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Optimization of the Preformulation and Formulation Parameters in the Development of New Extended-Release Tablets Containing Felodipine

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Abstract: Herein, new extended-release tablets containing felodipine were developed. For the orally administered formulations, optimization of the preformulation and formulation parameters was performed to assess the performance of the dosage form. Initially, the morphological and physical characterization of two forms of felodipine (microcrystalline and macrocrystalline) using Fourier transform infrared spectroscopy, differential scanning calorimetry and optical microscopy was performed. The pharmaco-technical properties of the two felodipine forms were also determined. Subsequently, formulation studies for felodipine extended-release tablets were performed. Mathematical modelling of release kinetics of felodipine from developed formulations using a power law model was also performed. Based on the influence of formulation factors on the in vitro availability of felodipine in experimental tablets, a new extended-release tablet formulation was established.

Keywords: felodipine; extended-release tablet; tablet formulation; preformulation studies

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1. Introduction

Preformulation studies provide important information on active ingredients and are useful for developing new drug delivery systems, for the selection of the excipients, pharmaceutical technology and process parameters to ensure the quality and stability of the final product and in vivo behaviour [1–3]. Preformulation studies focus on the physical and chemical properties of the active ingredient which could affect its performance and the development of a prolonged-release dosage form. The formulation considerations are also essential for achieving a pharmaceutical form suitable for commercial use and for administration to humans.

According to the World Health Statistics 2019 report released in Geneva in August 2021, the number of adults suffering from raised blood pressure has increased from 650 million to 1.28 billion in the last thirty years. Hypertension is a condition that causes around half of all deaths from stroke and heart disease. About 53% of women and 62% of men with hypertension, or a total of 720 million people, were not taking any medication, even though

there is clear evidence that the medicines are effective in bringing blood pressure into the normal range [4].

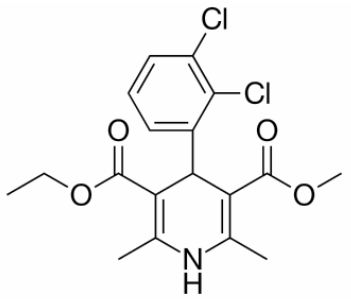
In the early 1970s, a new class of calcium channel blockers (CCB), calcium channel antagonists or calcium antagonists, dihydropyridines (nifedipine, amlodipine, felodipine, nimodipine) was discovered and introduced in the therapy of high blood pressure [5].

Currently, dihydropyridine (DHP) calcium channel blockers are often used to reduce systemic vascular resistance and arterial pressure. Sometimes when they are used to treat angina, the vasodilation and hypotension can lead to reflex tachycardia, which can be detrimental to patients with ischemic symptoms because of the resulting increase in myocardial oxygen demand.

Calcium channel blockers prevent the opening of calcium channels and thereby reduce the concentration of intracellular calcium. They mainly affect arterial vascular smooth muscle and lower blood pressure by causing vasodilation [6].

For the present study, felodipine was selected as an active ingredient for extended-release tablets. Felodipine has the advantages of being more selective as a vasodilator and having fewer cardiac effects than other calcium antagonists, but it has poor bioavailability of only 15% after oral administration [7].

Felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate) (Scheme 1), along with other substituted dihydropyridine compounds, is a class II drug according to the Biopharmaceutics Classification System, with low water solubility (around 3 μg/mL) and high permeability [8–10]. Ingredients with low water solubility cause formulation problems due to their reduced dissolution rate in aqueous media, and therefore in the gastrointestinal tract. These characteristics result in low absorption of the therapeutically active substance, thus having a reduced bioavailability after oral administration. Furthermore, the bioavailability of felodipine decreases with the effect of the first hepatic passage [11].



Scheme 1. Chemical structure of felodipine.

To ensure optimal felodipine absorption, the composition of the solid oral pharmaceutical form must provide an extended release profile that provides therapeutic plasma concentrations for a duration of about 10–12 h.

Extended release is preferable in the case of drugs that require repeated, long-term and high-frequency administration due to their short half-life [12]. An immediate-release formulation could cause fluctuations in hemodynamic effects due to repeated administration at short intervals.

Reducing plasma concentrations of the drug before the next dose, most often in the morning, result in reduced blood pressure control in the patients, with large effect variations. Formulations with diurnal blood pressure trough-to-peak ratios, the ratio between the minimum concentration and the maximum concentration of drug measured in the blood following the administered dose (C_{min}/C_{max} ratios), of more than 50% over 24 h are preferred [13].

Extended-release formulations result in a prolonged absorption phase of felodipine, which is directly proportional to its plasma concentration (C_{pl}) and dose. Avoidance of blood pressure fluctuations increases the safety profile in the administration of higher-dose

slow-release treatment without danger, as felodipine has no risk of toxicity due to a narrow therapeutic index or range. Dose spacing is allowed at longer intervals of about 12 h, with slow absorption of the active substance, thus enhancing patient compliance with long-term treatment [14,15].

As felodipine is sensitive to light, the core tablets must be coated with a protective film, and due to the risk of oxidation, it is advisable to add an antioxidant in the formulation [16].

In addition, felodipine, due to its low water solubility, can benefit from combination with a solubilizing agent. Therefore, the aim of the present research was to perform preformulation studies on two different crystallization types of felodipine, establishing the structure, the nature, the purity, and the physical–chemical properties of the raw materials and finding the most suitable form to be utilised. Under the conditions given by the structural features of the used felodipine type, extended-release tablets containing 10 mg felodipine were manufactured and assessed to meet the quality requirements of the compendial standards. The novelty of the research was to develop improved core tablets containing felodipine incorporated in a hydrophilic matrix, coated with new HPMC films and subsequently, to establish the exact influence of different formulation factors on the in vitro dissolution performance of the innovative prolonged-release pharmaceutical system.

2. Materials and Methods

2.1. Materials

Two types of felodipine compounds were used in this study: felodipine macrocrystalline form—lot number E0055518 and felodipine microcrystalline form—lot number 0057505 (Everlight Chemical Industrial Corporation, Taiwan). The other used chemicals were Plendil® 10 mg prolonged-release tablets (as references) (Astra Zeneca, Gothenburg Sweden), hydroxypropyl methylcellulose, Methocel (Colorcon, Dartford, England), lactose monohydrate (DMV, Veghel, The Netherlands), microcrystalline cellulose—Vivapur 101 (JRS Pharma, Rosenberg, Germany), polyethylene glycol—PEG 4000 (Merck, Darmstadt, Germany), sodium lauryl sulfate—LSNa (Merck, Darmstadt, Germany), propyl gallate (Eastman Chemical, Newport, England), magnesium stearate (JRS Pharma, Rosenberg, Germany) and Polyvinyl pyrrolidone K 30—Vivapharm® PVP K30 (JRS Pharma, Rosenberg, Germany).

2.2. Methods

2.2.1. Physical and Chemical Characterization

The FTIR analysis was performed using a JASCO FTIR 410 spectrophotometer. A mixture of 1 mg sample and 500 mg KBr of IR purity was prepared. The mixture was homogenised in an agate mortar. Then, the mixture was dried at 105 °C for one hour and cooled at room temperature. 500 mg of obtained sample was introduced into the hydraulic press and compressed. Finally, a perfect transparent tablet was obtained, without material inclusion. It was placed inside the spectrophotometer and its spectrum was recorded. The obtained spectra were compared with a standard reference. The FTIR spectra are presented in transmittance (%).

The thermal experiments were performed on a Mettler Toledo DSC 853e differential scanning calorimeter, within the temperature range 30–250 °C. The thermal DSC curves were recorded in a nitrogen atmosphere with a flow rate of 80 mL.min^{-1} and at a heating rate of 10 K·min^{-1}. The samples were held in aluminium crucibles with a pinhole in the lid. The sample mass was approximately 2 mg.

Optical microscopy analysis was performed using a NIKON® Eclipse 50i optical microscope (Natori City, Miyagi Prefecture, Japan). The lenses were used were 4×, 10×, 40× and 100×. The obtained images were used to measure particle diameters and surface areas using the MoticImagesPlus® 2.0 ML digital microscopic imaging program.

Determination of felodipine particle size

Particle size analysis was performed using two methods: (i) by direct microscopic examination with computerised image processing using specialised software and (ii) by the sieving and sorting method.

(i) Microscopic evaluation

In the optical microscopic examination, the particle sizes were measured using the MoticImagesPlus® program. Measurements were made in multiple fields of view and the particles' diameters and appearance were determined. Statistical data were processed with the XLSTAT® program.

(ii) Sieving and sorting method was performed on standardised RETSCH analytical sieves from the AS 200 Basic apparatus, equipped with sieves of mesh sizes 500 µm, 300 µm, 100 µm, 75 µm, 53 µm and 32 µm. A quantity of substance (25 g) was transferred to the upper sieve, the time was set to 15 min and the vibration amplitude to 1.5 mm. In the end, the residual materials on each sieve were weighed on a Mettler Toledo AT261 balance (0.01 mg sensitivity).

The bulk and tapped density were determined using Vankel Tap Density Tester, produced by Vankel Industries Inc., Los Angeles, CA, USA. The flowability and compressibility properties of the powder were established by calculating the Hausner ratio (HR) and Carr Index (CI). The bulk density represents the ratio between the analysed powder mass (100 g) and the occupied volume from a graduated cylinder. The tapped volume is measured after subjecting the same amount of powder to a different number of mechanical shocks. The Hausner ratio (HR) is calculated as the ratio between tapped and bulk density, a value above 1.25 being considered a low flowability indicator. The Carr index is given by Equation (1)

$$\text{CI\%} = \frac{(\text{tapped density} - \text{bulk density}) \times 100}{\text{tapped density}} \quad (1)$$

where values greater than 25% represent low flowability and compressibility attributes and values below 15% expresses good flow and compression qualities [17].

2.2.2. Formulation Studies for Felodipine Extended-Release Tablets

A starting formulation based on the qualitative formula of the reference product was used. The formula comprising the active ingredient, an antioxidant (propyl gallate), two fillers (microcrystalline cellulose and lactose monohydrate), a lubricating agent (magnesium stearate), a coating film with a protective role (hydroxypropyl methylcellulose) and most importantly, the release control system as a hydrophilic cellulosic matrix (hydroxypropyl methylcellulose with different degrees of polymerization, respectively viscosities), was developed [18,19].

The ingredients were mixed for 20 min in a rotating device with a speed of 20 rpm, at room temperature, then lubricated with magnesium stearate for another 5 min under the same conditions. The direct tableting powders were compressed with different forces in a Korsch EK-O type single-post eccentric machine, equipped with 8 mm flat punches.

In the formulation optimization process, the objectives were (i) to determine the suitability of using microcrystalline felodipine, (ii) to determine the influence of excipients on the availability of felodipine included in the prolonged-release pharmaceutical system, (iii) to establish the structure of the hydrophilic matrix system for obtaining a delayed release profile of felodipine, and (iv) to choose the technological parameters like compression force in relation to felodipine dissolution rate [20–22].

The main control parameter for the formulation characteristics was the in vitro dissolution profiles of felodipine in the newly developed pharmaceutical systems compared to a reference product.

In vitro dissolution rate

The dissolution apparatus (Hanson Research SR8 Plus) USP type II was used. It contains eight stations arranged in two rows. Operation is through an alphanumeric digital keyboard LCD front panel, equipped with an external heating system with recirculation

(DH 2000) that guarantees a constant water distribution at medium temperature and without vibration.

Dissolution media were chosen as follows:

- 0.4% cetrimide (CTAB), according to the specification of the reference product. 400 mg cetrimide was dissolved in phosphate buffer (NaH_2PO_4) pH = 6.5;
- 1% sodium lauryl sulphate (LSNa) (m/V), according to USP specifications. 1 g of sodium lauryl sulphate was dissolved in phosphate buffer (NaH_2PO_4) pH = 6.5;

The standard solution was prepared by dissolving the pure felodipine in a quantity of alcohol in a volumetric flask then diluting with dissolution medium, 0.4% CTAB or 1% LSNa. The working parameters were set at a stirring speed of 100 rpm and a temperature of 37 °C. Finally, 15 mL of suspension was filtered and used for quantitative determination.

The amount of felodipine dissolved at 2, 4, 8 and 12 h was determined on 6 tablets using the UV spectrophotometric method, at 363 nm and 450 nm. Absorbances were determined using a Jasco V-530 UV VIS spectrophotometer [23].

The similarity factor f_2 which quantifies the distance between the dissolution curves for the two products is defined according to Equation (2):

$$f_2 = 50log\left\{\left[1 + \frac{\sum_{i=1}^{P}(\mu_{ri} - \mu_{ti})^2}{P}\right]^{-1/2} \times 100\right\} \quad (2)$$

where μ_{ri} and μ_{ti} are the means of the population of results at time t_i for the reference and tested products and P the size of the population. This factor was estimated by Equation (3):

$$\hat{f_2} = 50log\left\{\left[1 + \frac{\sum_{i=1}^{P}(\overline{x}_{ri} - \overline{x}_{ti})^2}{P}\right]^{-1/2} \times 100\right\} \quad (3)$$

where $\overline{x}_{ri}$ and $\overline{x}_{ti}$ are the experimentally observed means for the reference and tested products at time t_i.

The f_1 factor represents the difference factor and is used to describe the difference in the dissolution profiles achieved by the drugs.

The f_1 factor is calculated using Equation (4):

$$f_1 = \{[\sum_{t=1} n|R_t - T_t|]/[\sum_{t=1} nR_t]\} \times 100 \quad (4)$$

where R_t represents the percent released from the reference drug at time t, and T_t represents the percent released from the tested drug at time t [22].

Influence of formulation factors on the in vitro *availability of felodipine in experimental tablets*

Considering the fact that some of the ingredients were used in the same amounts in all studied formulations, and to avoid repetition, they are expressed as non-variable ingredients (NVI) and their composition is shown in Table 1. In accordance with regulatory agencies' recommendations, only therapeutically inactive excipients are included in NVI, the active ingredient (felodipine) being mentioned in all formulations, even where its concentration doesn't differ.

Table 1. The non-variable ingredients (NVI) in all studied formulations.

Ingredients	% of the Tablets' Total Mass
PEG 4000	5.4
Propyl gallate	0.05
Magnesium stearate	1
PVP K 30	20
Total	26.45

(i) Type and percentage of matrix-forming polymer

The chosen extended-release structure was a hydrophilic matrix system. As mentioned above, a hydroxypropyl methylcellulose (HPMC) matrix with varying degrees of polymerization and different viscosities was selected.

For the formulation's studies, four types of HPMC were used to develop an extended-release formulation with dissolution profiles similar to the reference product and resembling behaviour in different media, namely 1% LSNa according to the United States Pharmacopoeia USP monograph [23] and 0.4% bromide cetyl trimethyl ammonium (CTAB) provided by the manufacturer of the extended-release felodipine reference formula (Plendil®).

The influence of the amount and type of hydrophilic matrix (hydroxypropyl methylcellulose) on the availability of felodipine in experimental extended-release formulations was determined.

Experimental formulations containing different proportions of HPMC matrix of different viscosities (viscosity of 2% aqueous solutions measured at 20 °C) were developed: HPMC E5, with a viscosity of 4–6 mPa; HPMC E 10 MP CR, with a viscosity of 10 mPa; HPMC E50, with a viscosity of 40–60 mPa and HPMC K100, with a viscosity of 100 mPa.

The formulations of felodipine with different proportions of HPMC matrix in experimental tablets using the same excipients are presented in Table 2.

Table 2. Formulation of different batches of tablets containing felodipine associated with different proportions of HPMC matrix.

Formulation Code	% of the Tablets' Total Mass								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Felodipine	5	5	5	5	5	5	5	5	5
HPMC E5	-	-	25	-	-	-	-	-	-
HPMC E10	-	-	-	-	15	35	38	-	-
HPMC E50	-	-	-	23	35	15	-	27.5	27.5
HPMC K100M	15	30	15	10	-	-	12	19	15
Microcrystalline cellulose	26.05	18.55	13.55	17.25	8.55	8.55	8.55	12.05	12.05
Lactose monohydrate	27.5	20	15	18.3	10	10	10	10	14
NVI	26.45	26.45	26.45	26.45	26.45	26.45	26.45	26.45	26.45

(ii) Influence of the active ingredient granulometry on the dissolution profile

To study the influence of crystal diameter on the in vitro availability of felodipine, F10, containing felodipine crystals with an average diameter of 3.573 mm (macrocrystalline), and F11, containing microcrystalline felodipine with 30 µm particle dimensions, were manufactured and investigated (Table 3).

Table 3. The formulation of tablets containing felodipine with particles of different diameters.

Formulation Code	% of the Tablets' Total Mass	
	F10	**F11**
Felodipine macrocrystalline	5	-
Felodipine microcrystalline	-	5
HPMC E50	27.5	27.5
HPMC K100M	15	15
Microcrystalline cellulose	12.05	12.05
Lactose monohydrate	14	14
NVI	26.45	26.45

(iii) The influence of the compression force

Two quantitatively identical formulations, F12 and F13 were manufactured, each compressed at different tableting forces: 45 N (average force) for F12 and 90 N (high force) for F13, followed by the assessment of in vitro release behaviour of felodipine (Table 4).

Table 4. The formulation of tablets compressed with different tableting forces.

Formulation Code	% of the Tablets' Total Mass	
	F12 (45N)	F13 (90N)
Felodipine	5	5
HPMC E50	27.5	27.5
HPMC K100M	15	15
Microcrystalline cellulose	12.05	12.05
Lactose monohydrate	14	14
NVI	26.45	26.45

(iv) The influence of the amount of lactose monohydrate associated with the polymeric matrix

Decreased lactose content

To study the influence of lactose monohydrate filler on the felodipine availability in extended-release tablets, two formulations were manufactured: F14, containing 10 mg lactose (5% of tablet mass), and F15, with 33 mg lactose (16.5% of tablet mass) (Table 5).

Table 5. F14 and F15 formulations, differing in the quantity of lactose monohydrate used.

Formulation Code	% of the Tablets' Total Mass	
	F14	F15
Felodipine	5	5
Methocel K100	15	15
Methocel E50	27.5	27.5
Microcrystalline cellulose	21.05	9.55
Lactose monohydrate	5	16.5
NVI	26.45	26.45

Increased lactose proportion and decreased microcrystalline cellulose amount

The study aimed to determine the influence of the proportion between the two associated fillers, on the felodipine availability in experimental formulations with extended-release profiles.

Formulations F16 and F17, which contain different amounts of fillers are mentioned in Table 6.

Table 6. F16 and F17 formulations, differing in the proportion between microcrystalline cellulose and lactose monohydrate.

Formulation Code	% of the Tablets' Total Mass	
	F16	F17
Felodipine	5	5
Methocel K100	15	15
Methocel E50	27.5	27.5
Microcrystalline cellulose	12.05	5.05
Lactose monohydrate	14	21
NVI	26.45	26.45

The influence of polyvinyl pyrrolidone (PVP) amount in the tablet formulation

The study of polyvinyl pyrrolidone (PVP) addition influence on in vitro felodipine release was performed on two tablets formulations: F18 and F19, containing a double amount of PVP (Table 7).

Table 7. F18 and F19 formulations, differing in PVP amounts.

Formulation Code	% of the Tablets' Total Mass	
	F18	F19
Felodipine	5	5
PEG 4000	5.4	5.4
Propyl gallate	0.05	0.05
Methocel K100	15	15
Methocel E50	5527.5	27.5
Microcrystalline cellulose	17.05	12.05
Lactose monohydrate	19	14
Magnesium stearate	21	21
PVP K 30	10	20

Final tablets formulation

Based on the results provided by performed preformulation and formulation studies, it was established the final extended-release tablet formulation, and the experimental data were presented in Table 8.

Table 8. Felodipine extended-release tablet formulation.

Ingredients	Quantity (mg)	% of the Tablets' Total Mass
Felodipine	10.00	5
PEG 4000	10.80	5.40
Propyl gallate	0.10	0.05
Methocel K100	30.00	15
Methocel E50	55.00	27.50
Microcrystalline cellulose	24.10	12.05
Lactose monohydrate	28.00	14
Magnesium stearate	2.00	1
PVP K 30	40.00	20
Total mass	200.00	100.00

2.2.3. Release Kinetic Studies

In order to evaluate the mechanism of the felodipine release kinetics, dissolution data were fitted to the power law kinetic model [24,25].

3. Results and Discussion

3.1. Organoleptic Evaluation of the Compounds

An evaluation of the colour and aspect of the two felodipine forms was made according to the European Pharmacopoeia specifications [26]. The organoleptic evaluation of the two crystalline forms of felodipine revealed visible, bright yellow (macrocrystalline form) and yellowish white (microcrystalline form) homogenous crystals. The two forms corresponded organoleptically and differed macroscopically in appearance and crystallinity.

3.2. Physical and Chemical Characterization

FTIR analysis. The purity of the two felodipine forms used in this study was investigated by infrared spectroscopy (FTIR) according to European Pharmacopoeia (Ph. Eur.) 10th Edition monograph [26]. The FTIR spectra are presented in Figure 1a–d.

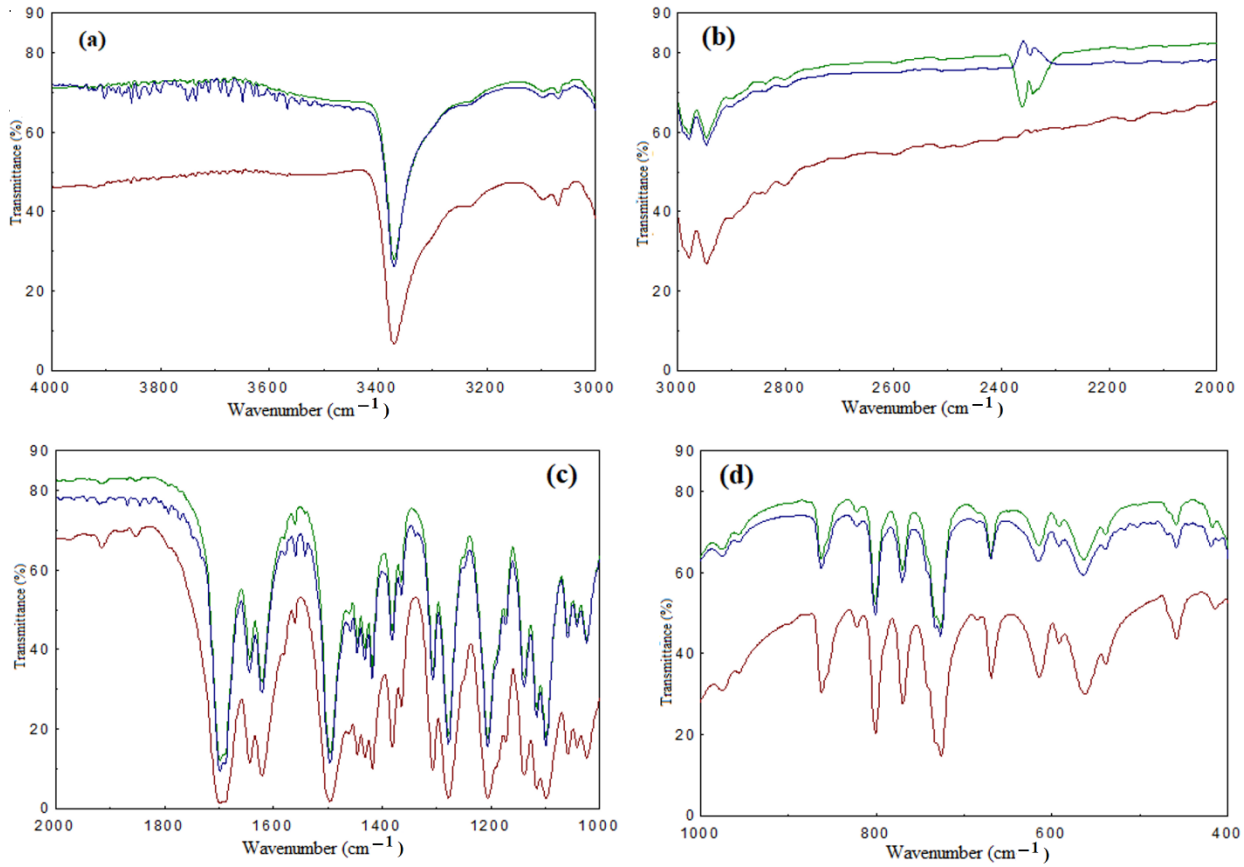


Figure 1. FTIR spectra of felodipine: macrocrystalline form—green line, microcrystalline form—blue line, reference—red line. (**a**) 4000–3000 cm^{-1} range; (**b**) 3000–2000 cm^{-1} range; (**c**) 2000–1000 cm^{-1} range; (**d**) 1000–400 cm^{-1} range.

From the FTIR spectra it was observed that the two felodipine forms have approximatively the same spectra as the reference. From Figure 1a can be seen that the peak attributed to the stretching vibration of the amino group ν(N-H) appears at 3342 cm^{-1}, characteristic of the amorphous felodipine compound [27,28]. This N-H stretching peak was shifted to 3370 cm^{-1} in the crystalline felodipine forms. The peaks at 2942 cm^{-1} and 1688 cm^{-1} are attributed to C-H stretching and C=O stretching vibration, respectively. All the spectral bands, which appear in the FTIR spectra of the compounds are consistent with the FTIR spectra of the reference felodipine compound [29].

Thermal analysis: The DSC curves of the two felodipine forms, compared with the reference sample, are represented in Figure 2.

The DSC analysis showed that the felodipine reference material had a lower melting point (143.9 °C) and the characteristic endothermal melting peaks of the two analysed felodipine forms were higher than the reference, proving the purity of the two samples. The melting point increased in the following order: felodipine reference sample (143.9 °C) < microcrystalline felodipine form (146.8 °C) < macrocrystalline felodipine form (148.51 °C). The higher melting points of the two felodipine forms may be explained by the more crystalline morphology of these samples. The lower melting point of microcrystalline felodipine form is due to the increased surface area of felodipine particles. This increase leads to an increase in heat-exchange efficiency [30]. The determined melting points agree with literature data [27,31].

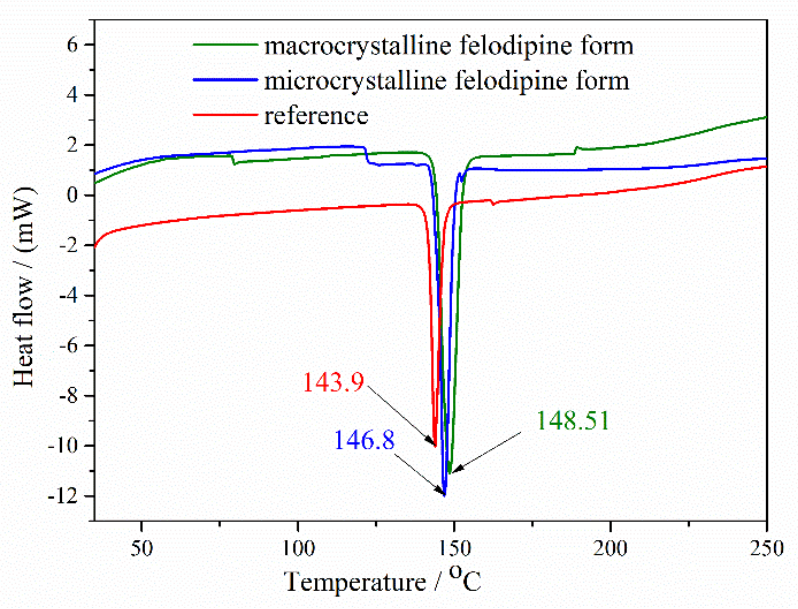


Figure 2. DSC curves of macrocrystalline and microcrystalline felodipine forms and reference sample in a nitrogen atmosphere with a heating rate of 10 °C/min.

Optical microscopy analysis. Images of the two studied felodipine types, macrocrystalline felodipine (batch E0055518) and microcrystalline felodipine (batch 0057505) at different resolutions (4×, 10×, 40× and 100× objective) were collected. The optical images are represented in Figure 3 for macrocrystalline felodipine and Figure 4 for microcrystalline felodipine.

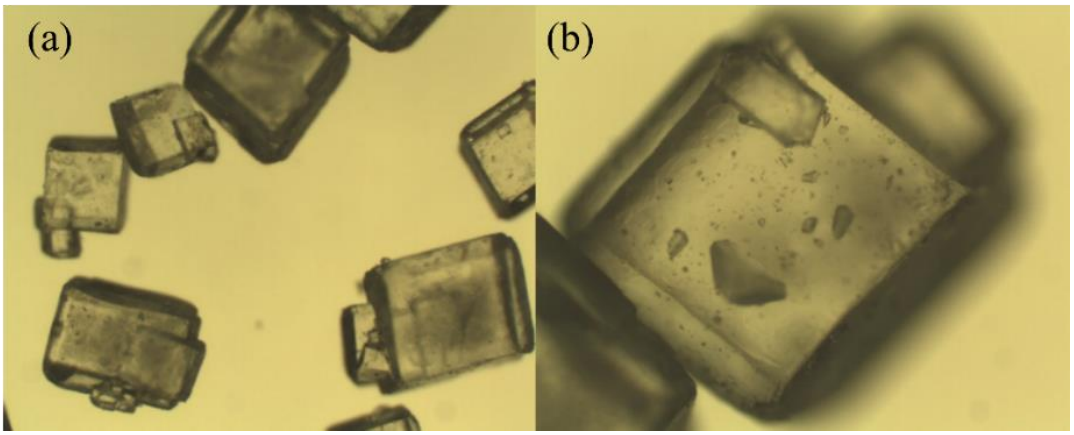


Figure 3. Microscopic appearance of macrocrystalline felodipine particles: (**a**) 4×; (**b**) 10×.

In Figure 3, the tetrahedral aspect of the crystals and the surface heterogeneity can be seen.

From Figure 4, the irregular round appearance of the microcrystalline felodipine form and the particles' tendency to agglomerate can be seen.

Optical microscopy analysis of the pure and crystalline forms of the two felodipine types showed a significant difference in morphology, depending on the raw material processing.

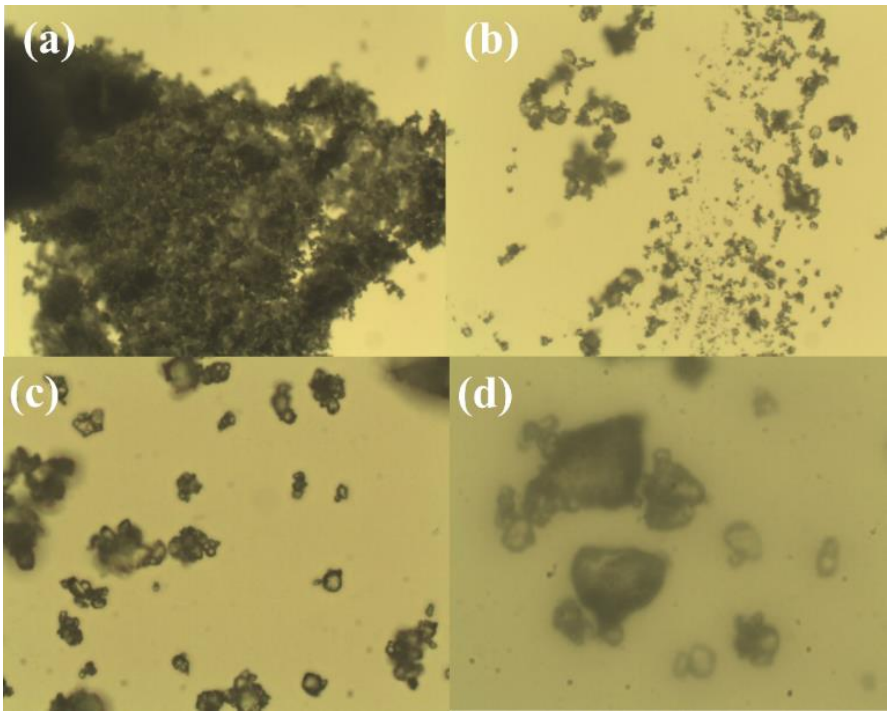


Figure 4. Microscopic appearance of the particles of microcrystalline felodipine form (**a**) 4×; (**b**) 10×; (**c**) 40×; (**d**) 100×.

Determination of felodipine particle size

Microscopic evaluation

The size of crystals for each crystalline form was evaluated. The results of the performed measurements are presented in Table 9, Figure 5 for the macrocrystalline form and Figure 6 for the microcrystalline form.

Table 9. Determination of medium particle size for felodipine, macro- and microcrystalline forms (performed on 24 samples of each type).

Felodipine Crystalline Type	Macrocrystalline Form		Microcrystalline Form	
Parameter	**Particle Size (μm)**	**Particle Surface Area (mm^2)**	**Particle Size (μm)**	**Particle Surface Area (mm^2)**
Average value	3573.71	14.683	30.3621	0.924
STDEV *	1412.23	10.465	17.55609	5.298
SAMPLE MEAN	565.00	4.187	6.389642	2.576

* STDEV—standard deviation.

The felodipine macrocrystalline form had an average diameter 117.70 times larger than the microcrystalline form. Within the same type of particle size, the standard deviation was over 10%, the particle size having a great intravariability.

Sieving and sorting method

This test was applied under laboratory conditions only for the macrocrystalline sample as the microcrystalline sample had particles of diameter smaller (in the range of 6–50 μm) than the smallest 32 μm mesh sieve. The mass of each determined fraction was calculated and expressed as a percentage and the results are given in Figure 7.

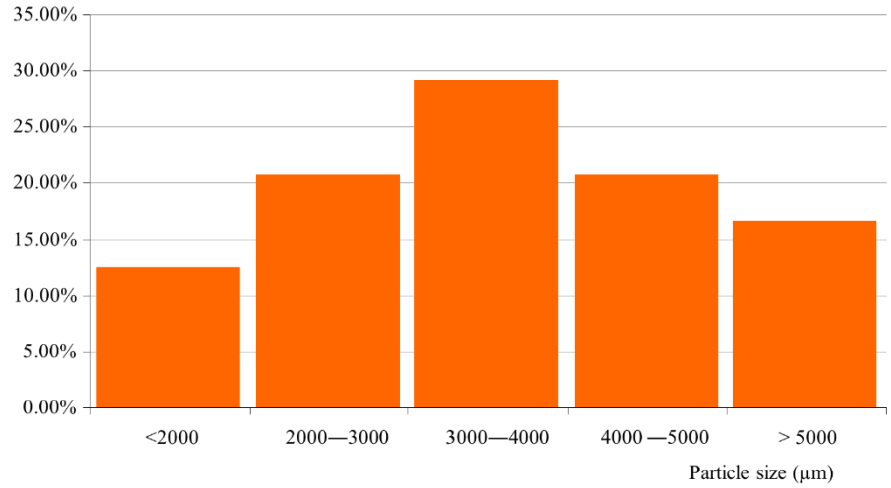


Figure 5. Histogram of granulometric analysis of macrocrystalline felodipine.

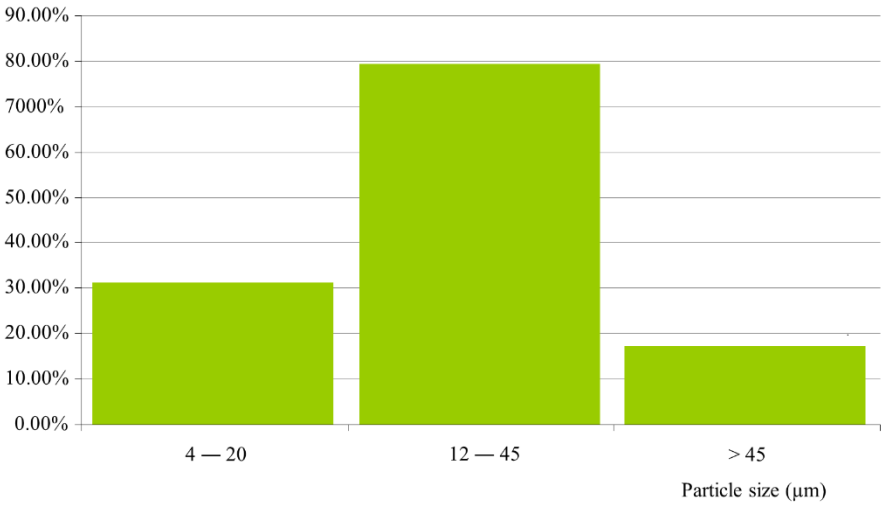


Figure 6. Histogram of granulometric analysis of microcrystalline felodipine.

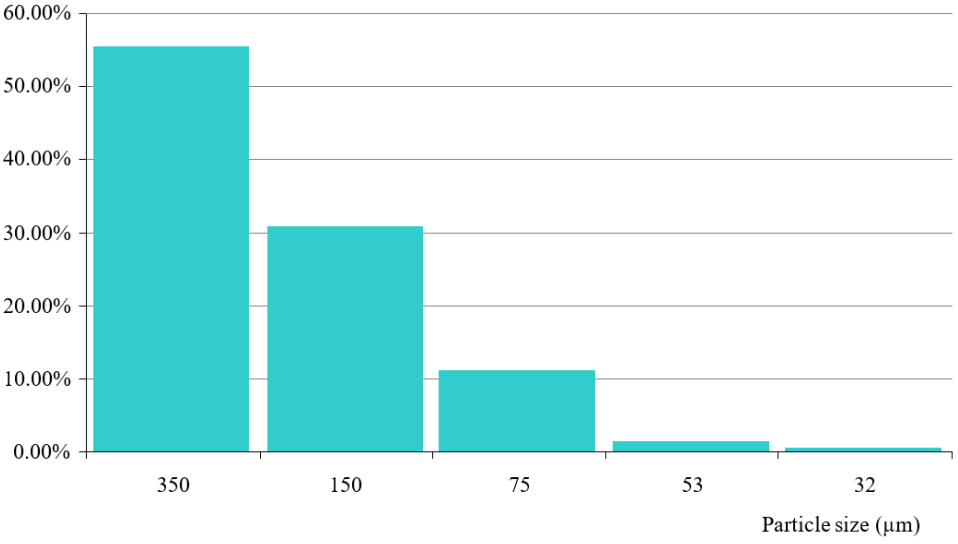


Figure 7. Mass histogram of granulometric analysis of macrocrystalline felodipine using the sieving and sorting method.

Volumetric characteristics of felodipine powders

The results regarding the volumetric characteristics of felodipine powders are represented in Table 10 and in Figure 8.

Table 10. Volumetric characteristics of felodipine powders.

Ingredient	Density (g/mL)		Flowability and Compressibility Indexes	
	Bulk	Tapped	CI	HR
macrocrystalline felodipine	0.7461	0.8318	11.49	1.11
microcrystalline felodipine	0.2882	0.3440	19.36	1.19

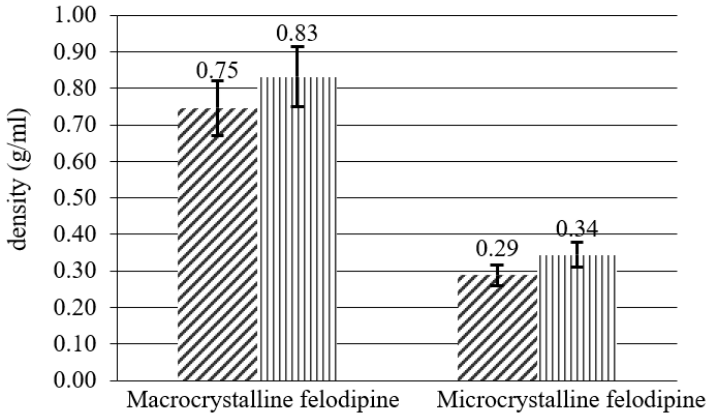


Figure 8. Bulk and tapped densities of felodipine powders.

The bulk density of the macrocrystalline form was 0.75 g/mL and the tapped density was 0.83 g/mL. For the microcrystalline sample, the bulk density of the powder was 0.29 g/mL, and 0.34 g/mL in the compacted state. It should be noted that in the tapped form, the density of microcrystalline felodipine powder was 2.5 times lower than that of the high crystallinity felodipine, revealing the high electrostatic charge of the particles.

Microcrystalline felodipine had poor flowing and lower compressibility properties due to the electrostatic interaction forces of the microparticles, which was also observed on microscopic evaluation. On the contrary, the macrocrystalline felodipine powder had excellent flowability and compressibility, which is remarkable for a pure active ingredient [32,33].

3.3. Influence of Formulation Factors on the In Vitro Availability of Felodipine in Experimental Tablets

Type and percentage of matrix-forming polymer

The obtained results are shown in Figure 9a for 1% LSNa dissolution medium and Figure 9b for 0.4% CTAB dissolution medium.

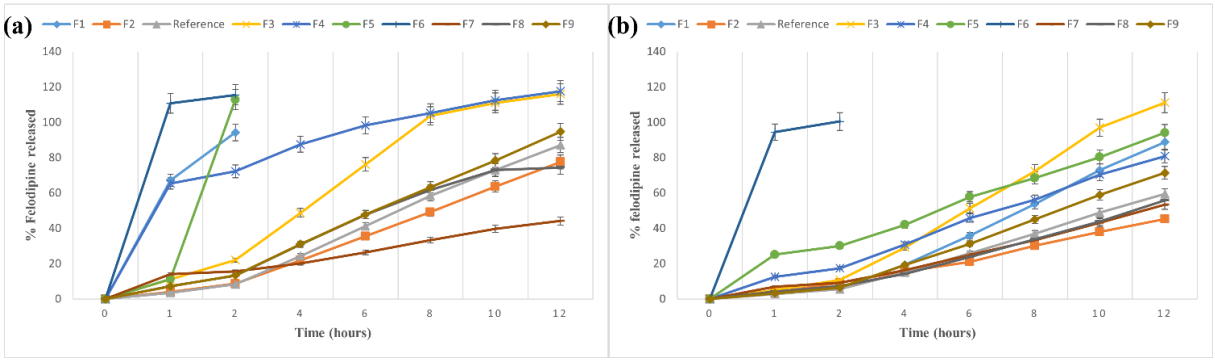


Figure 9. (**a**) Felodipine release rate in 1% LSNa medium; (**b**) Felodipine release rate in 0.4% CTAB medium.

The mean and standard deviation for $n = 6$ samples were calculated and the similarity factor (f_1) and difference factor (f_2) were determined (Table 11a,b).

Table 11. (**a**) The results obtained when comparing the dissolution profiles in the case of the innovative product and the developed formulations, in two dissolution media. (**b**) The results obtained when comparing the formulation profiles and the reference profile, in two different dissolution media.

(a)			
Medium		**Difference Factor f_1**	**Similarity Factor f_2**
LSNa 1.00%-CTAB 0.40%	REF	32.24	37.85
LSNa 1.00%-CTAB 0.40%	F1	-	-
LSNa 1.00%-CTAB 0.40%	F2	37.89	36.99
LSNa 1.00%-CTAB 0.40%	F3	22.90	36.76
LSNa 1.00%-CTAB 0.40%	F4	128.12	14.32
LSNa 1.00%-CTAB 0.40%	F5	23.82	58.34
LSNa 1.00%-CTAB 0.40%	F6	-	-
LSNa 1.00%-CTAB 0.40%	F7	36.22	35.46
LSNa 1.00%-CTAB 0.40%	F8	15.50	57.20
LSNa 1.00%-CTAB 0.40%	F9	17.62	55.69
(b)			
Medium		**Difference Factor f_1**	**Similarity Factor f_2**
REF–F1	LSNa 1.00%	-	-
REF–F2	LSNa 1.00%	12.53	58.87
REF–F3	LSNa 1.00%	31.56	37.43
REF–F4	LSNa 1.00%	92.45	4.86
REF–F5	LSNa 1.00%	35.68	40.47
REF–F6	LSNa 1.00%	-	-
REF–F7	LSNa 1.00%	11.79	56.67
REF–F8	LSNa 1.00%	33.60	40.49
REF–F9	LSNa 1.00%	14.55	58.74
REF–F1	CTAB 0.40%	43.98	39.44
REF–F2	CTAB 0.40%	21.35	55.83
REF–F3	CTAB 0.40%	31.35	37.43
REF–F4	CTAB 0.40%	15.70	51.27
REF–F5	CTAB 0.40%	38.68	39.38
REF–F6	CTAB 0.40%	-	-
REF–F7	CTAB 0.40%	33.66	39.30
REF–F8	CTAB 0.40%	11.57	62.91
REF–F9	CTAB 0.40%	37.24	51.48

Tablets containing 15% HPMC K 100 lead to 94% felodipine dissolution in two hours on 1% LSNa medium, the active ingredient being almost completely released during this period. In the same medium, F2, with a concentration of 30% HPMC K100, showed 8.70% felodipine dissolution in two hours and 77.50% felodipine dissolution in 12 h, compared to dissolution rates of 8.35% and 87.08% after 2 h and 12 h, respectively, for the reference product. In the 0.4% CTAB aqueous solution, F1 had a dissolution rate of 6.00% at 2 h and 88.8% at 12 h, which are better values compared to those registered in LSNa medium. For F2 the felodipine dissolution was 9.16% at 2 h and 45.30% at 12 h, displaying a slight difference compared to 5.57% and 59.43% for the reference product. Difference and similarity factor values reveal that F1 did not exhibit a dissolution behaviour similar to the reference product in the two media under study. Meantime, F2 showed a release profile with a similarity factor of more than 50 in the CTAB medium and with statistically similar values in the LSNa medium, having a difference factor of 12.53 and a similarity factor of 58.87 (Table 11b).

Increasing the amount of the cellulose polymer HPMC K100, which possesses the highest viscosity degree, in the composition of the experimental formulations lead to a delay in the release of felodipine correlating with the added percentage in all investigated dissolution media.

The felodipine release was significantly higher in LSNa medium than in CTAB for all studied formulations and also for the reference product. Experimental formulation F2,

containing 30% HPMC K100, showed a release profile similar to the reference product in both dissolution media, in comparison with F1 which contained only 15% HPMC K100. When supplementing the 15% high viscosity HPMC K100 matrix with 25% HPMC of the lowest viscosity in F3, the felodipine release in 1% LSNa was significantly delayed and the release in CTAB at 6 h was slightly reduced; however, the obtained profiles are obviously different from the reference product ones. Replacing the high viscosity HPMC K100 matrix with 35% medium viscosity HPMC E50 and 15% HPMC E5, the felodipine release increased from 94.23% at two hours for F1 to 112.80% for F5 and 115.50% for F6, which are much higher values than the 11.10% achieved by the reference formula. In the CTAB medium, the dissolution rate increased to 30.05% for F5 and 100.50% for F6.

The considerable differences in availability depend on the anionic or cationic surfactant. Practically, in the 1% LSNa medium, both F5 and F6 released the active substance in the first two hours, which is not in accordance with the dissolution requirements for extended-release products. In the CTAB 0.4% medium, dissolution was complete in two hours for the 35% HPMC E10 [34–37].

Obviously, in the experimental formulations, the differences of dissolution in aqueous media were significant between surfactants of various categories (LSNa and CTAB).

The use of HPMC E10 and HPMC E50 in F5 and F6 resulted in much higher felodipine availability compared to the reference product; in LSNa the release was almost complete in the first two hours of the study for both formulations, as opposed to dissolution in 0.4% CTAB medium, which was probably due to the anionic surfactant effect on the hydrophilic matrix. The inclusion of the low-polymerization HPMC matrix lead to much faster felodipine release from tablets, compared to the reference formulation, despite the large proportion used; 50% of the total mass. The felodipine dissolution in the investigated media was dependent on the type (viscosity) and on the proportions of the HPMC matrix.

At two hours, the felodipine dissolution in 1% LSNa medium was 15.70% for F7, which contained 38.00% HPMC E10 and 12.00% HPMC K100, higher than the percentage of 8.35% felodipine dissolved from the reference formula.

For F7, the dynamics of the active ingredient release were faster in the first 6 h, but after 12 h the percentage of dissolved felodipine was only 44.16%, in comparison with 87.08% for the reference formula.

F7 showed a reduction in felodipine release at 12 h on 0.1% LSNa medium, but no changes in the 0.4% CTAB medium were detected.

When analysing the similarity, f_1, and difference, f_2, factors, the results for the reference formulation resemble F4 in 0.4% CTAB medium, but contrast in 1% LSNa medium. In this case, in the two different media, the dissolution behaviour showed important differences between the experimental formulation profiles and the slower release reference product (Table 11b).

The association of water-soluble matrix-forming polymer E50 with a medium viscosity HPMC K100 increased felodipine release compared to the formulation containing only 30% HPMC K100 polymer (F2). Dissolution in 1% LSNa medium for F8 was 13.2% at 2 h and 74.4% at 12 h. For F9, the percentage of felodipine dissolved was 13.4% at 2 h and 94.7% at 12 h [38,39].

Considering the difference and similarity factors, F8 and F9 profiles were close to the reference formulation in LSNa 1%. On 0.4% CTAB medium, F9 presented dissolution profiles very much like the reference, with a 14.55 difference factor and a 58.74 similarity factor. The highest correlation degree was presented by F8, with values of 11.57 for f_1 and 62.91 for f_2.

The optimum ratio of the matrix was displayed by F9, consisting of two types of HPMC mixture, 35% high viscosity and 65% medium viscosity hydrophilic polymer, representing a total proportion of 42.5% of the total formulation mass.

When two HPMC polymers were combined in the formulation, it was found that the presence of a larger proportion of higher-polymerization-degree or -viscosity polymer led to a decrease in the felodipine release rate. Release in the higher-surfactant-content dissolution

media led to an increase in the released amount, respecting the above particularity [40–42]. The release was lower in CTAB than in LSNa medium.

Influence of the active ingredient granulometry on the dissolution profile

In 1% LSNa medium, the felodipine release from F10 was 12.9% at 2 h and 85.3% at 12 h. For F11 manufactured using microcrystalline felodipine, the felodipine dissolution was 42.2% at 2 h and 98.4% at 12 h. In CTAB, F10 showed percentages of 7.2% felodipine dissolved at 2 h and 60.5% felodipine dissolved at 12 h, while F11 released 4.7% percent of felodipine at 2 h and only 47.3% at 12 h (Figure 10).

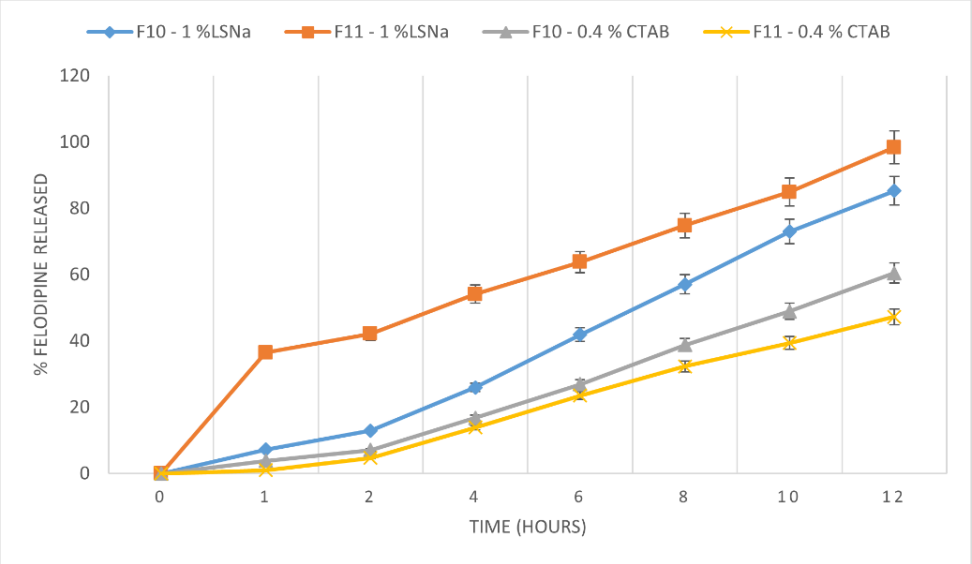


Figure 10. Percentage of felodipine dissolved over time from the investigated formulations in 1% LSNa and 0.4% CTAB solutions.

The correlation degree of the dissolution profiles was determined by the difference factor and similarity factor (Table 12), with values of 49.86 for f_1 and 32.16 for f_2 in LSNa medium. Meanwhile, f_1 was 20.05, and f_2 was 57.61 in CTAB medium. In 1% LSNa medium, the felodipine dissolution differed significantly between F10 and F11, but in CTAB medium, the dissolution profiles for experimental formulations containing macrocrystalline (F10) and microcrystalline (F11) felodipine showed similarity factors of more than 50.

Table 12. Results obtained when comparing dissolution profiles of F10 and F11.

Formulation	Dissolution Media	Difference Factor f_1	Similarity Factor f_2
F10–F11	LSNa 1.00%	49.86	32.16
F10–F11	CTAB 0.40%	20.05	57.61

Figure 10 shows the dissolution curves of the two formulations containing felodipine in two different particle sizes, in the two different surfactants dissolution media.

The felodipine release from tablets containing the microcrystalline form was complete at 12 h in 1% LSNa medium, while from the macrocrystalline-form tablets, it was only 85%.

In a 0.4% CTAB surfactant dissolution medium, the felodipine release rate from tablets with macrocrystalline particles was slightly slower than that from microcrystalline particle tablets, but it was much faster in the 1% LSNa medium. An immediate release profile of microcrystalline felodipine was observed in a 1% LSNa medium in the 2 to 6 h interval, confirming the faster dissolution properties of microcrystalline forms due to the increase in total particle area. In this case, the release of felodipine into the LSNa medium was

significantly higher than into the CTAB dissolution medium, regardless of the type of formulation [43–45].

The influence of the compression force

Figure 11 presents the values corresponding to the felodipine dissolution profiles in two tablet formulations prepared at different compression strengths. The results obtained by comparing the dissolution profiles in different dissolution media for F12 and F13 are shown in Table 13.

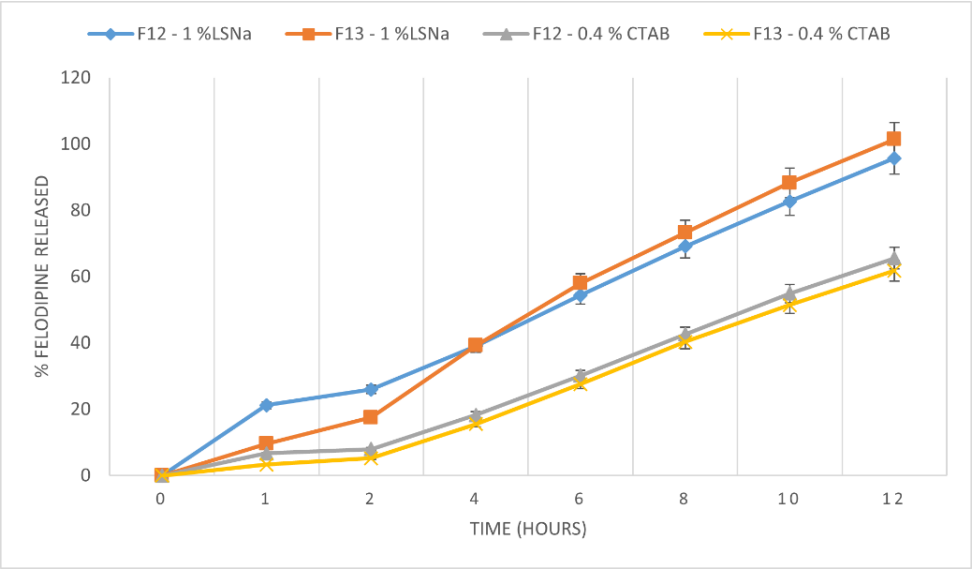


Figure 11. Percentage of felodipine dissolved over time from the formulations investigated in 1% LSNa and 0.4% CTAB media.

Table 13. The results obtained by comparing the dissolution profiles in different dissolution media for F12 and F13.

Formulation	Dissolution Media	Difference Factor f_1	Similarity Factor f_2
F12–F13	LSNa 1.00%	7.13	64.42
F12–F13	CTAB 0.40%	9.35	74.57

Statistically, in both media, the felodipine dissolution degree does not differ significantly for the experimental formulations manufactured using different compression forces.

For technological reasons, the use of a higher compression force of 80–90 N is more convenient to ensure higher mechanical strength of the tablets, which is required in the subsequent polymer film coating operation.

Increasing the compression force decreased the dissolution rate, but statistically, it was insignificant [46,47].

Tablets prepared with a compressive strength of 45 N have a porous appearance, they are friable, and they do not withstand the filming step of the manufacturing process. Therefore, it was necessary to use a compression force in the range of 80–90 N.

The influence of the amount of lactose monohydrate associated with the polymeric matrix decreased lactose content

The results of felodipine dissolution from experimental formulations F14, F15 and reference in 1% LSNa and 0.4% CTAB media are presented in Figure 12.

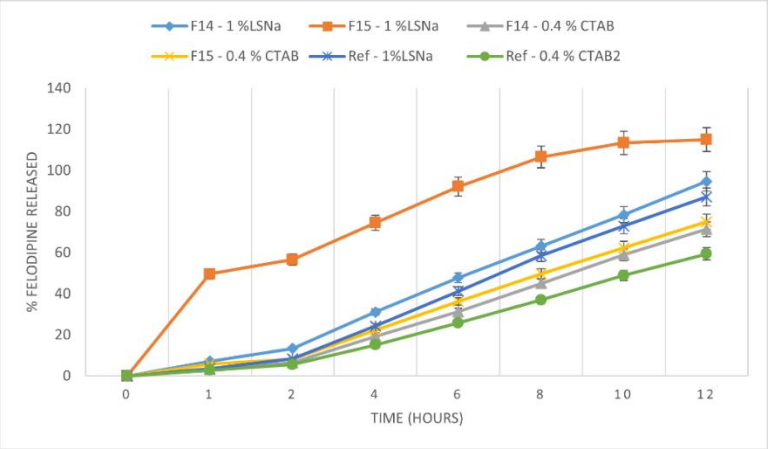


Figure 12. Felodipine release rate for F14 and F15 compared with the reference product.

The release profiles for F14 and F15 differed by 42.59 and 134.18 respectively, between the two averages (Table 14). The highest degree of correlation was obtained for the formula containing a lower amount of lactose monohydrate (4.5%).

Table 14. The results obtained when comparing the dissolution profiles of the innovative product and the formulations under study, in different dissolution media (for F14 and F15).

Formulation	Dissolution Media	Difference Factor f_1	Similarity Factor f_2
REF–F14	LSNa 1.00%	17.06	53.68
REF–F15	LSNa 1.00%	111.07	16.85
REF–F14	CTAB 0.40%	17.90	53.86
REF–F15	CTAB 0.40%	11.51	63.03
LSNa–CTAB	F14	42.59	40.12
LSNa–CTAB	F15	134.18	15.01

The reduced amount of lactose in F14, determined its similar profile to the reference product (f_1 was 17.06 in LSNa and 17.90 in CTAB, and f_2 was 53.68 in LSNa and 53.86 in the CTAB).

A higher amount of lactose led to a marked enhancement in the release of felodipine from HPMC-matrix tablets and caused an increased difference in dissolution in the two media of 1% LSNa and 0.4% CTAB. This phenomenon can be attributed to the dissolution in the polymer matrix increasing of the pore-forming excipient content and thus, extending the contact surface between the felodipine particles inside the matrix and the solvent [48–50].

Increased lactose proportion and decreased microcrystalline cellulose amount

The in vitro release profile of felodipine in the formulations is shown in Figure 13.

By increasing the amount of lactose by 7% and decreasing the amount of microcrystalline cellulose by 10%, the felodipine availability was enhanced in LSNa surfactant medium. In 1% LSNa, the felodipine release was 108.1% at 2 h for F17, containing an increased amount of lactose, compared to 22.11% for F16, containing a higher amount of microcrystalline cellulose.

The obtained results agree with the previous experiment, confirming lactose's role in accelerating the dissolution rate by pore formation inside the matrix.

This fact must be correlated with the presence of other excipients in the formulation, such as the hydrophilic polymers, highlighting their role in release [51–54].

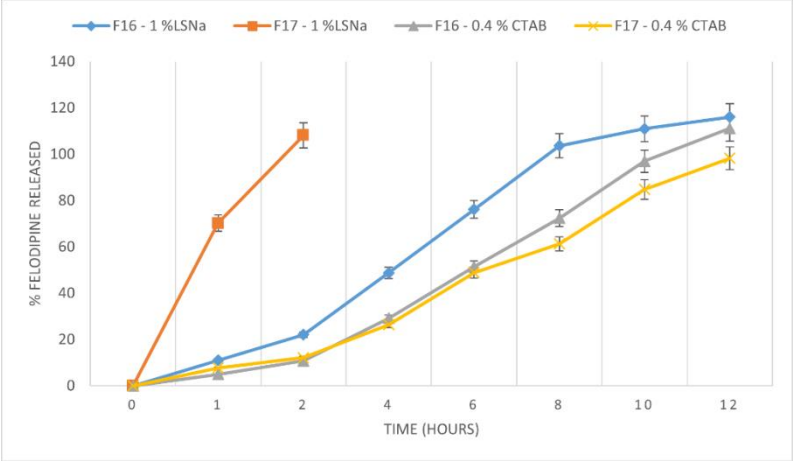


Figure 13. Percentage of dissolved felodipine in 0.4% CTAB and 1% LSNa for F16 and F17 formulations with different amounts of lactose and microcrystalline cellulose.

The influence of polyvinyl pyrrolidone (PVP) amount in the tablet formulation

The in vitro release study regarding the influence of polyvinyl pyrrolidone (PVP) amount in the tablet formulation is illustrated in Figure 14.

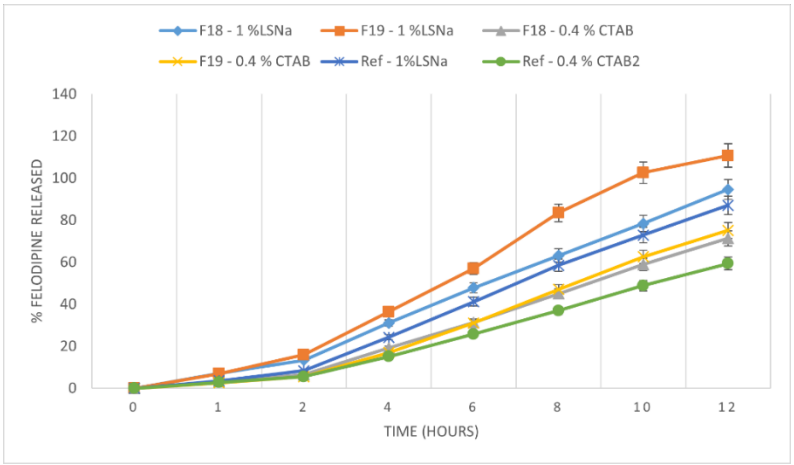


Figure 14. Percentage of dissolved felodipine in 0.4% CTAB and 1% LSNa for two formulations with different amounts of polyvinyl pyrrolidone (PVP).

In the 0.4% CTAB medium there were no important differences between F18 and F19 release profiles. In the LSNa 1% medium, the dissolution rate was superior for tablets with a higher amount of PVP.

Increasing the concentration of PVP in the formulation significantly enhanced the in vitro release rate in LSNa medium but the effect was less obvious in the CTAB medium. This phenomenon is possibly due to an increased degree of hydrophilicity and thus, the PVP dissolving faster than the main matrix-forming polymer [55–60].

Final tablet formulation

The in vitro release study for the final tablet formulation is illustrated in Figure 15.

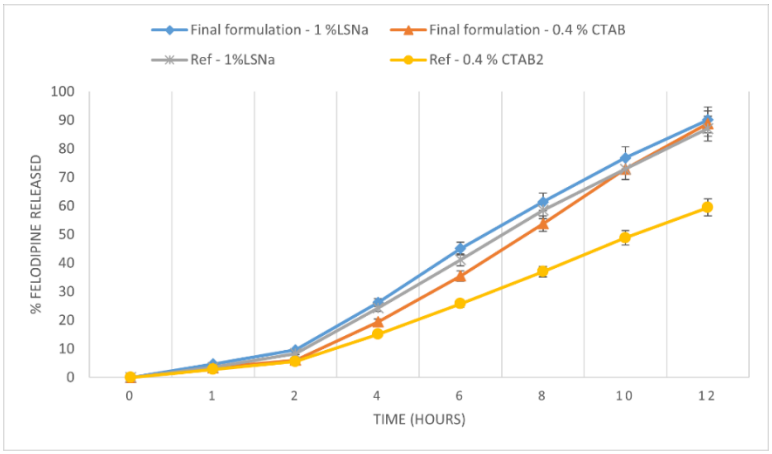


Figure 15. Dissolution profiles of the tested formulation compared with the reference product.

The felodipine release profile, in both media, showed a higher dissolution rate for the studied formulation compared with the reference product.

3.4. Modelling of Release Kinetics

The release of the active compounds from their matrix structure is controlled by several methods (dissolution, diffusion and swelling). These processes are strongly dependent on the matrix structure. The use of mathematical models to evaluate and to predict the drug release processes can be very helpful. Korsmeyer and Peppas [61] developed a simple semi-empirical model known as the "power law" to describe the fraction of drug release, $\frac{M_i}{M_\infty}$, especially from a polymetric matrix, which exhibits a power law dependence on the elapsed time (t), given by Equation (5) [62]:

$$\frac{M_i}{M_\infty} = kt^n \tag{5}$$

where $\frac{M_i}{M_\infty}$ is the fractional release of drug at time t, M_∞ is the amount of the drug at the equilibrium state (expressed as the amount of the drug at the beginning of the release process), M_i is the amount of drug at time t, k is a constant which incorporates the structural and geometrical characteristics of the drug dosage form and n is the release exponent, which corresponds to the drug release mechanism.

The constants k and n were obtained from the linear logarithm form of Equation (5). This gives Equation (6):

$$\ln\left(\frac{M_t}{M_0}\right) = \ln k + n \ln t \tag{6}$$

where the values of k and n were obtained from the intercepts and gradients of the plots of $\ln\left(\frac{M_t}{M_0}\right)$ versus $\ln t$.

This equation model can be used to analyse the release of pharmaceutical dosage forms in the following cases: (i) when the release mechanism is not well-known or (ii) when more than one type of release mechanism is involved [63]. The power law model has been widely used for the portion of the release curve where $\frac{M_i}{M_\infty} < 0.6$ [64]. In the present paper, the release was well described using this model for the entire drug release profile. According to Peppas [25], the value of the release exponent, n, could be used to characterise the different type of release mechanisms, as follows:

(i) n = 0.5 corresponds to the Fickian model (Case I) mechanism and the kinetics for the drug release are characterised by the diffusion process;

(ii) n = 1 corresponds to the non-Fickian model (Case II transport) mechanism. This corresponds to a zero-order release kinetic where the mechanism is governed by the swelling process;

(iii) $0.5 < n < 1$ corresponds to the non-Fickian or anomalous transport, in which case the drug release mechanism is governed by the diffusion and swelling processes;

(iv) $n > 1$ corresponds to the Super Case II model, an extreme form of transport.

Table 15 shows the values of n obtained by applying Equation (6) for all studied formulations (F1 to F19) and for the final tablet formulation in vitro release in LSNa and in the CTAB medium. In the present study, from the values of the correlation coefficient (shown in Table 15), it was observed that the power release law satisfactorily described the release in both media (1% LSNa and 0.4% CTAB) (Figure 16).

Table 15. Summary of drug release exponents, n, in the two media—1.0% LSNa and 0.4% CTAB, for all studied formulations.

Dissolution Medium/ Tablet Formulation	Drug Release Exponents, n and Regression Coefficient, R^2					
	1.0% LSNa			0.4% CTAB		
	Equation	n	R^2	Equation	n	R^2
F1	y = 0.48x + 2.20	0.48	-	y = 1.38x − 4.59	1.38	0.9893
F2	y = 1.20x − 3.52	1.20	0.9989	y = 0.97x − 2.62	0.97	0.9893
F3	y = 0.99x − 1.63	0.99	0.9850	y = 1.29x − 3.71	1.29	0.9972
F4	y = 0.24x + 3.14	0.24	0.9880	y = 0.77x − 0.75	0.77	0.9873
F5	y = 3.32x − 11.20	3.32	-	y = 0.54x + 0.88	0.54	0.9650
F6	y = 0.06x + 4.45	0.06	-	y = 0.09x + 4.17	0.09	-
F7	y = 0.47x + 0.53	0.47	0.9248	y = 0.84x − 1.67	0.84	0.9697
F8	y = 0.99x − 2.08	0.99	0.9880	y = 1.05x − 2.98	1.05	0.9909
F9	y = 1.05x − 2.38	1.05	0.9878	y = 1.28x − 4.16	1.28	0.9961
F10	y = 1.01x − 2.26	1.01	0.9969	y = 1.13x − 3.39	1.13	0.9971
F11	y = 0.39x + 1.90	0.39	0.9579	y = 1.51x − 5.87	1.51	0.9746
F12	y = 0.62x + 0.34	0.62	0.9675	y = 0.98x − 2.38	0.98	0.9625
F13	y = 0.97x − 1.72	0.97	0.9950	y = 1.25x − 4.09	1.25	0.9847
F14	y = 1.05x − 2.38	1.05	0.9970	y = 1.28x − 4.16	1.28	0.9961
F15	y = 0.37x + 2.32	0.37	0.9750	y = 1.09x − 2.89	1.09	0.9817
F16	y = 0.99x − 1.63	0.99	0.9850	y = 1.29x − 3.71	1.29	0.9972
F17	y = 0.62x + 1.70	0.62	-	y = 1.07x − 2.47	1.07	0.9862
F18	y = 1.05x − 2.38	1.05	0.9970	y = 1.28x − 4.16	1.28	0.9961
F19	y = 1.14x − 2.69	1.14	0.9960	y = 1.47x − 4.89	1.47	0.9957

In the case of 1.0% LSNa dissolution medium, it is interesting to observed that for F7, F11 and F15, the values of n are close to those of Fickian diffusion (n= 0.5). In the case of F4, the drug release exponent n = 0.24, which suggests that in parallel with the diffusion mechanism a significant contribution comes from another mechanism. The non-Fickian Case II transport mechanisms are observed for F3, F8, F9, F10, F13, F14, F16 and F18 which have values of n closed to 1. For this type of release, the mechanism is by polymer matrix relaxation. F2, F19 and the final formulation are governed by an extreme form of transport since the drug release exponents are higher than 1. Sigmoidal anomalous transport was observed for F12, which had an n value of 0.62 which is an indication that the release of drug is a controlled by more than one process. Because in the case of F1, F5, F6 and F17 only two points are represented for the linear fitting due to the fact that these formulations have a rapid release, the obtained values cannot be used to determine the mechanism of release of the drug in the 1.0% LSNa dissolution medium. For this reason, these formulations were excluded from further studies. The same conclusion can be drawn in the case of F6 obtained in 0.4% CTAB dissolution medium.

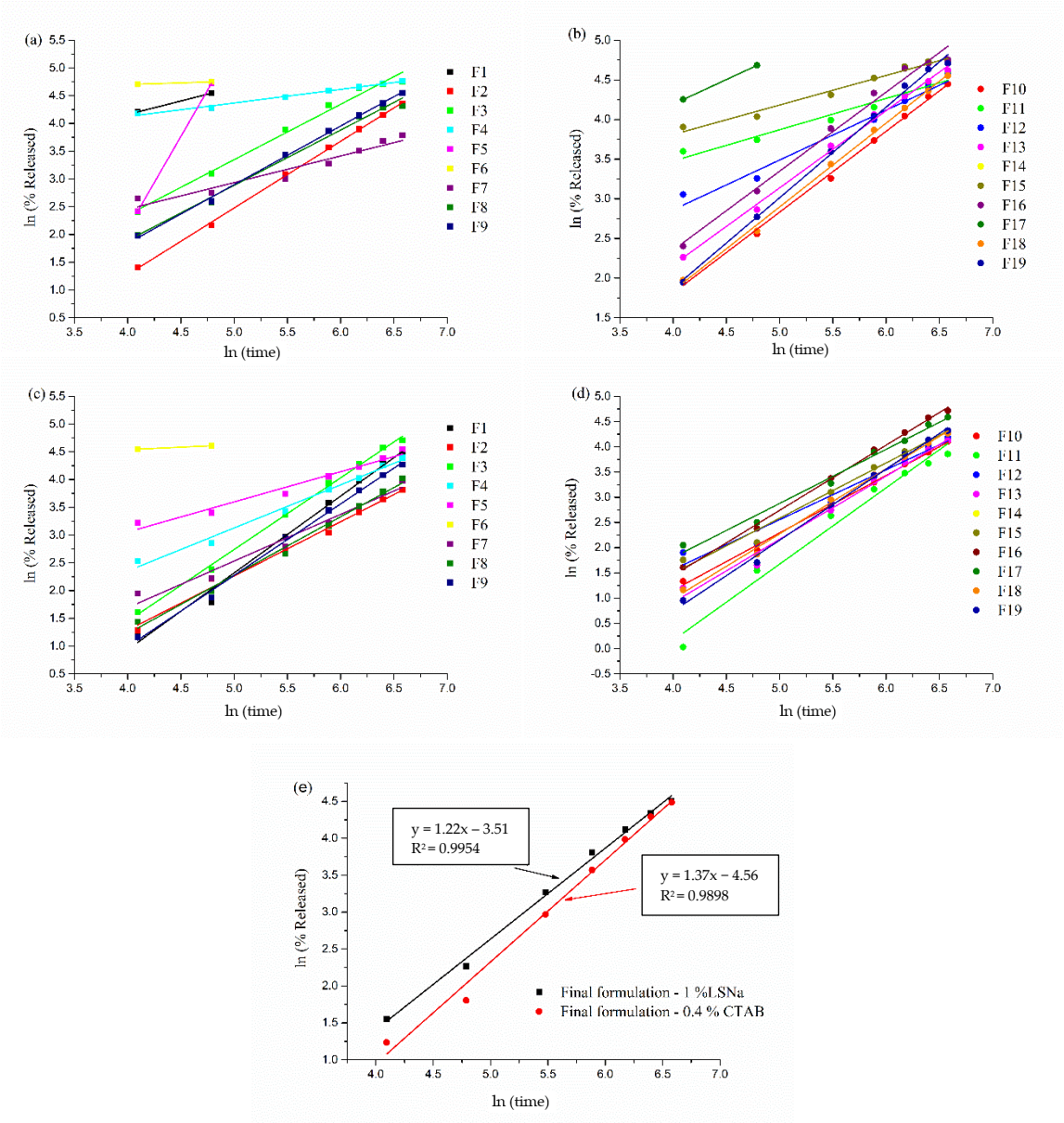


Figure 16. Power law fitting model (**a**) F1–F9 in 1% LSNa medium; (**b**) F10–F19 in 1% LSNa medium; (**c**) F1–F9 in 0.4% CTAB medium; (**d**) F10–F19 in 0.4% CTAB medium; (**e**) final tablet formulation in both media.

In the case of 0.4% CTAB dissolution medium, the following mechanisms for the release of the pharmaceutical dosage forms could be reported: (i) a predominant diffusion mechanism for F5 which had a value of n = 0.54, close to 0.5; (ii) sigmoidal anomalous transport mechanisms for F4 and F7; (iii) Case II non-Fickian transport mechanism for F2, F8, F12, F15 and F17; (iv) super Case II transport mechanisms reported for F1, F3, F9, F10, F11, F13, F14, F16, F18, F19 and the final formulation correspond to values greater than 1 suggesting a rapid drug release.

We can conclude that the drug release mechanism in the present formulations is more influenced by the type and the amount of the polymer matrix. Moreover, the Case II transport type was the dominant mechanism, advancing towards Super Case II transport.

4. Conclusions

New extended-release felodipine tablets for orally retained formulations were developed. The experimental results demonstrate that the in vitro release of felodipine from the

experimental tablets was influenced by different formulation factors. The present study reveals that some factors considerably modify the dissolution rate: felodipine particle sizes, proportions, the type of matrix-forming polymers and the amount of some excipients like lactose or PVP. The release was not significantly affected by the microcrystalline cellulose quantity or by the compression force. The drug release process is well described by the power law model, which supports diffusion-controlled release processes combined with some swelling and relaxation of the polymer matrix. In summary, in the dissolution study several factors must be considered: dissolution medium, due to the different influence of the used surfactant and the use of a reference product in order to establish a correlation for in vitro studies of experimental formulations.

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