURING PROCESS OF SOME CHEWABLE TABLETS CONTAINING CARBAMAZEPINE – B – CYCLODEXTRIN INCLUSION COMPLEX

Ghaleb Abdalameer Abdalrb, Emma Adriana Budura*, Corina Dalia Toderescu, Iulian Sârbu
University of Medicine and Pharmacy „Carol Davila" Bucharest, Faculty of Pharmacy, 6 Traian Vuia St., 020956, Bucharest, Romania

ABSTRACT: Carbamazepine, the most widely used anticonvulsant in the world, has a variable and delayed absorption and a low oral bioavailability due to its poor aqueous solubility. In order to increase its dissolution, we choose to include it in the cavity of beta-cyclodextrin (β-CD), and the solid binary system was prepared in a 1:1 molar ratio by kneading technique. The inclusion complex was used as the active ingredient in a formulation of chewable tablets. The first party of our study presents the preformulation studies on the powder obtained after mixing the active ingredient with the excipients for direct compression (F-MELT® and magnesium stearate). After we established that our material has a good fowability and compressibility, the chewable tablets were prepared using the direct compression method. The final part of the study presents the pharmacotechnical properties of the tablets.

Keywords: Carbamazepine, Inclusion complex, beta-cyclodextrin, chewable tablets

INTRODUCTION:

Carbamazepine (CBZ) - Scheme 1, (IUPAC chemical name - 5H-Dibenz (b, f) azepine-5-carboxamide and molecular formula – $C_{15}H_{12}N_2O$), is a sodium channel blocker recommended for the treatment of epilepsy, simple and complex seizures, maniac-depressive illness, bipolar affective disorder and trigeminal neuralgia for over 40 years.(Bauer J *et. al.* 2009*;* Goodman, L.S. *et. al.* 2001.)

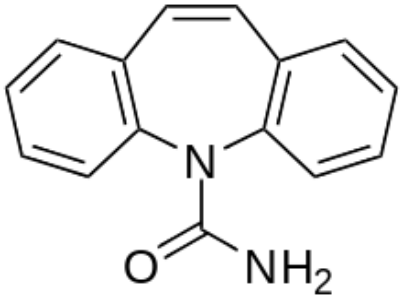

Fig. 1. Structure of Carbamazepine

Currently, carbamazepine is still the most widely used anticonvulsant in the world, which acts by reducing polysynaptic responses and blocking post-tetanic potentiation. (Kwan P *et al.* 2001) Although it has a favorable therapeutic profile that recommends it for emergency medication, it has a variable and delayed absorption and a low oral bioavailability (under 50 %); the time required to attain peak plasma concentrations after oral administration varies between 4 to 24 h.(Ankitkumar *et al.* 2011). These pharmacokinetic properties are due to its poor aqueous solubility of CBZ (~35.4 μg/mL).

According to Biopharmaceutical Classification System (BCS), carbamazepine is included in class II of drug substances (high permeability, low solubility), meaning it has a high absorption, but a low dissolution rate (Mohd et al., 2010) (170 μg/mL, at room temperature (Levy et al., 1975; Moneghini *et al.*, 2002). Moreover, CBZ has four different known anhydrous polymorphic phases and a dehydrate forms (Majeed *et al.*, 2015), so the evaluation of the influence of excipients on its polymorphic form is a great interest for research. The most stable anhydrous form, at ambient conditions, is CBZ Form III polymorph (aqueous solubility of CBZ form III is 380 μg/mL, while that of dehydrate is around 130 μg/mL at 25°C(Murphy *et al.*, 2002).

Considering the importance of using CBZ in both pediatric and emergency therapy (two of the most critical areas for medical practice), it is mandatory to have adequate pharmaceutical formulations able to assure a good and rapid absorption and also a good bioavailability of drug. During the last years, a lot of methods such as: drug dispersion in carriers (Wang et al., 2012; Raghavendra et al., 2010; Rane et al., 2007) particle size reduction (Mohanachandran et al., 2010; Nesamony et al., 2013) complexation (Mirza et al., 2011) and solubilization by surfactants (Kokare et al., 2013; Nan et al., 2012) were developed to increase CBZ oral bioavailability (Neduri et al., 2013; Marko et al., 2015; Wang et al., 2012; Majeed et al., 2015) by

Correspondence*: *Emma Adriana Budura , University of Medicine and Pharmacy „Carol Davila" Bucharest, Faculty of Pharmacy, 6 Traian Vuia St., 020956, Bucharest, Romania, email: emmacretu@yahoo.com*

enhancing CBZ's dissolution rate in the gastrointestinal tract.

Our study aimed to process the inclusion complex of CBZ in beta-cyclodextrin's cavity (1.1 molar ratio) in the form of chewable tablets, using the method of preparation direct compression, together with modern excipients in order to insure the stability of the active and to increase the dissolution rate.

Beta-cyclodextrin (β-CD, fig 2) is the most suitable candidate for the inclusion of CBZ due to the dimension of its internal cavity in which the active drug can fit properly and because it is readily available.

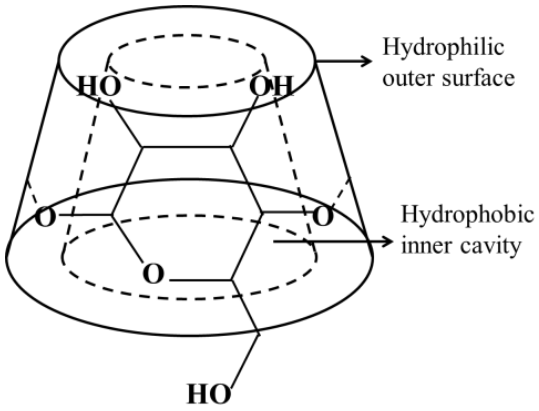

Fig. 2. Structural feature of β – cyclodextrin

The inclusion complex between CBZ and β-CD using kneading methods, at the 1:1 molar ratio, was prepared and characterized by different analytical methods, and then it was mixed with the selected excipients in order to obtain a powder suitable to be compressed in chewable tablets.

In the first stage the powder was formulated, prepared and analyzed establishing its flowing characteristics, in the second stage we prepared the chewable tablets using the direct compression method, and in the end we determined their pharmacotechnical properties.

MATERIALS AND METHODS:

We prepared a powder for direct compression containing as active ingredient the inclusion complex CBZ-β-CD obtained in molar ratio of 1:1, F-MELT® and magnesium stearate. The excipients are selected so we can obtain chewable tablets containing 200 mg carbamazepine per tablet.

The formulation of the chewable tablets is presented in the table no. I:

Tab 1
The formulation of chewable tablets with 200 mg of carbamazepine

Ingredients	**Quantity mg / tablet**	**Role in formulation**	**Producer**
Inclusion complex CBZ- β-CD (1:1)	1161,00	Active ingredient	Baoji Guokang Bio-Technology Co., Ltd, China
F-MELT®	225,00	Filler Superdisintegrant Taste masking agent	Fuji Chemical Industries Co., Ltd., Japan
Magnesium stearate	14,00	Lubricant	Peter Greven, Netherlands
TOTAL	1400,00		

The substances weighted according to the mentioned quantities were physically mixed for 15 minutes, at the room temperature, in an agate mortar, until a homogeneous powder was obtained.

The following tests were performed on the powder:

- flow rate, with an Automated Powder and Granulate Testing System PTG-S3, fabricated by Pharma Test Apparatebau GmbH, Germania;
- powder density, Hausner ratio (HR), compressibility with Vankel Tap Density Tester, produced by Vankel Industries Inc., USA;
- particle size by the sieving method, using a CISA Sieve Shaker Mod. RP 10, produced by Cisa Cedaceria Industrial, Spain;
- loss on drying, by the Karl Fisher method with a Mettler Toledo DL 35 apparatus.

After preparation, the resulting tablets were subjected to quality control tests, as imposed by the rules into force.

The resulting tablets were evaluated using the following tests:

- Organoleptic evaluation, according to Romanian Pharmacopoeia Xth edition (Farmacopeea

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Română, 2004) and European Pharmacopoeia specifications (European Pharmacopoeia, 2004).

- Dimensions (diameter and height), with VK 200 Tablet Hardness Tester, produced by Vanderkamp, USA.
- Mass uniformity, according to Romanian Pharmacopoeia Xth edition (Farmacopeea Română, 2004)
- Disintegration time, according to the Romanian Pharmacopoeia Xth edition (Farmacopeea Română, 2004)
- Friability, with the Vankel friabilator (European Pharmacopoeia, 2004).
- Hardness, with the VK 200 Tablet Hardness Tester (Farmacopeea Română, 2004).
- loss on drying, by the Karl Fisher method with a Mettler Toledo DL 35 apparatus.

RESULTS AND DISCUSSIONS:

In table no. 2 are presented the values obtained after 5 determinations on 60 g of powder containing the inclusion complex CBZ-β-CD, using the 10 mm nozzle and a 25 rpm stirring. The measurements using the 10 mm nozzle without stirring or with 5 rpm, 10 rpm, 15 rpm and 20 rpm indicated the fact that the powder is not flowing under these conditions. In Figure 3, the flowing rate is registered, reporting the mass of powder that flew in a certain time, stirring with a speed of 25 rpm.

Tab. 2.
Flowing parameters obtained for the powder containing CBZ-β-CD complex

Probe	***Flowing time (s)***	***Angle of repose (°)***	***The volume of powder remained on the circular surface (ml)***	***Mass of Masa de powder remained on the circular surface (g)***	***Powder's density (g/ml)***	***Flowing rate (g/s)***
1.	28,0	31,7	81,0	52,6	0,649	1,878
2.	27,9	32,0	81,2	52,7	0,649	1,889
3.	28,0	31,9	80,9	52,3	0,646	1,868
4.	28,1	31,7	81,2	52,7	0,649	1,875
5.	27,9	31,8	81,1	52,4	0,646	1,878
Media	**27,98**	**31,82**	**81,08**	**50,60**	**0,648**	**1,878**

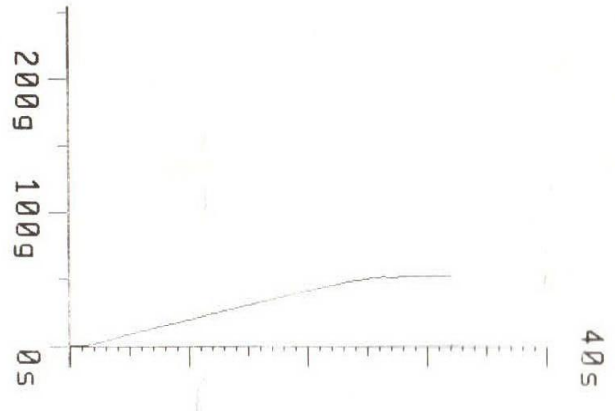

Fig.3 – Flowing rate for the powder containing CBZ-β-CD complex

Flowing time was between 10 and 30 seconds, the angle of repose around 32° and the flowing rate was 1,878 g/s, values which indicate a medium flow, but considering the fact that the determination could be done only after stirring with 25 rpm, we can consider that the powder has a free flow rather weak, but still enough to be proceed in tablets.

The results for volumetric characteristics of the powder are presented in table no. 3.

Tab. 3.
Volumetric characteristics of the powder

Characteristic	***Results***
M (g)	50
V_0 (ml)	89
V_{10} (ml)	83
V_{500} (ml)	61
V_{1250} (ml)	60
V_{10} - V_{500}	22
ρ_0 (g/cm³)	0,562
ρ_f (g/cm³)	0,833
HR	1,48
CI %	32,53

We can notice that the decrease of the volumes is more pronounced during the first 500 tapping, after this all the changes are irrelevant. The values for Hausner ratio and Carr index demonstrate that the powder has a medium to weak flowability, characteristic for the smooth fluid powders.

Concerning the particle size, by representing the distribution of particle size on granulometric classes, the histogram was obtained (Figure 4)

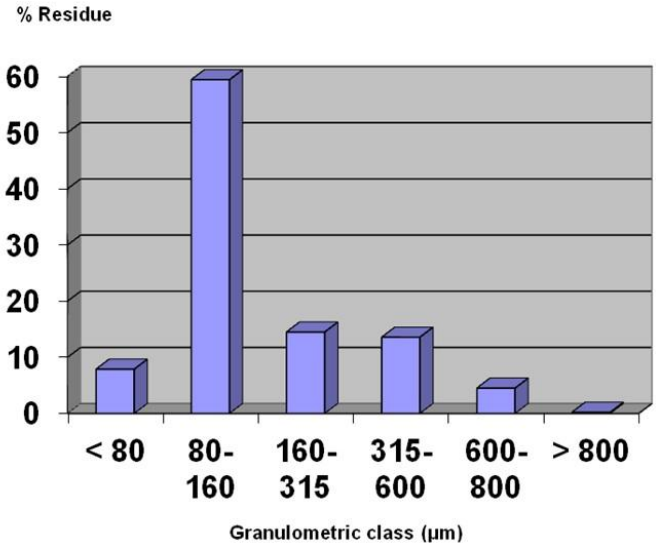

Fig. 4. Granulometric analysis of the powder

The histogram is showing us that the powder contains a significant part of particles with small sizes between 80 and 160 µm.

The table no. 4 presents the results obtained after measuring the moisture content of the powder.

Tab. 4.
Moisture content of the powder

Initial quantity (g)	***30 seconds % MC***	***60 seconds % MC***	***90 seconds % MC***	***Final quantity (g)***	***% final MC***
2,921	1,11	1,74	2,55	2,856	2,55
2,834	1,17	1,83	2,59	2,760	2,59
2,589	1,12	1,79	2,71	2,519	2,71
2,692	1,15	1,77	2,52	2,624	2,52
2,534	1,12	1,82	2,55	2,469	2,55

The powder has a certain moisture content, but not so important to have a significant influence on the compression process or on the tablets characteristics.

The final chewable tablets (Figure 5) have a round shape, a smooth and uniform surface, colored in white, with a diameter of 14 mm.

Fig. 5 – The chewable tablets with CBZ-β-CD inclusion complex

The experimental results of the tests performed on these tablets are shown in table no. 5.

Tab. 5.
The pharmacotechnical properties of the chewable tablets

Tested parameters	***Results***
Height, mm	4.59
Average weight, mg	1,3905
Moisture content, %	4.76
Disintegration time, min.	0.29
Friability, %	0.07
Hardness, N	67.07

The tested characteristics are satisfactory and within the limits imposed by rules into force.

CONCLUSIONS:

The powder for direct compression containing 1:1 CBZ-β-CD inclusion complex, F-MELT® and magnesium stearate, corresponding to 200 mg carbamazepine / tablet presented a medium to weak flowability, with low size particles under 160 μm, and a certain moisture content due either to the alcohol used at the inclusion complex manufacturing, either to the water absorbed by the powder.

The results obtained in the quality determinations performed on the final chewable tablets show that the tested characteristics are optimal and within the limits provided by current standards. They show a good mechanical resistance and a very low friability and excellent disintegration intervals, all these making them suitable for use in therapy.

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