

Journal Pre-proofs

Original article

Formulation and Development of Paediatric Orally Disintegrating Carbamazepine Tablets

R Canadell-Heredia, M Suñé-Pou, A Nardi-Ricart, P Pérez-Lozano, JM Suñé-Negre, E García-Montoya

PII: S1319-0164(22)00225-0
DOI: <https://doi.org/10.1016/j.jsps.2022.09.004>
Reference: SPJ 1505

To appear in: *Saudi Pharmaceutical Journal*

Received Date: 26 April 2022
Revised Date: 30 July 2022
Accepted Date: 4 September 2022

Please cite this article as: Canadell-Heredia, R., Suñé-Pou, M., Nardi-Ricart, A., Pérez-Lozano, P., Suñé-Negre, J., García-Montoya, E., Formulation and Development of Paediatric Orally Disintegrating Carbamazepine Tablets, *Saudi Pharmaceutical Journal* (2022), doi: <https://doi.org/10.1016/j.jsps.2022.09.004>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 The Author(s). Published by Elsevier B.V. on behalf of King Saud University.



Formulation and Development of Paediatric Orally Disintegrating Carbamazepine Tablets.

Canadell-Heredia R¹, Suñé-Pou M^{1,2}, Nardi-Ricart A^{1,*}, Pérez-Lozano P^{1,2}, Suñé-Negre JM^{1,2}, García-Montoya E^{1,2}

¹ Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII, 27-31, 08028 Barcelona.

² Pharmacotherapy, Pharmacogenetics and Pharmaceutical Technology research group. Bellvitge Biomedical Research Institute (IDIBELL), Av. Granvia de l'Hospitalet, 199-203, 08090 L'Hospitalet de Llobregat

*Correspondence: annanardi@ub.edu

Abstract: Carbamazepine is a medicine used to manage epilepsy and partial or tonic-clonic seizures. This study aimed at formulating and obtaining carbamazepine orodispersible tablets for paediatric use at a 50 mg dose, with a diameter not greater than 6 mm and a tablet weight of 80 mg, through a direct compression process. The SeDeM pre-formulation/formulation method was used to define the characteristics of both carbamazepine and the selected excipients for direct compression. This study succeeded in formulating and obtaining the proposed tablets. Following the application of the SeDeM method, the tablets met the mass uniformity test and showed appropriate hardness values for orodispersible tablets. The tablets also met the United States Pharmacopeia (USP) test specifications at t = 60 min. The orodispersible tablets obtained may improve compliance with paediatric treatment with carbamazepine, ensuring the safety and effectiveness of the medicine.

Keywords: Carbamazepine; Orodispersible; SeDeM method; Direct compression; Paediatric population, Superdisintegrants.

1. Introduction

Carbamazepine is listed as an effective and essential medicine for the treatment of paediatric epilepsy in basic healthcare systems. It is also an effective medicine for the treatment of partial or tonic-clonic seizures and other diseases related to epilepsy such as Rett syndrome (World Health Organisation, 2022; Pintaudi et al. 2015).

Carbamazepine is commercially available in different pharmaceutical forms for oral administration. These include sugar-free oral suspension (100 mg/5 ml); chewable tablets (100 mg, 200 mg); immediate-release tablets (100 mg, 200 mg and 400 mg); modified-release tablets (200 mg and 400 mg) and prolonged-release hard capsules (Vidal Vademecum Spain, 2016). These correspond to formulations for the adult population. Therefore, parents or hospital caregivers are expected to manually adjust the formulations to suit the needs of paediatric patients in terms of age and weight.

An initial dose of 10 to 20 mg/kg/day is usually recommended for oral administration in children under six years of age. These doses may be administered as two to three divided doses (immediate-release tablets); four doses (oral suspension) or one extended-release capsule every twelve hours. The divided doses should be increased at weekly intervals to achieve optimal clinical response. The maximum dose is set at 35 mg/kg/day (Drugs, 2020).

Some studies support the use of liquid pharmaceutical forms for paediatric drug development given their ease of dosing and administration (World Health Organisation, 2011; van Riet-Nales et al. 2016). In the case of carbamazepine, only a 2 % oral suspension is currently available. Therefore, to adjust doses, pharmaceutical services in Spanish hospitals often prepare suspensions using commercially available tablets.

Orodispersible tablets (ODT), also known as orally disintegrating or rapidly disintegrating tablets, are uncoated tablets designed to be placed in the mouth where they disperse rapidly before being swallowed (EDQM, 2016). Accordingly, ODTs can be used by paediatric, geriatric, dysphagic, bedridden, psychiatric or neurological patients. Unlike oral liquid dosage forms, ODTs ensure dose accuracy and are more stable (Conceição et al. 2020). However, although some researchers have made some interesting proposals (Kandilli et al 2021), tablets with carbamazepine as unique API is not currently available as an orodispersible tablet so more investigation it is desirable.

Predictive methods such as the SeDeM pre-formulation and formulation method may facilitate the formulation of new paediatric medicines (Orubu and Tuleu, 2017). This method enables the characterisation of medicine formulations in solid pharmaceutical forms, by providing information on the physical and galenic profile of powdered substances (API and excipients) (Suñé-Negre et al. 2005, 2008 and 2014). The SeDeM method has been successfully applied (as reported), in various studies (Aguilar-Díaz et al. 2013; Wan et al. 2019; Ahmed et al. 2019).

This study sought to develop orodispersible tablets at a dose of 50 mg to facilitate the preparation of dispersions suitable for the needs of paediatric patients (who may be uncooperative during swallowing). Particularly, the aim was to develop orodispersible tablets that can be dispersed before administration with intestinal absorption that serves as an alternative treatment with high acceptability by the paediatric population (aged 6 to 11 years). This would increase treatment adherence established by healthcare professionals (Mitchell et al., 2000; Alsous et al. 2018; Nazziwa et al. 2014).

More specifically, this study sought to formulate an orodispersible tablet from polymorph III of carbamazepine. The selection of polymorph III was due to its wide clinical use (given its well-known solubility and processability characteristics) (Raw, 2004). The formulation focused on pre-school (2 to 5 years) and school-aged children (6 to 11 years) to obtain small-diameter, low-drug-load tablets.

The SeDeM formulation and pre-formulation method was applied to define the characteristics of both carbamazepine and the selected excipients for direct compression. Direct compression was selected here due to its economic advantage in production and the simplicity of the process.

As a secondary objective, this study sought to obtain a rapid and correct release of the medicine through a synergistic action (Patil and Das, 2009; Kumar and Saharan, 2017) between two disintegrating excipients. This was expected to both reduce the disintegration time and to obtain dissolution values for carbamazepine consistent with those of commercially available medicines, typical of a class II molecule according to the Biopharmaceutical Classification System (BCS) (Bhise et al. 2009).

2. Materials and methods

2.1. Materials

The active pharmaceutical ingredient (API) used was carbamazepine (batches: 16CT000089 and 16CT000017), obtained from CTX Lifesciences Pvt. Limited, India.

The main excipients used were: L-HPC LH11 [(low-substituted hydroxypropylcellulose) (supplier: SHINETSU, Tokyo, Japan)]; L-HPC NBD022 [(low substituted hydroxypropyl cellulose) (supplier: SHINETSU, Tokyo, Japan)].

The adjuvant excipients used were: VIVASOL GF® [(croscarmellose) (batch: 7111601027, supplier: JRS PHARMA, Rosenberg, Germany)]; VIVAPHARM PVP PXL® [(crospovidone type A) (supplier: JRS PHARMA, Rosenberg, Germany)]; VIVAPHARM PVP PXL10® [(Crospovidone Type B) (supplier: JRS PHARMA, Rosenberg, Germany)]; PEARLITOL 200 SD® [(D-Mannitol) (supplier: ROQUETTE LAISA ESPAÑA, Valencia, Spain)]. The excipients used as lubricants and ligands were: Talc (supplier: Fagron, Barcelona, Spain); magnesium stearate (supplier: Fagron, Barcelona, Spain) and colloidal silicon dioxide (Aerosil®) (supplier: Fagron, Barcelona, Spain) as a standard lubrication blend. All components were stored at room temperature (20-30°C).

2.2. Methods

2.2.1. Characterisation of carbamazepine, excipients and blends using the SeDeM method

The SeDeM method was used to evaluate the suitability of the active ingredient, blends and excipients to be compressed by direct compression. It is important to note that the SeDeM method defines 12 characterisation parameters that are grouped into five incidence factors based on physical and functional characteristics. The value of the incidence factors is the result of the average of each parameter. These values are the average incidence radius.

The incidence factors are: dimensions, compressibility, flowability/powderflow, lubricity/stability and lubricity/dosage. See appendix three for a description of these incidence factors.

Once the values of the parameters were obtained through SeDeM, they were then converted into a diagram radius applying the equations proposed by Suñé-Negre et al. (2008, 2015). The figure formed indicated the characteristics of the product and each of the parameters determined whether the product was suitable for direct compression.

To determine whether the product was acceptable for direct compression in numerical form, the following indices were calculated:

- Parametric Profile Index (PPI). This index is the average value of all the calculated parameters. The acceptability limit is $r \geq 5$.
- Good Compression Index (GCI). This index is calculated from the equation $GCI = PPI \times f$, where f is the reliability factor and is calculated as $f = \text{area of the polygon} / \text{area of the circle}$. The acceptability must be $GCI > 5$ to enable a direct compression process.

The SeDeM diagrams shown in this work were calculated and printed on a validated Microsoft Excel® sheet developed at the Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry of the Faculty of Pharmacy and Food Sciences of the University of Barcelona.

2.2.2. Blends Preparation

The different blends were prepared according to the following procedures. First, the raw materials were weighed individually in polyethylene bags. The raw materials were then sieved through a 0.6 mm sieve, transferred to a suitable container and mixed for 25 min at 20 rpm in the Glatt biconical mixer (Glatt®Labortechnik, Spain). Finally, magnesium stearate was added, and the blend was mixed for 3 min at 20 rpm in the Glatt biconical mixer (Glatt®Labortechnik, Spain).

2.2.3. Tablet preparation

The different mixtures were compressed in a Bonals® eccentric compression machine (Cornellà de Llobregat, Spain). Different sets of round punches with diameters not greater than 6 mm were used to obtain tablets of 50 mg of carbamazepine (API) with a variable weight depending on the percentage of excipient added.

2.2.4. Tablet Characterisation

• Weight variation

Twenty tablets of each of the formulations were compressed, weighed and their average weight was calculated. The individual weights were compared with the average weight of the tablets according to the general method of Ph. Eur (Council of Europe, 2022a).

• Hardness

To characterise the tablets, 10 tablets of each of the formulations were tested, according to the general method of Ph. Eur (Council of Europe, 2022b). in a calibrated durometer (Dr. Schleuniger, Switzerland). The average hardness value was obtained from 6 determinations.

- Friability

The friability of the tablets was tested using a calibrated friabilometer (Dr. Schleuniger, Switzerland) according to general method of Ph. Eur (Council of Europe, 2022c). Friability is the measure of tablet strength and was calculated as a percentage using the following formula:

$$\text{Friability (\%)} = [(W1 - W2)/W1] \times 100$$

Where W1 and W2 are the weights of the tablets before and after the test.

- Disintegration time

The disintegration time was determined according to the general method of Ph. Eur (Council of Europe, 2022d) in a calibrated Schleuniger® Pharmatron DTG3000 apparatus (Solothurn, Switzerland). The disintegration medium was 500 mL deionised water at 37 ° C +/- 2 ° C. The tablets were placed in each disintegration basket with a disk. The disintegration time was recorded when all the disintegrated fractions of the tablet passed through the mesh of the disintegration basket.

- In vitro dissolution studies

The dissolution test was performed according to the USP carbamazepine tablet method (Alvarez-Lorenzo et al. 2000). The dissolution test was carried out in a calibrated dissolution apparatus using the paddle method (Apparatus II, Erweka DT700, Germany).

The speed of the blades was 75 rpm, at a temperature of 37 °C. The volume of the dissolution medium was 900 mL (1 % SLS). Sampling was carried out using six vessels at the indicated intervals (5, 10, 15, 20, 30, 45 and 60 minutes). A filtered sample of 10 mL was taken from each of the vessels. Vessels were not refilled. The samples obtained were diluted with the dissolution medium and filtered through 0.45 µm PTFE membranes (VWR International, USA). The samples were then analysed in a UV spectrophotometer (Thermo Spectronic Helyos Alfa & Beta, UK) at 288 nm for the quantification of carbamazepine.

- Compatibility studies

The differential scanning calorimetry (DSC) study were done considering binary mixtures (1:1 p/p) between the excipients and carbamazepine in a Mettler Toledo DSC-822e equipment. Dry nitrogen was used as purge gas with a flow of 50 mL/min. The sample was placed in a 40 µL aluminium melting pot. The heating rate was 10 °C/min, between 30 and 300 °C.

- Stability studies

An accelerated stability study, according to international conference on Harmonization guidelines (reference) for zones I and II was performed for 2 batches of carbamazepine orodispersible tablets (Stab01 and Stab02). The tested tablets were packed in an aluminium / aluminium strip. The strips were stored at 40 ± 2°C/ 75 ± 5% RH during a test time of six months in a qualified stability chamber.

3. Results and Discussions

3.1 Characterisation of components.

3.1.1 Characterisation of carbamazepine.

The first step taken in this study was to characterise carbamazepine (API), to establish the determining factor to be compensated. The characterisation of carbamazepine was carried out using the SeDeM method, determining the average incidence values for each of the factors in two batches. The results indicated in

Table A1 (Appendix 1) correspond to the three measurements carried out per batch. The active principle showed a good initial capacity for compression in both batches, with an average IGC index value of 5.68 for batch 16CT000089 and 5.72 for batch 16CT000017. The factors that presented a value higher than 5.0 (established as a minimum value by the SeDeM method) were: the dimension factor, with a mean value of 6.65 and 6.44; and the flowability/powder flow factor with an average value of 7.01 and 7.28. Both the dimension and the flowability/powder flow factors showed adequate values for a direct compression process. However, the incidence factors for compressibility (average value: 3.19 and 2.92) and lubricity/dosage of the tablets (average value: 4.44 and 4.53) were below the target value of 5.0. The compressibility factor presented an average value lower than 5 and was selected, as it was considered a determining factor in the direct compression process.

The results obtained in the characterisation of carbamazepine corresponded with the results obtained by other authors, thus confirming the deficiencies observed in the active principle (Campiñez, Casas and Caraballo, 2016). To compensate for the compressibility factor, the excipients that showed a compensatory value equal to or greater than 5.0 were selected.

3.1.2. Characterisation of excipients.

The characterisation of carbamazepine was followed by the selection and characterisation of excipients, which compensated for the deficiencies presented by this active principle.

The excipients L-HPC LH11 and L-HPC NBD022 were used to compensate for the compressibility factor of carbamazepine. Both are superdisintegrants that provide porous structures and are commonly used in formulations using direct compression. These excipients act both as capping protectants and as disintegrators due to tablet swelling (Al-khattawi and Mohammed, 2013). Their use in high concentration could improve the disintegration of tablets and decrease the dissolution time of the medicine (Alvarez-Lorenzo et al. 2000).

The SeDeM characterisation of L-HPC LH11 and L-HPC NBD022 confirmed the suitability of these compensatory excipients. It is important to note that although the IGCs were lower than 5.0, the compressibility factor values were 6.0 for L-HPC NBD022 and 5.90 for L-HPC LH11, as can be seen in Table A2 (Appendix 1). Although the compressibility values were higher than 5, the flowability values obtained were lower than 5. This led to a decrease in the flowability of carbamazepine as an isolated component.

To improve the disintegration characteristics, Vivasol GF®, Vivapharm PVP XL®, Vivapharm PVP XL10® and Pearlitol 200D® were used. According to some studies, the selected non-cellulosic adjuvant excipients (croscarmellose and mannitol) could improve dissolution times in the case of croscarmellose, as it is a superdisintegrant with capillary action (Flicker and Betz, 2011; Babu et al. 2014). Finally, it has been suggested that the addition of crospovidone to the formulation of carbamazepine tablets could prevent its passage to the dihydrate form (insoluble form) and contribute to the rapid disintegration of the tablets (Flicker and Betz, 2011). The incidence values of these excipients in terms of compressibility were higher than 5.0 except for Vivapharm PVP PXL. These adjuvant excipients compensated for the deficiencies exhibited by the main excipients. These adjuvant excipients prevented a decrease in compressibility capacity. In fact, the most favourable case was that shown by Pearlitol 200 SD. Both the value of the compressibility and flow factors were higher than 5.0 for this excipient. Table A2 (in Appendix 1) presents the SeDeM results for compensatory and adjuvant excipients.

3.2. Formulation.

Following the results of the selected excipients, this study proceeded to carry out formulation studies.

The quantitative composition was established using the mathematical model described by the SeDeM method, according to the equation Eq1. The application of this model establishes that the compensatory excipient should be in a proportion that complies with an average incidence radius value equal to 5 (Suñe-Negre et al. 2008, 2014, 2015; Aguilar-Díaz, 2013).

$$CP = 100 - [(((RE-R) / (RE-RP)) 100] \quad \text{Eq1}$$

Where:

CP = % of excipient to be added.

RE = average value of the radius of incidence of the excipient for compressibility.

R = average value of the incidence radius to be obtained in the mixture.

RP = API average incidence radius value for compressibility.

Finally, the compression effectiveness of the main excipient was verified to optimise its concentration without losing its compensatory capacity. To verify such effectiveness, the incidence radius values were selected for the blend in a range between 5.0 and 3.5 (in the Eq1 R value). A radius specification smaller than the SeDeM standard was selected to obtain tablets with less excipient content.

However, for the RE variable, the value of 6.0 (value obtained from the compressibility factor of L-HPC NBD022) and an RP value of 2.92 (value obtained from the compressibility factor of carbamazepine batch 16CT000017) were selected (see tables A1 and A2, Appendix 1). The resulting formulations are shown in Table 1.

Table 1. Blend composition for compression study

Formulation composition (%)	R=5.0 (%)	R=4.5 (%)	R=4.0 (%)	R=3.5 (%)
Carbamazepine	26.70	43.48	60.26	77.04
L-HPC LH11	69.80	53.02	36.24	19.46
Talc	2.36	2.36	2.36	2.36
Colloidal silicon(Aerosil®)	0.14	0.14	0.14	0.14
Magnesium stearate	1.00	1.00	1.00	1.00
Carbamazepine	28.97	45.20	61.44	77.67
L-HPC NBD022	67.53	51.30	35.06	18.83
Talc	2.36	2.36	2.36	2.36
Colloidal silicon(Aerosil®)	0.14	0.14	0.14	0.14
Magnesium stearate	1.00	1.00	1.00	1.00

The results obtained indicated that both excipients (L-HPC LH11 and L-HPC NBD022) preserved their compensatory compressibility properties for radius values equal to 3.5. The hardness values obtained occurred between 62.5 N and 24.8 N, respectively. The hardness values obtained indicated good cohesion between particles. They were considered suitable for ODT formulations, as these are expected to be low as shown in Table A4 (Appendix 1). To obtain these hardness results, a maximum compression force allowed by the blend was applied. Additionally, the diameter of the tablet was modified to preserve the 50 mg dose of carbamazepine. The value of R = 3.8 (middle value of the range 4.0 to 3.5) was set as the new specification incidence radius value for the proposed development. This means that direct compression could be obtained from blends obtained with compensatory radius values of less than five. This highlighted the potential for the SeDeM method to be further enhanced (Suñe-Negre et al. 2015) as it allows for the percentage of excipients to be optimised.

The compensatory excipient result was a value of 28.80 % after applying Eq. 1. Table A5 shows the different formulations resulting from the binary blends of the main and adjuvant excipients.

In summary, the use of the SeDeM method and the resulting mathematical equation were key steps to obtain the compensatory excipient percentage of 28.80. The percentage also enabled the application of the direct compression technology and reduced the number of experiments to be carried out in this study.

3.3.- Characterisation of blends and tablets.

Experiments were subsequently carried out with the eight formulas obtained. It is important to note that the binary combination of the selected excipients sought to produce an innovative paediatric formulation (EMA, 2013; Younes et al. 2018; Freeman et al. 2003; Nunn and Williams, 2005).

In particular, as previously stated, this study aimed at obtaining a rapid and better release of the medicine through a synergistic action (Patil and Das, 2009; Kumar and Saharan, 2017) between both excipients. Furthermore, a decrease in the disintegration time was expected to improve the degree of dissolution of carbamazepine as a class II molecule (Bhise et al. 2009).

Using the SeDeM method, the different carbamazepine blends were prepared and characterised, according to the composition indicated in Table 2. The SeDeM diagrams of the different formulations (F1 to F8) are shown in Figure B1 (Appendix 2).

Table 2: Blends composition

Formulation composition (%)	F1	F2	F3	F4	F5	F6	F7	F8
Carbamazepine	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
L-HPC LH11	28.80	28.80	28.80	28.80	-	-	-	-
L-HPC NBD022	-	-	-	-	28.80	28.80	28.80	28.80
Vivasol® GF	5.00	-	-	-	5.00	-	-	-
Vivapharm®PVP XL	-	5.00	-	-	-	5.00	-	-
Vivapharm®PVP XL10	-	-	5.00	-	-	-	5.00	-
Pearlitol® 200 SD	-	-	-	5.00	-	-	-	5.00
Talc	2.36	2.36	2.36	2.36	2.36	2.36	2.36	2.36
Colloidal silicon dioxide (Aerosil®)	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20

The carbamazepine formulation with the proposed binary blends were considered adequate since the results obtained (Table A4 and A5, Appendix 1) indicated that most of the formulas presented values of good compression index (IGC) higher than 5.0. It is important to note that direct compression following the SeDeM guidelines, can only be carried out when IGC values are greater than 5. Accordingly, the binary Vivasol GF® blends, F1 and F5, were discarded due to their IGC being lower than 5.0.

The rest of the formulas presented values higher than 5.0 in all the factors, except in the dosage/lubricity factor. This factor presented values lower or equal to 2.2 for the L-HPC LH11 binary combinations, and lower or equal to 1.9 for those of NBD022. The inadequacy of these values might have prevented the homogeneity of the filling of the punches.

This study proceeded to compress all blends through a direct compression technology. A galenic characterisation process was subsequently carried out on the tablets obtained. The galenic characterisation process specified the disintegration speed of the tablets. Formulations F2 (with its binary combination L-HPC LH11/Vivapharm PVP PXL) and F6 (with its binary combination NBD022/Vivapharm PVP PXL) obtained the best disintegration time (Table 3 and figure 1). Despite the inadequate results obtained for the dosage/lubricity factor, formulas F2 and F6 were selected due to their adequate flowability values, 7.1 and 6.3 respectively (fundamental parameter for direct compression). These formulations (F2/F6) additionally complied with the mass uniformity test according to European Pharmacopeia guidelines and presented suitable hardness values for orodispersible tablets to be obtained (Table A6 – Appendix 1).

Table 3. Disintegration time for the formulations

	Components	Disintegration time (s)
F1	CBZ+LH11+VIVASOL® GF	21
F2	CBZ+LH11+VIVAPHARM® PVPPXL	10
F3	CBZ+LH11+VIVAPHARM® PVPPXL10	24
F4	CBZ+LH11+Perlitol® 200 SD	55
F5	CBZ+NBD022+VIVASOL® GF	12
F6	CBZ+NBD022+VIVAPHARM® PVPPXL	12
F7	CBZ+NBD022+VIVAPHARM® PVPPXL10	32
F8	CBZ+NBD022+Perlitol® 200 SD	31

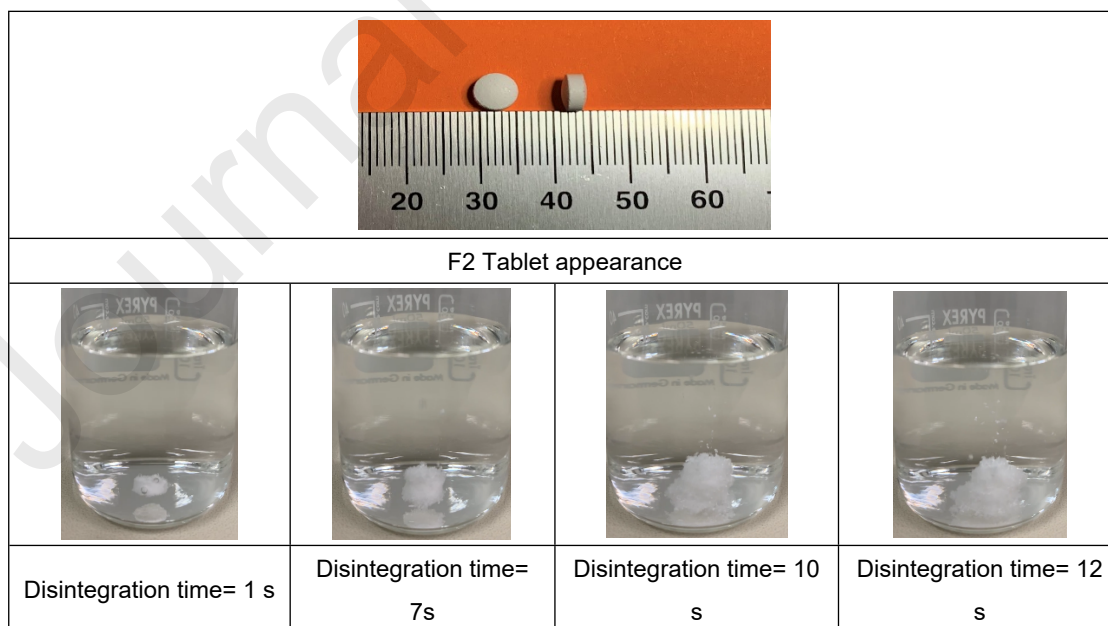
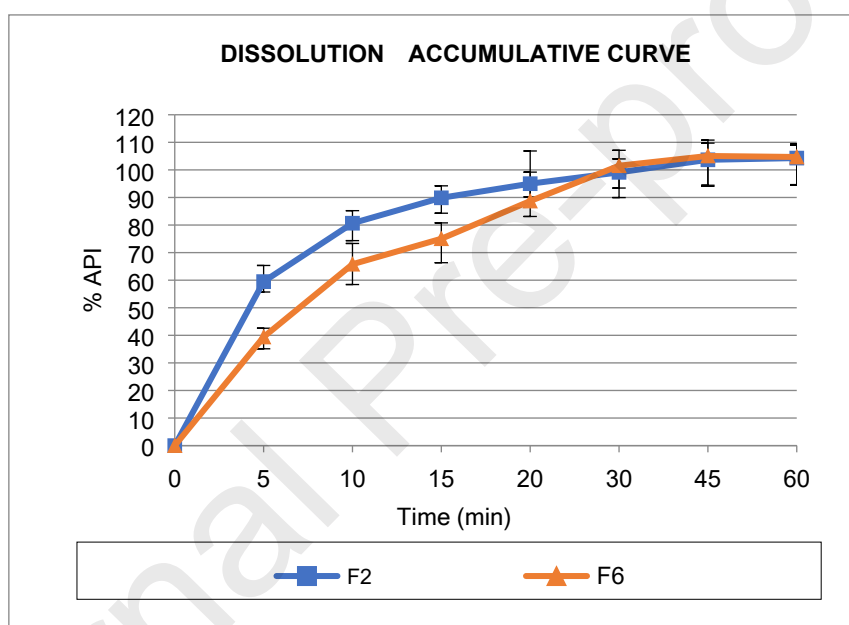


Figure 1: F2 Tablet appearance (units in cm) and photos showing tablet disintegration on distilled water medium

3.4 Selection of the final formulation.

Having selected F2 and F6, this study proceeded to determine the definitive formulation. A dissolution profile of both formulations was carried out using the USP-NF method (United States Pharmacopeia, 2022; Siewert et al. 2003; Shah et al. 1997). The dissolution results obtained are shown in Figure 2.

Figure 2. Dissolution accumulative curve for F2 and F6 formulations.



As can be seen in Figure 2, the curve of both formulas showed a rapid initial dissolution of carbamazepine, exceeding the range established for carbamazepine in USP at $t = 15$ min (45 – 75 %). The addition of L-HPC (Low hydroxypropyl cellulose) combined with Vivapharm PVP XL® (crospovidone) in both formulations, resulted in 100 % carbamazepine release at 60 minutes, meeting the USP requirement (United States Pharmacopeia, 2022).

Having obtained a favourable percentage of dissolved carbamazepine in both formulations (F2 / F6), this study proceeded to compare the dissolution values at $t = 15$ min and $t = 60$ min for F2 and F6. The USP monograph guidelines for carbamazepine was used to carry out this comparison (United States Pharmacopeia, 2022). Formulation F2 obtained a dissolution value of carbamazepine at $t = 60$ min of 104 % and at $t = 15$ min of 90 %. In contrast, whilst formulation F6 obtained a value of 105 % at $t = 60$ min, at $t = 15$ min it only obtained a value of 75 % and was therefore discarded.

In order to demonstrate the compatibility of the formula F2 components, a differential scanning calorimetry (DSC) study was performed considering binary mixtures (1:1 p/p) between the excipients and carbamazepine. The results obtained are shown in table A7-Appendix 1 and the thermograms in figure B2-Appendix 2. The thermogram corresponding to polymorph III, the polymorph form considered in this formulation, shows two thermal transitions, one at 175.57 °C (melting of polymorph III) and another one at 192.25 °C (melting of polymorph I). These endothermic peaks were present in the thermograms of the binary

mixtures of the different excipients without showing the production of new peaks, thus concluding their compatibility with carbamazepine.

However, the thermograms corresponding to the carbamazepine-talc and carbamazepine-magnesium stearate blends showed an anticipation in the Tonset values of the endothermic peaks. Both anticipations were associated with physical adsorption of carbamazepine on talc surface or a reduction in the crystalline state of carbamazepine due to the formation of a solid dispersion of the active ingredient in the melted magnesium stearate. Such anticipations were not considered an incompatibility of carbamazepine with either talc or magnesium stearate.

Additionally, a stability study for tablets from two batches (Stab01 and Stab02) of formula F2 was performed according to the ICH guidelines at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for 6 months. The samples were stored in a qualified stability chamber. The tablets did not show appreciable changes in physical characteristics (appearance and colour). For hardness, disintegration time, dissolution test and drug content (assay) the values observed did not show appreciable variation keeping inside of the study specifications, as indicated on table A8-Appendix 1. In conclusion, the final formulation F2 was considered stable.

4. Conclusion

With a paediatric focus, this study sought to formulate and obtain carbamazepine orodispersible tablets at a dose of 50 mg, a diameter of 6 mm and a weight of 80 mg, by means of a direct compression process.

The tablets obtained by direct compression for formulations F2 and F6 showed the best disintegration values. Additionally, both tablets complied with the galenic requirements (mass uniformity and hardness test). However, the results obtained for formulation F2 in the dissolution profiles showed better dissolution results (according to USP monograph). Accordingly, F2 was selected as the most suitable formulation.

The SeDeM method enabled the development of a formulation suitable for direct compression, using paediatric-appropriate excipients (at a very low percentage with respect to that of the API).

This percentage reduction of the excipient was enabled by the experimental study, which reduced the value of the incidence factor. Although SeDeM method recommends an incidence factor value of 5, this study found that suitable tablets can indeed be obtained with even lower values. Note that the values of 5, 4.5, 4 and 3.5 were experimented with to verify the interval (3.5-5). The value of 3.8 was then selected.

In particular, the dimensions and doses of the orodispersible tablets obtained were deemed suitable for paediatric patients. The proposed prototype could be used to adjust paediatric doses, complementing the use of suspensions prepared with tablets in hospital pharmaceutical services.

Author Contributions:

“Conceptualisation, Canadell-Heredia R. and García-Montoya E; methodology, Suñé-Negre JM.; validation, Nardi-Ricart A., Pérez-Lozano P. and García-Montoya E.; formal analysis, Suñé-Pou M.; investigation, Canadell-Heredia R.; resources, Suñé-Negre JM.; writing—original draft preparation, Canadell-Heredia R.; writing—review and editing, Nardi-Ricart A.; visualisation, Pérez-Lozano P.; supervision, García-Montoya E.; All authors have read and agreed to the published version of the manuscript.”

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: The authors declare no conflict of interest.

References

Aguilar-Díaz, J., García-Montoya, E., Pérez-Lozano, P., Suñé-Negre, J., Miñarro, M. and Ticó, J., 2013. SeDeM expert system a new innovator tool to develop pharmaceutical forms. *Drug Dev. Ind. Pharm.*, 40(2), 222-236. <https://doi.org/10.3109/03639045.2012.756007>.

Ahmed, F. R., Shoaib, M. H., Yousuf, R. I., Ali, T., Geckeler, K.E, Siddiqui, F., Ahmed, K. and Qazi, F., 2019. Clay nanotubes as a novel multifunctional excipient for the development of directly compressible diclofenac potassium tablets in a SeDeM driven QbD environment. *Eur. J. Pharm. Sci.*, 133, 214-227. <https://doi.org/10.1016/j.ejps.2019.03.028>.

Al-khattawi, A. and Mohammed, A., 2013. Compressed orally disintegrating tablets: excipients evolution and formulation strategies. *Expert Opin Drug Deliv.*, 10(5), 651-663. <https://doi.org/10.1517/17425247.2013.769955>.

Alsous, M., Hamdan, I., Saleh, M., McElnay, J., Horne, R. and Masri, A., 2018. Predictors of nonadherence in children and adolescents with epilepsy: A multimethod assessment approach. *Epilepsy Behav.*, 85, 205-211. <https://doi.org/10.1016/j.yebeh.2018.06.022>

Alvarez-Lorenzo, C., Gómez-Amoza, J., Martínez-Pacheco, R., Souto, C. and Concheiro, A., 2000. Evaluation of low-substituted hydroxypropylcelluloses (L-HPCs) as filler-binders for direct compression. *Int. J. Ph.*, 197(1-2), 107-116. [https://doi.org/10.1016/s0378-5173\(99\)00456-1](https://doi.org/10.1016/s0378-5173(99)00456-1).

Babu, G.S.; Kumar, N.Y.D.; Veeram, J.; Malathy, P.S.; Sandeepthi, B., 2014. Formulation and Evaluation of Fast Dissolving Tablets of Carbamazepine by Direct Compression Using Superdisintegrants. *Int. J. Ph. sciences letters.* 4 (5), 432–436.

Bhise, S.; Chaulang, G.; Patel, P.; Patel, B.; Bhosale, A.; Hardikar, S., 2009. Superdisintegrants as Solubilizing Agent. *Research J. Pharm. and Tech*, 2 (2), 387-391. <https://doi.org/>

Campiñez, M.D., Casas, M. and Caraballo, I., 2016. Characterisation of the ability of carbamazepine for processing it through direct compression applying the new expert system SeDeM. *Int J Clin Pharmacol Pharmacother.* 1: 105. <https://doi.org/10.15344/2456-3501/2016/105>.

Conceição, J., Adeoye, O., Cabral-Marques, H., Concheiro, A., Alvarez-Lorenzo, C. and Sousa Lobo, J., 2020. Orodispersible Carbamazepine/Hydroxypropyl- β -Cyclodextrin tablets obtained by direct compression with five-in-one co-processed excipients. *AAPS PharmSciTech*, 21(2). <https://doi.org/10.1208/s12249-019-1579-5>

Council of Europe (2022a). *European Pharmacopoeia: supplement 10.6. 10th ed. Strasbourg: Council of Europe. 2.9.5 Uniformity of mass of single-dose preparations.*

Council of Europe (2022b). *European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.8 Resistance To Crushing of Tablets.*

Council of Europe (2022c). *European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.7 Friability of uncoated tablets.*

Council of Europe (2022d). *European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.1. Disintegration of Tablets.*

Council of Europe (2022e). *European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.34 Bulk Density.*

Council of Europe (2022f). *European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.36. Powder flow.*

Council of Europe (2022g) *European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.16. Flowability.*

Council of Europe (2022h). European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.2.32. Loss on Drying.

Council of Europe (2022i). European Pharmacopoeia: supplement 10.6. 10 th ed. Strasbourg: Council of Europe. 2.9.12. Sieve Test.

Drugs. (2020) Carbamazepine dosage. Available at: <https://www.drugs.com/dosage/carbamazepine.html> (Accessed 7 April 2022).

EDQM - European Directorate for the Quality of Medicines & HealthCare (2016). European Pharmacopoeia, 9th ed. Available at: <https://www.edqm.eu/en/-/shutdown-of-european-pharmacopoeia-9th-edition> (Accessed 8 April 2022).

EMA - European Medicines Agency (2013) Guideline on pharmaceutical development of medicines for paediatric use. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf (Accessed 8 April 2022).

Flicker, F. and Betz, G., 2011. Effect of crospovidone and hydroxypropyl cellulose on carbamazepine in high-dose tablet formulation. *Drug Dev. Ind. Pharm.*, 38(6), 697-705. <https://doi.org/10.3109/03639045.2011.623166>.

Freeman, C., Weiner, M., Kotkoskie, L., Borzelleca, J. and Butt, M., 2003. Subchronic and Developmental Toxicity Studies in Rats with Ac-Di-Sol Croscarmellose Sodium. *Int. J. Toxicol.*, 22(3), 149-157. <https://doi.org/10.1080/10915810305108>.

Kandilli, B., Kaplan, A., Cetin, M., Taspınar, N., Genc, S., Yeni, Y., Sait Ertugrul, M., Cagri Aydin, I. and Hacimuftuoglu, A., 2021. Orally disintegrating tablet containing carbamazepine and levetiracetam: formulation and in vitro and in vivo characterization, *Drug Dev. Ind. Pharm.*, 47:7, 1153-1165, <https://doi.org/10.1080/03639045.2021.1988094>

Kumar, A. and Saharan, V., 2017. A comparative study of different proportions of superdisintegrants: Formulation and evaluation of orally disintegrating tablets of salbutamol sulphate. *Turk J Pharm Sci*, 14(1), 40-48. <https://doi.org/10.4274/tjps.74946>.

Mitchell, W., Scheier, L. and Baker, S., 2000. Adherence to treatment in children with epilepsy: Who follows "doctor's orders"? *Epilepsia*, 41(12), 1616-1625. <https://doi.org/10.1111/j.1499-1654.2000.001616.x>.

Nazziwa, R., Mwesige, A., Obua, C., Ssenkusu, J. and Mworozzi, E. (2014). Adherence to antiepileptic drugs among children attending a tertiary health unit in a low resource setting. *Pan Afr Med J*, 17. <https://doi.org/10.11604/pamj.2014.17.44.3399>.

Nunn, T. and Williams, J., 2005. Formulation of medicines for children. *Br. J. Clin. Pharmacol.*, 59(6), 674-676. <https://doi.org/10.1111/j.1365-2125.2005.02410.x>.

Orubu, E. and Tuleu, C., 2017. Medicines for children: flexible solid oral formulations. *Bull. World Health Organ.*, 95(3), 238-240. <https://doi.org/10.2471/BLT.16.171967>

Patil, C. and Das, S., 2009. Effect of various superdisintegrants on the drug release profile and disintegration time of Lamotrigine orally disintegrating tablets. *Afr. J. Pharm. Pharmacol.*, 5(1), 76-82. <https://doi.org/10.5897/AJPP10.279>.

Pintaudi, M., Calevo, M., Vignoli, A., Baglietto, M., Hayek, Y., Traverso, M., Giacomini, T., Giordano, L., Renieri, A., Russo, S., Canevini, M. and Veneselli, E., 2015. Antiepileptic drugs in Rett Syndrome. *Eur. J. Paediatr. Neurol.*, 19(4), 446-452. <https://doi.org/10.1016/j.ejpn.2015.02.007>.

Raw, A.; 2004. Regulatory considerations of pharmaceutical solid polymorphism in abbreviated new drug applications (ANDAs). *Adv. Drug Delivery Rev.*, 56(3), 397-414. <https://doi.org/10.1016/j.addr.2003.10.011>

Shah, V., Lesko, L., Fan, J., Fleischer, N., Handerson, J., Malinowski, H., Makary, M., Ouderkirk, L., Roy, S., Sathe, P., Singh, G., Tillman, L., Tsong, Y. and Williams, R., 1997. FDA guidance for industry. Dissolution testing of immediate release solid oral dosage forms. *Dissolution Technol.*, 4(4), 15-22. <https://doi.org/10.14227/dt040497p15>

Siewert, M., Dressman, J., Brown, C., Shah, V., Aiache, J., Aoyagi, N...and Williams, R. (2003). FIP/AAPS guidelines to dissolution/in vitro release testing of novel/special dosage forms. *AAPS PharmSciTech*, 4(1), pp.43-52. <https://doi.org/10.1208/pt040107>.

Suñe-Negre, J.M, Pérez-Lozano, P., Miñarro, M., Roig, M., Fuster, R., Hernández, C., Ruhí, R., García-Montoya, E. and Ticó, J., 2008. Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation. *Eur. J. Pharm. Biopharm.*, 69(3), 1029-1039. <https://doi.org/10.1016/j.ejpb.2008.01.020>.

Suñe-Negre, J.M.; Roig Carreras, M.; Fuster García, R.; Hernández Pérez, C.; Ruhí Roura, R.; García Montoya, E.; Miñarro Carmona, M.; Pérez Lozano, P.; Ticó Grau, J.R. (2015) Nueva metodología de preformulación galénica para la caracterización de sustancias en relación a su viabilidad para la compresión: Diagrama SeDeM. *Cienc. y Tecnol. Pharm.* 15, 125–136.

Suñe-Negre, J.M, Roig, M., Fuster, R., Hernández, C., Ruhí, R., García-Montoya, E., Pérez-Lozano, P., Miñarro, M. and Ticó, J.; 2014. New classification of directly compressible (DC) excipients in function of the SeDeM Diagram Expert System. *Int. J. Pharm.*, 470 (1-2), 15-27. <https://doi.org/10.1016/j.ijpharm.2014.04.068>.

United States Pharmacopeia (2022). USP Monographs, Carbamazepine Tablets. USP-NF. Rockville, MD: United States Pharmacopeia.

Van Riet-Nales, D., Schobben, A., Vromans, H., Egberts, T. and Rademaker, C., 2016. Safe and effective pharmacotherapy in infants and preschool children: importance of formulation aspects. *Arch Dis Child*, 101(7), 662-669. <https://doi.org/10.1136/archdischild-2015-308227>.

Vidal Vademecum Spain. 2016. Tegretol tablete 200 mg. Available from: https://www.vademecum.es/equivalencia-lista-tegretol+tablete+200+mg-austria-n03af01-10004262-at_1 (accessed 4.7.22).

Wan, S., Yang, R., Zhang, H., Li, X., Gu, M., Guan, T., Ren, J., Sun, H. and Dai, C., 2019. Application of the SeDeM Expert System in studies for direct compression suitability on mixture of rhodiola extract and an excipient. *AAPS Pharm Sci Tech*, 20(3):105. <https://doi.org/10.1208/s12249-019-1320-4>.

World Health Organisation. (2011) Development of paediatric medicines: points to consider in formulation. Available at: <https://www.who.int/publications/m/item/trs970-annex-5-development-of-paediatric-medicines-points-to-consider-in-formulation> (Accessed 7 April 2022).

World Health Organisation. (2022) Model lists of essential medicines for children 8th List, 2021. 1–43. Available from: <https://www.who.int/medicines/publications/essentialmedicines/en/> (Accessed 7 April 2022).

Younes, M., Aggett, P., Aguilar, F., Crebelli, R., Dusemund, B., Filipič, M...and Gott, D., 2018. Safety of low-substituted hydroxypropyl cellulose (L-HPC) to be used as a food additive in food supplements in tablet form. *EFSA J.*, 16(1). <https://doi.org/10.2903/j.efsa.2018.5062>.

Appendix 1

Table A1. Results of the SeDeM method for three replicates of carbamazepine (lot: 16CT000089 and 16CT000017)

BATCH 16CT000089									
Parameter	SeDeM 1	(r)	SeDeM 2	(r)	SeDeM 3	(r)	(r) Average	Incidence	Average Incidence
Bulk density	0.57	5.71	0.59	5.89	0.58	5.83	5.81	Dimensions	6.65
Tapped density	0.76	7.53	0.74	7.44	0.75	7.74	7.57		
Inter- particleporosity	0.42	3.53	0.35	2.95	0.38	3.14	3.21	Compressibility	3.19
Carrindex	24.17	4.83	20.53	4.17	21.95	4.39	4.46		
Cohesionindex	37.60	1.88	33.50	1.66	41.80	2.09	1.88		
Hausner index	1.32	8.41	1.26	8.89	1.28	8.80	8.70	Flowability/ powder flow	7.01
Angle of repose	29.55	4.09	28.27	4.35	31.25	3.75	4.06		
Powder flow	4.00	8.00	3.66	8.17	2.00	9.00	8.39		
Loss on Drying	1.44	8.56	0.07	9.93	0.05	9.95	9.48	Lubricity/ Stability	9.47
Hygroscopicity	1.07	9.46	1.07	9.46	1.07	9.46	9.46		
Particles < 50 µm	11.95	7.61	14.27	7.15	14.85	7.03	7.26	Lubricity/ Dosage	4.44
Homogeneity index	0.00	1.90	0.00	1.25	0.00	1.70	1.62		
IGC		5.67		5.64		5.74			
BATCH 16CT000017									
Parameter	SeDeM 1	(r)	SeDeM 2	(r)	SeDeM 3	(r)	(r) Average	Incidence	Average Incidence
Bulk density	0.60	6.01	0.57	5.71	0.58	5.81	5.84	Dimensions	6.44
Tapped density	0.73	7.26	0.69	6.88	0.69	6.93	7.02		
Inter- particleporosity	0.29	2.38	0.30	2.48	0.28	2.32	2.39	Compressibility	2.92
Carrindex	17.22	3.44	17.01	3.40	16.16	3.23	3.36		
Cohesionindex	46.20	2.31	63.20	3.16	70.80	3.54	3.00		
Hausner index	1.21	8.96	1.21	8.98	1.19	9.04	8.99	Flowability/ powder flow	7.28
Angle of repose	28.80	4.38	26.72	4.66	24.86	5.03	4.69		
Powder flow	4.00	8.00	4.00	8.00	3.00	8.50	8.17		
Loss on Drying	0.44	9.56	0.36	9.64	0.20	9.80	9.67	Lubricity/ Stability	9.81
Hygroscopicity	0.11	9.95	0.10	9.95	0.09	9.96	9.95		
Particles < 50 µm	13.21	7.36	8.28	8.34	11.43	7.71	7.80	Lubricity/ Dosage	4.53
Homogeneity index	0.00	1.10	0.00	1.40	0.00	1.25	1.25		
IGC		5.61		5.76		5.80			

Table A2. SeDeM results for excipients

Incidence factor	Parameter	Symbol	Units	LH11		NBD022		Vivasol GF®		Vivapharm PVP PXL		Vivapharm PVP PXL10		Pearlitol 200 SD	
				Radius Value	Incid	Radius Value	Incid	Radius Value	Incid	Radius Value	Incid	Radius Value	Incid	Radius Value	Incid
Dimensions	Bulk density	Da	g/mL	3.84		3.52		4.94		2.53		2.06		0.47	
	Tapped density	Dc	g/mL	5.52	4.68	5.51	4.52	6.26	5.60	3.21	2.87	3.01	2.54	0.55	5.11
Compressibility	Inter-particle porosity	Ic	-	6.61		8.55		3.56		6.98		10.00		0.30	
	Carr Index	IC	%	6.09	5.90	7.22	6.00	4.22	5.93	4.24	3.83	6.31	5.52	14.24	5.12
	Cohesion Index	Icd	N	4.99		2.22		10.00		0.27		0.26		2.00	
Flowability /Powderflow	Hausner Index	IH	-	7.81		7.18		8.67		8.66		7.70		1.17	
	Angle of repose	(α)	°	1.19	3.00	3.10	3.42	6.07	4.91	5.22	6.96	5.12	4.27	20.52	6.77
	Powder flow	t	s	0.00		0.00		0.00		7.00		0.00		9.50	
Lubricity /Stability	Loss on Drying	%HR	%	3.10		6.02		1.24		5.43		4.49		0.34	
	Hygroscopicity	%H	%	4.77	4.93	3.89	4.95	3.05	2.15	0.00	2.72	0.00	2.24	0.32	9.75
Lubricity /Dosage	Particles< 50 μ m	%Pf	μ	0.00		0.00		0.00		0.00		0.00		0.80	
	Homogeneity Index	(I Θ)	-	6.00	3.00	7.65	3.83	10.00	5.00	6.20	3.10	10.00	5.00	0.01	7.40
Good compression index (IGC)					4.12		4.35		4.60		3.95		3.88		6.36

Table A3. Compression results for different R value

R value / Quality parameter	Carbamazepine	Carbamazepine
	+ L-HPC LH11	+ L-HPC NBD022
5.0	Tablet aspect	Correct shape and surface without adherings
	Mean Weight (mg)	187.6
	Hardness (N)	147.7
4.5	Tablet aspect	Correct shape and surface without adherings
	Mean Weight (mg)	160.9
	Hardness (N)	121.9
4.0	Tablet aspect	Correct shape and surface without adherings
	Mean Weight (mg)	83.0
	Hardness (N)	77.0
3.5	Tablet aspect	Correct shape and surface without adherings
	Mean Weight (mg)	67.0
	Hardness (N)	62.5

Table A4. SeDeM diagram results for the blends described in Table 5

Incidence factor	Parameter	Symbol	Units	F1		F2		F3		F4	
				Radius Value	Incidence	Radius Value	Incidence	Radius Value	Incidence	Radius Value	Incidence
Dimensions	Bulk density	Da	g/mL	0.49	5.71	0.47	5.36	0.49	5.62	0.49	5.72
	Tapped density	Dc	g/mL	0.65		0.60		0.63		0.65	
Compressibility	Inter-particleporosity	Ic	-	0.48	5.63	0.45	5.40	0.45	6.08	0.49	5.93
	Carr index	IC	%	23.92		21.33		22.31		24.15	
	Cohesion index	Icd	N	161.00		163.60		202.80		177.40	
Flowability /Powderflow	Hausner index	IH	-	1.31	3.93	1.27	7.08	1.29	6.84	1.32	6.63
	Angle of repose	(α)	°	33.26		29.50		31.00		32.52	
	Powderflow	T	s	24.00		3.00		3.67		4.00	
Lubricity /Stability	Loss on Drying	%HR	%	2.80	7.84	2.31	7.94	2.52	7.78	1.61	8.28
	Hygroscopicity	%H	%	3.02		3.62		3.85		3.65	
Lubricity /Dosage	Particles< 50 μ m	%Pf	μ	37.19	2.18	33.60	2.22	39.62	1.94	32.90	2.18
	Homogeneity index	(I Θ)	-	0.00		0.00		0.00		0.00	
Good compression index (IGC)		-		4.77		5.43		5.51		5.56	

Table A5. SeDeM diagram results for the blends described in Table 5

Incidence factor	Parameter	Symbol	Units	F5		F6		F7		F8	
				Radius Value	Incidence	Radius Value	Incidence	Radius Value	Incidence	Radius Value	Incidence
Dimensions	Bulk density	Da	g/mL	0.50	5.68	0.47	5.35	0.47	5.39	0.50	5.80
	Tapped density	Dc	g/mL	0.64		0.60		0.61		0.66	
Compressibility	Inter-particleporosity	lc	-	0.43	4.45	0.47	5.28	0.50	6.27	0.48	5.30
	Carr index	IC	%	21.66		21.83		23.28		23.98	
	Cohesion index	lcd	N	108.00		151.60		212.80		142.20	
Flowability /Powderflow	Hausner index	IH	-	1.28	4.02	1.28	6.30	1.30	6.46	1.31	6.31
	Angle of repose	(α)	°	32.74		30.12		24.73		29.20	
	Powderflow	t	s	23.00		7.33		8.33		7.33	
Lubricity /Stability	Loss on Drying	%HR	%	3.22	7.65	2.05	8.04	2.52	7.83	3.00	7.64
	Hygroscopicity	%H	%	2.96		3.72		3.63		3.44	
Lubricity /Dosage	Particles< 50 μ m	%Pf	μ	42.76	1.57	39.62	1.86	45.45	1.35	39.10	1.64
	Homogeneity index	(I Θ)	-	0.00		0.00		0.00		0.00	
Good compression index (IGC)		-		4.38		5.18		5.34		5.15	

Table A6. Results for tablets of formulas F2 and F6.

CBZ+LH11+Vivapharm PVPPXL (F2)					CBZ+NBD022+Vivapharm PVPPXL (F6)			
Tablet number	Tablet aspect	Weight (mg)*	Thickness (mm)	Disintegration time (s)	Tablet aspect	Weight (mg)*	Thickness (mm)	Disintegration time (s)
1	Correct	83.9	3.12	10	Correct	83.8	3.13	12
2	Correct	81.8	3.13	10	Correct	85.7	3.16	12
3	Correct	77.3	3.08	10	Correct	85.5	3.15	12
4	Correct	82.7	3.12	10	Correct	84.4	3.15	12
5	Correct	82.5	3.11	10	Correct	84.9	3.13	12
6	Correct	81.5	3.09	10	Correct	82.0	3.12	12

(*) Limit for tablet weight: 80 mg \pm 4.0 mg

Formula	Mass Uniformity	Hardness (N)	Tablet diameter (mm)
CBZ+LH11+Vivapharm PVPPXL (F2)	Correct (CV:3.5 %)	57	6
CBZ+NBD022+Vivapharm PVPPXL (F6)	Correct (CV:1.8 %)	51	6

Table A7. DSC results for the different binary mixtures.

	DSC		Entalpia J g ⁻¹ Fusion / Crystallization
	T _{onset} °C Fusion / Crystallizaion	T _{peak} °C Fusion / Crystallization	
Carbamazepine (API)	175.57 / 190.45	176.21 / 192.25	-23.45 / 114.76
excipient - carbamazepine (binary mixtures)			
LH11	175.62 / 190.61	177.39 / 192.70	-25.72 / -42.66
Vivapharm PVPXL	175.57 / 190.96	178.04 / 192.63	-37.42 / -3.41
Talc	172.93 / 190.30	176.32 / 193.05	-5.57 / -47.07
Aerosil	174.87 / 190.02	177.85 / 192.60	-46.06 / -7.43
Magnesium Sterarate	170.88 / 185.05	173.69 / 190.62	-8.01 / -42.55

Table A8. Results for stability study.

Test	Specification	Batch Stab01		Batch Stab02	
		t= 0	t= 6 months	t= 0	t= 6 months
Appearance	Round biconvex tablet without score	Conform to specification	Conform to specification	Conform to specification	Conform to specification
Colour	White	Conform to specification	Conform to specification	Conform to specification	Conform to specification
Hardness	20 – 40 N	22	23	30	33
Disintegration time	NMT 30 seconds	21	16	18	17
Dissolution	NLT 75 % (Q) 60 minutes	105.3	107.8	109.0	107.5
Assay	95 – 105 %	97.2	100.9	101.9	104.1

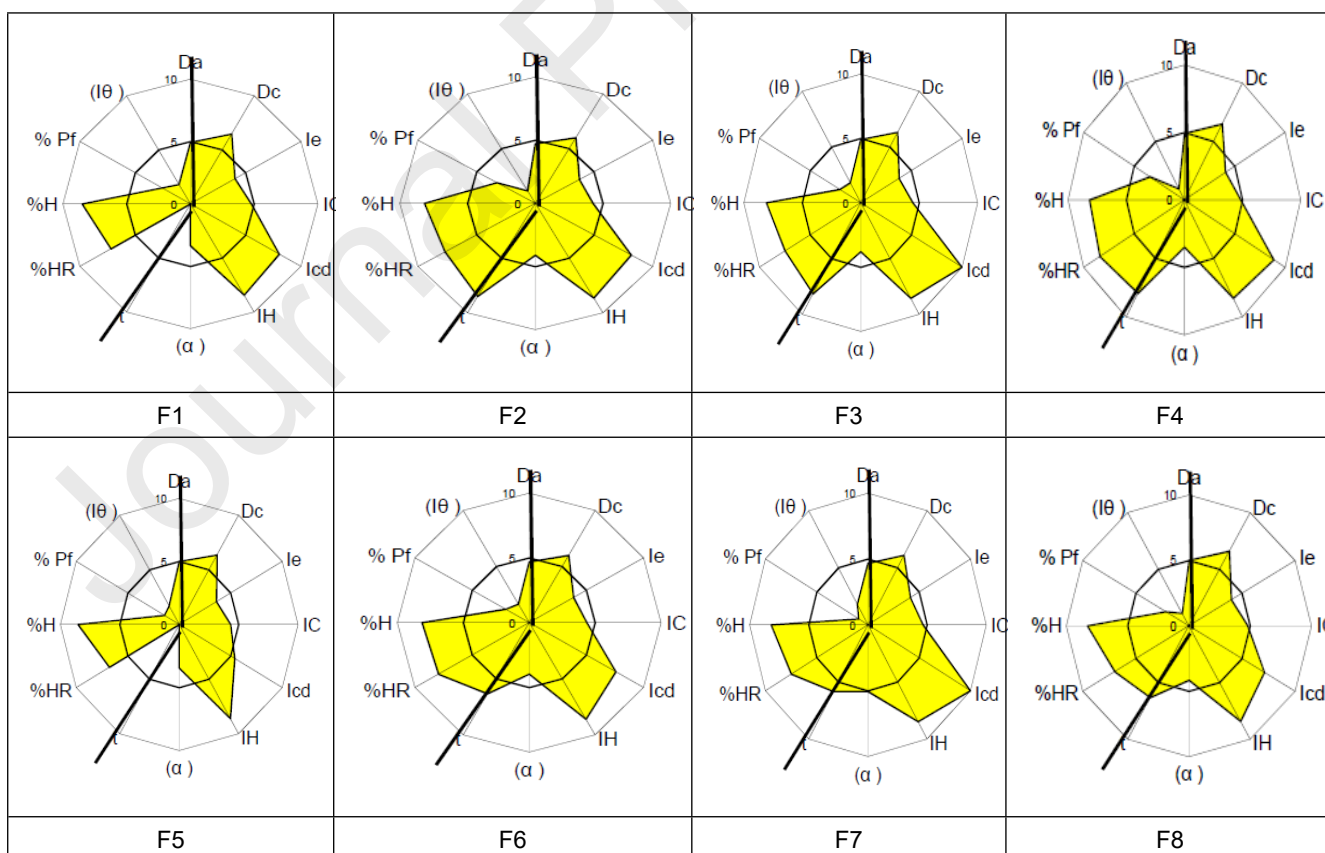
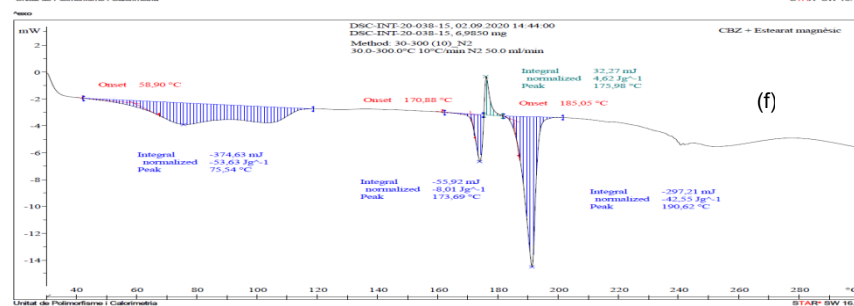
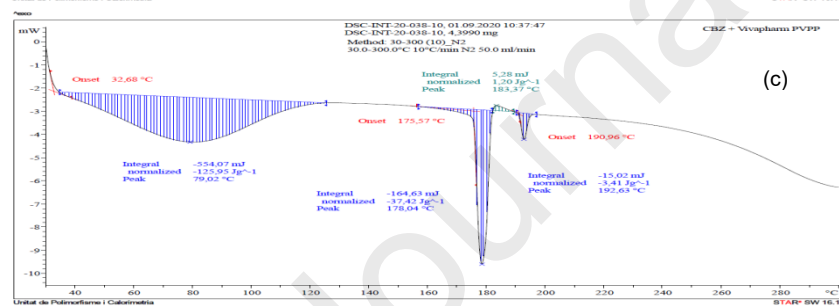
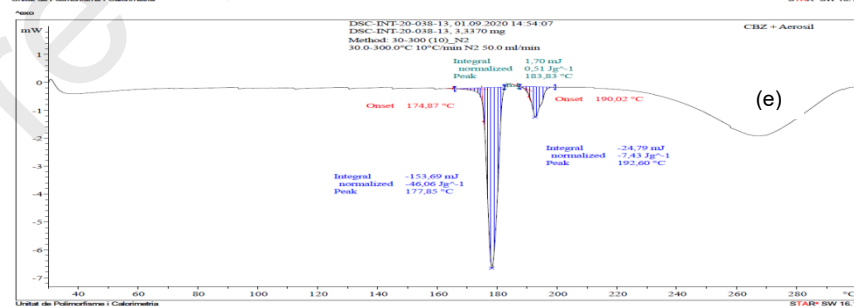
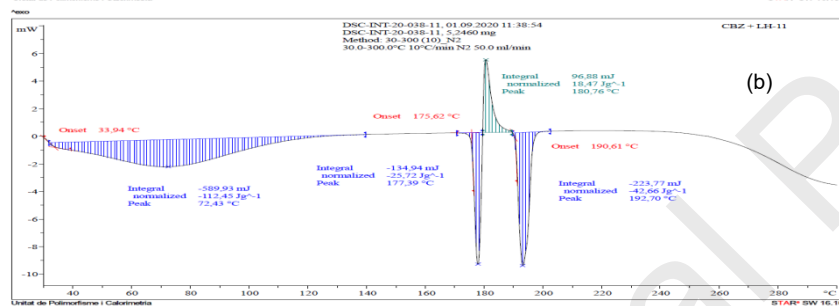
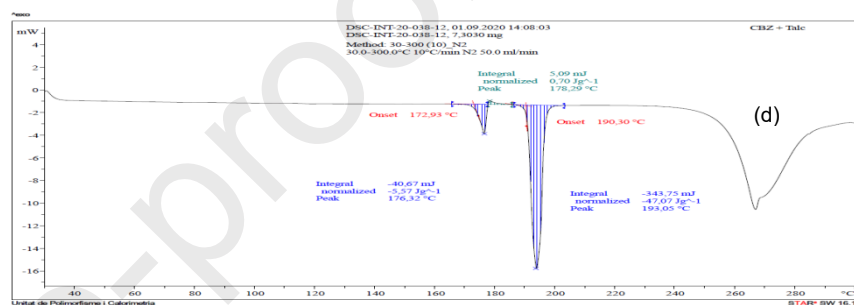
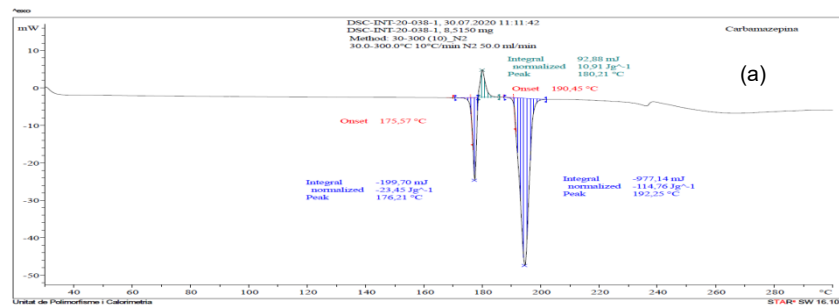
Appendix 2**Figure B1.** SeDeM Graphical representations: carbamazepine + 2 excipients combination

Figure B2. DSC curve of: (a) CBZ, (b) CBZ+LHPC-H11, (c) CBZ+Vivapharm PVPXL®, (d) CBZ+talco, (e) CBZ+ Colloidal silicon dioxide (Aerosil®), (f) CBZ+Magnesium stearate.



Appendix 3

- Dimensional incidence factor.

This incidence factor affects the size of the tablet and its compressibility. The associated parameters are:

- Bulk density (D_a): The method used is described in section 2.9.34 of the European Pharmacopoeia (Council of Europe, 2022e).

- Tapped density (D_c): The method used is described in section 2.9.34 of the European Pharmacopoeia (Council of Europe, 2022e). The resulting volume is the value obtained after 2500 strokes using a decanter with a graduated cylinder (volume meter).

- Compressibility incidence factor.

This incidence factor affects the compressibility of the powder. The associated parameters are:

- Inter-particle porosity (I_e): The inter-particle porosity of the powder is calculated from the following equation:

$$I_e = D_c - D_a / D_c \times D_a$$

- Carr's index (IC): This parameter is calculated from D_a and D_c as: $IC = (D_c - D_a / D_c) 100$.

- Cohesion index (I_{cd}): This index is determined by compressing the powder, preferably in an eccentric compressing machine. To compress the powder, 3.5% (w/w) of the following blend was added: talc 2.36% (w/w), Aerosil ® 200 0.14% (w/w) and magnesium stearate 1.00% (w/w). This parameter indicates the maximum hardness of the tablets.

- Flowability/Powder Flow incidence factor.

This incidence factor influences the flowability of the powdered substance when compressed. The associated parameters are:

- Hausner ratio (HI): The method is described in section 2.9.34 of the European Pharmacopoeia (Council of Europe, 2022e). It is calculated from D_a and D_c as: $IH = D_c / D_a$.

- Angle of repose (α): The method is described in section 2.9.36 of the European Pharmacopoeia (Council of Europe, 2022f).

- Powder flow (t''): The method is described in section 2.9.16 of the European Pharmacopoeia (Council of Europe, 2022g). It is expressed in seconds and tenths of a second per 100 grams of sample, with an average value of three measurements.

- Lubricity/Stability incidence factor.

This incidence factor affects the lubricity and future stability of the tablets. The associated parameters are:

- Loss on drying (% RH): It is measured by the method described in section 2.2.32 of the European Pharmacopoeia (Council of Europe, 2022h). The sample is dried in an oven at $105^\circ\text{C} \pm 2^\circ\text{C}$, until a constant weight is obtained.

- Hygroscopicity (% H): Determination of the percentage of increase in the weight of the sample after remaining in a humidifier at a relative humidity of 76% ($\pm 2\%$) and a temperature of $22^\circ\text{C} \pm 2^\circ\text{C}$ for 24 h.

- Lubricity/Dosage incidence factor.

This incidence factor influences the lubricity and dosage of the tablets. The associated parameters are:

- Particle size <math><50 \mu\text{m}</math> (% Pf): The particle size is determined by the sieve test following the general method 2.9.12 of the European Pharmacopoeia (Council of Europe, 2022i). The returned value is the % of particles that pass through a 0.05 mm sieve when vibrating for 10 min at speed 10 (CISA® vibrator).
- Homogeneity index (I₀): It is calculated according to the general method 2.9.12 of the European Pharmacopoeia (Council of Europe, 2022i).

Journal Pre-proofs