ORIGINAL ARTICLE

PREPARATION AND *IN VITRO* CHARACTERIZATION OF PELLETS CONTAINING FELODIPINE SOLID DISPERSIONS

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Abstract

The aim of the study was the preparation and characterization of prolonged release pellets loaded with felodipine (FD) solid dispersions (SD) and coated with different polymeric coatings in order to release the active pharmaceutical ingredient (API) over a 12 hours period. A central composite experimental design with three factors and three levels was developed in order to determine the influence of the polyvinylpyrrolidone (PVP)/FD ratio in the SD, the percentage of polymeric coating and the percent of pore forming polymer in the coating on the kinetics release of FD. The good data fit with the chosen model indicates that the results dependent on the studied formulation factors. All the studied formulations released the API over a 12 hours period. The DSC analysis showed that in the PVP:FD = 2 SD, the FD is found in an amorphous state. The SEM studies showed that the pellets were evenly loaded and coated throughout the entire preparation process. The statistical analysis of the experimental data highlighted that the increase of PVP ratio in the SD and the increase in the percent of pore forming polymer in the coating increases the release rate of FD and that the increase in the percent of the polymeric coating determines a reduction in the release rate of the chosen model drug. In this research there were developed and characterized some prolonged release coated pellets with FD solid dispersions, pellets that released the model drug over a 12 hours period and the release kinetics of the API fitted best with the Peppas, Higuchi, Baker-Lonsdale and First order mathematical equations.

Rezumat

Studiul a avut ca scop prepararea şi caracterizarea unor pelete cu cedare prelungită încărcate cu dispersii solide (DS) de felodipină (FD) şi acoperite cu diferite filme polimerice, în vederea prelungirii cedării pe o perioadă de 12 ore a substanţei active. A fost dezvoltat un plan experimental „*central composite*" cu trei factori şi trei nivele de variaţie pentru a determina influenţa raportului dintre polivinipirolidonă şi felodipină (PVP)/(FD) în DS, a procentului de film de acoperire şi a proporţiei de formator de pori din amestecul de acoperire asupra cineticii de cedare a felodipinei. Buna fitare a datelor experimentale cu modelul statistic ales, indică faptul că rezultatele obţinute sunt dependente de factorii de formulare studiaţi. Toate formulările dezvoltate au cedat substanţa activă pe o perioadă de minim 12 ore. Analizele DSC au arătat că în DS cu raportul de combinare PVP:FD = 2, FD se găseşte în stare amorfă. Studiile SEM au arătat că peletele preparate au fost încărcate cu DS şi acoperite cu filmele polimerice într-un mod uniform, iar filmul format a fost unul continuu. Analiza statistică a datelor experimentale a subliniat faptul că, prin creşterea proporţiei de PVP în DS şi prin creşterea procentului de formator de pori din filmul polimeric, se determină creşterea vitezei de cedare a FD, iar prin creşterea încărcării cu film polimeric, se determină scăderea vitezei de cedare a substanţei model. În acest studiu s-au dezvoltat şi caracterizat pelete acoperite cu eliberare prelungită încărcate cu DS de FD, pelete care au cedat substanţa medicamentoasă pe parcursul a minim 12 ore iar cinetica de cedare a substanţei active din formulările studiate au fost descrise cel mai bine de ecuaţiile matematice Peppas, Higuchi, Baker-Lonsdale şi cinetica de ordinul I.

Keywords: felodipine, solid dispersion, pellets, coated multiple-unit, prolonged release, ethylcellulose

Introduction

In the last decades the pharmaceutical industry developed more and more active pharmaceutical ingredients (APIs) that have low solubility and low wettability [24]. These two characteristics are influencing the dissolution behaviour of the drug from the pharmaceutical preparation and are influencing the overall bioavailability of the drug [30]. For this reason the chosen model drug substance for this study was felodipine (FD). This is a dihydropyridine calcium antagonist used for its anti-hypertension and antianginal properties. According to the Biopharmaceutical Classification System it is classified as an IInd class drug substance that indicates a high permeability but a low solubility [24, 30, 31]. The low solubility of APIs included in the pharmaceutical drug delivery systems can be increased if the drug is formulated

as a solid dispersion (SD). The increase in the solubility of the API it's motivated by the fact that the drug is found under an amorphous state [17, 28].

The coated multiple-unit dosage forms are widely used in therapy because they offer several advantages in comparison with the single-unit dosage form preparations, such as tablets [1, 6, 7, 18, 20, 22]. From these multiple-unit preparations the drug is released over a long period of time and they are uniformly distributed in the gastrointestinal (GI) tract, avoiding the local irritation of the stomach or intestines due to high drug concentration in the dosage form, making them a more convenient choice of therapy [5, 15, 19, 21]. Using this type of formulation we can also avoid the "burst-effect" that can be observed sometimes in the case of single-unit coated preparations [26, 29]. The main advantage is that these pharmaceutical systems are releasing the drug in a constant manner from the pellets, assuring constant plasmatic drug concentrations and constant therapeutic effect with less adverse effects due to dose dumping [26, 29].

The release characteristics of the APIs from the coated pellets can be modulated using different film coatings, different amounts of film coating polymers and different pore formers. Based on these parameters the drug can follow a prolonged, sustained, pulsatile or controlled release, depending on the characteristics of the API and the needs in therapy [3, 7, 12, 19, 25].

The aim of the study was the preparation and *in vitro* characterization of FD SD loaded prolonged release coated pellets, in order to release the API over a 12 hours period. In order to prepare these multiple-unit preparations the FD was formulated as a SD loaded in pellets. The SDs were characterized by differential scanning calorimetry (DSC) thermo-gravimetric studies and the pellets by scanning electronic microscopy (SEM) imaging, the pharmaco-technical properties, *in vitro* dissolution and release kinetics. These pellets were coated with an insoluble but permeable polymeric film (ethyl-cellulose based coating) in order to control the release of FD over a period of 12 hours. To determine the influence of the formulation factors on the release of the FD from the pellets, a central composite experimental design with three factors and three variables was developed.

Materials and Methods

Materials

Felodipine (FD) (Nivedita Chemicals PVT Ltd, India, serial number NCL/XIX/59) and polyvinyl-pirrolidone (PVP) (Kollidon K30, BASF, Germany) were used to prepare the SD that were loaded into the inert pellets. The solid substrate for the FD SD was represented by sugar pellets (Suglets MESH 14/16, Colorcon, UK), aqueous dispersion of ethyl-cellulose (Surelease E719040, Colorcon, U.S.A) was used as film forming polymer and low viscosity hydroxipropylmethylcellulose – HPMC (Methocel E5LV, Colorcon, U.S.A.) was used as a pore forming agent in the polymeric coating. All other regents used in this research were of analytical grade and were purchased from Merck, Germany. All the employed materials were used as received.

Methods

Experimental design

A central composite experimental design with three factors and three levels was developed in order to study the influence of some formulation factors on the release of FD from pellets. The studied formulation variables (independent variables) and studied responses (dependent variables) are presented in Table I.

Table I

The studied formulation variables of the experimental design and the studied responses

Independent variables	**Symbol**	**Levels**		
		Low (–)	**Center point (0)**	**High (+)**
PVP:FD ratio in the SD	X_1	0.5	1.25	2
Film coating ratio (%)	X_2	3	5.5	8
Pore forming polymer ratio in the coating mixture (%)	X_3	8	15	22
Studied responses				
No.	**Responses**			**Symbols**
1	The % of FD released at 0.5 hours			Y_1
2	The % of FD released at 1 hour			Y_2
3	The % of FD released at 1.5 hours			Y_3
4	The % of FD released at 2 hours			Y_4
5	The % of FD released at 3 hours			Y_5
6	The % of FD released at 4 hours			Y_6
7	The % of FD released at 5 hours			Y_7
8	The % of FD released at 6 hours			Y_8
9	The % of FD released at 8 hours			Y_9
10	The % of FD released at 10 hours			Y_{10}
11	The % of FD released at 12 hours			Y_{11}
12	k Peppas			Y_{12}

The experimental matrix with the developed formulations is presented in Table II and it was developed using Modde 10.0 (Umetrics, Sweden) statistical optimization software.

Table II

Experimental design matrix

Experiment name	X_1	X_2	X_3
N1	0.5	3	8
N2	2	3	8
N3	0.5	8	8
N4	2	8	8
N5	0.5	3	22
N6	2	3	22
N7	0.5	8	22
N8	2	8	22
N9	0.5	5.5	15
N10	2	5.5	15
N11	1.25	3	15
N12	1.25	8	15
N13	1.25	5.5	8
N14	1.25	5.5	22
N15	1.25	5.5	15
N16	1.25	5.5	15
N17	1.25	5.5	15

Pellet drug loading and coating procedure

The neutral sugar pellets were loaded with the FD SD in the Aeromatic Strea 1, fluid bed coating system, equipped with Würster insert (Aeromatic, Switzerland) using the bottom-spray method. The composition of the three types of FD loaded pellets, the pellet drug loading conditions and the coating conditions are presented in Table III. Before loading or coating, the pellets were pre-heated to 30-32ºC and at the end of the loading and coating process a drying procedure was applied for 5 minutes. The coating of the FD loaded pellets with the ethyl-cellulose dispersion (Surelease E719040) containing HPMC (Methocel E5LV), as pore forming polymer, was performed in the same apparatus.

Each pellet dose contained an equivalent of 10 mg felodipine.

Differential scanning calorimetry (DSC)

DSC analysis of the FD, PVP and the three FD SD was performed using a Mettler Toledo DSC 822 cell using aluminium crucibles with about 2 mg of samples, under dynamic N_2 atmosphere (flow rate: 50 mL/min) and at a heating rate of 10°C/min in the temperature range from 25 to 400°C.

Table III

The pellet loading composition with the SD for a 150 g laboratory scale charge and drug loading and coating conditions on pellets

Pellet loading composition	PVP:FD = 0.5 ratio	PVP:FD = 1.25 ratio	PVP:FD = 2 ratio
Pellets 14/16 MESH	141 g	136,5 g	132 g
FD	6 g	6 g	6 g
PVP - for 10% solution	3 g	7.5 g	12 g
Ethanol (not found in the final product)	30 g	75 g	120 g
Loading conditions	**Drug loading**	**Coating**	
Inlet air temperature (ºC) (set/real)	54/59	47/51	
Outlet air temperature (ºC)	43	42	
Fan air (m^3/min)	5.5	5.5	
Atomizing pressure (atm)	1.7	1.7	
Spray rate (g/min)	7	5	
Nozzle diameter (mm)	0.8	0.8	

In vitro dissolution test

Dissolution testing was performed according to an adapted method from the USP 30th Edition. The test was conducted at 37 ± 0.5ºC in the PharmaTest PT-DT7 dissolution equipment using the basket apparatus at a 50 rpm rotation speed. The dissolution medium consisted of 500 mL phosphate buffer pH = 6.5 with 1% sodium lauryl sulphate. At different time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours) 2 mL samples were withdrawn and then replaced with fresh dissolution medium. The drug assay was performed at 240 nm using a HPLC Agillent 1100 series apparatus with auto-sampler, equipped with a Zorbax SB-C18, 5 µm x 4.6 x 150 mm chromatographic column, mobile phase:acetonitrile:phosphoric acid 0.1% in water = 75:25 at a flow of 1.5 mL/minute and 2.3 minutes FD retention time. The *in vitro* dissolution testing was performed on a weighed mass of pellets. All the tested prolonged release coated pellets contained an equivalent of 10 mg felodipine in the form of SD and all the determinations were performed in triplicate and the results are the mean of the three determinations.

Release kinetics

In order to determine the release profiles of FD from the studied pellets, several release models were tested (Table IV), such as Baker-Lonsdale [2], Peppas [16, 23], Hixson and Crowell [10, 11], Higuchi [5, 8, 9], First order [4, 27] and Zero order [4, 27]. These models where used to fit the individual experimental data, obtained after the *in vitro* dissolution testing, using the regression module of Kinetica 4.4. (Thermo Scientific,

U.S.A.). Based on this regression analysis the release constant k, the correlation coefficient R and the Akaike Information Criterion (AIC) were determined. To distinguish which mathematical model best describes the release of the API, the AIC was employed. A lower value for this criterion indicates a better fit and the chosen mathematical model describes with the greatest accuracy the release profile of FD.

Scanning electron microscopy (SEM)

Whole and crushed in half SD loaded coated pellets and formulation N6 were analysed from the point of view of the external and internal aspect. The images were taken by a scanning electron microscope (Quanta 3D, FEG, FEI Company, U.S.A.). On the studied samples a 6 - 7 nm Pt/Pd coating was applied.

Table IV

Tested release models

Baker – Lonsdale	$(3 / 2) [1 - (1 - (Q_t / Q_8)^{2/3}] - (Q_t / Q_8) = K_b t$
Peppas	$Q_t / Q_8 = K_p t^n$
Hixson-Crowell	$Q_0\ 1 / 3 - Qt\ 1 / 3 = K_s t$
Higuchi	$Q_t / Q_8 = K_h t^{0.5}$
First order	$Q_t / Q_8 = K_1 t$
Zero order	$Q_t = Q_0 + K_0 t$

Results and Discussion

The effect of the PVP ratio in the SD (DSC thermo-gravimetric studies)

The aim of this physical characterization was to demonstrate that the loaded FD as SD on the pellets is found under an amorphous state. A drug substance that is found in an amorphous state has a greater solubility than the same substance found in a crystalline state. The increase in the FD solubility is needed because this model drug substance has a low solubility in water.

The DSC thermogram of FD is presented in Figure 1 (black curve). The DSC curve of FD showed a first endothermic event between 142.06 and 146.68°C (ΔH_{fusion} = -180.77 mJ), with a melting temperature of T_{peak} = 144.33°C. The decomposition of FD occurs after 300°C.

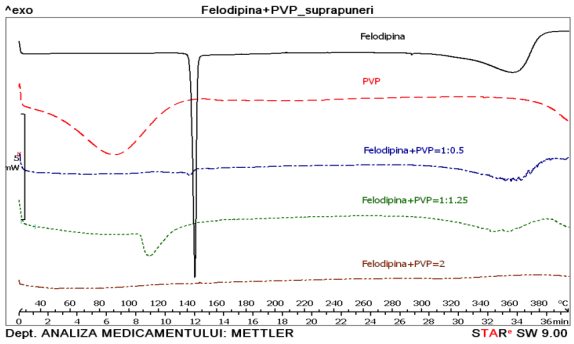

Figure 1.

The DSC thermograms for FD and PVP in comparison with the three SDs

The DSC thermograms of the FD SD with different proportions of PVP are shown in Figure 1 (blue, green, brown curves). In case of PVP:FD = 0.5 SD a small FD melting point peak was observed suggesting that some crystalline FD still remained. In the PVP:FD = 1.25 solid dispersion DSC thermogram the melting point peak of FD still remained, but it shifted through a lower melting temperature T_{peak} = 113.89°C and the melting temperature domain was larger (107.80 - 129.15°C) than in the case of pure FD (142.06 - 146.68°C), that demonstrates a degree of amorphisation of FD dispersed in this proportion with PVP. The melting point peak of pure FD was not observed in the SD prepared with PVP:FD = 2, suggesting that in this case FD was molecularly dispersed and found in an amorphous form.

Experimental design analysis

The results for the data fit of the experimental data are presented in Figure 2.

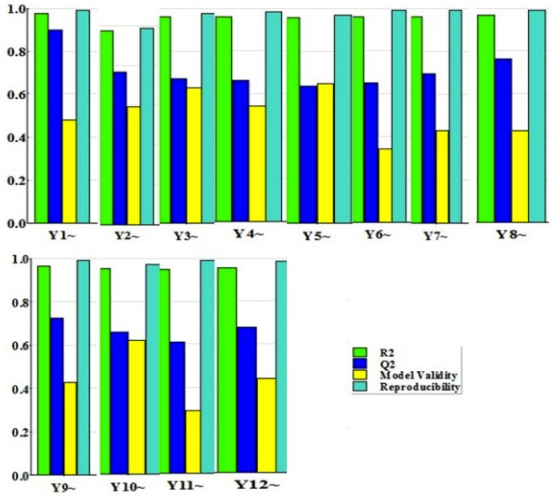

Figure 2.

Summary of fit for the experimental data

Y_1 – the % of FD released at 0.5 hours, Y_2 – the % of FD released at 1 hour, Y_3 – the % of FD released at 1.5 hours, Y_4 – the % of FD released at 2 hours, Y_5 – the % of FD released at 3 hours, Y_6 – the % of FD released at 4 hours, Y_7 – the % of FD released at 5 hours, Y_8 – the % of FD released at 6 hours, Y_9 – the % of FD released at 8 hours, Y_{10} – the % of FD released at 10 hours, Y_{11} – the % of FD released at 12 hours, Y_{12} – k Peppas.

The results were statisticaly analysed using the Partial Least Square method. In all cases, the data

fit was good or very good. This indicates that the results are reproducible and fit well to the chosen mathematic model.

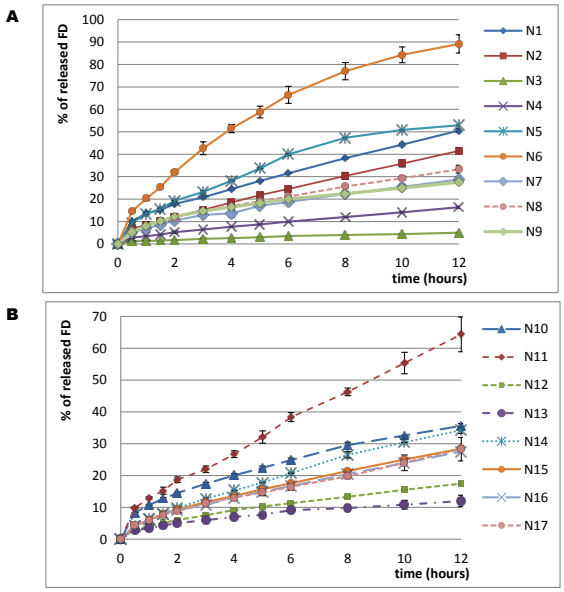

Figure 3.
The release profiles of FD from studied pellets:A – N1 - N9, B – N10 - N17

In vitro dissolution test

The FD was slowly released, over a 12 hours period, from all the experimental formulations. The release profiles of FD from the 17 coated pellets formulations are shown in Figure 3 A, B. In the case of formulation N6 it can be observed that around 90% of the FD content was released in a constant manner over the 12 hours period.

Influence of the formulation factors on the release characteristics of FD

To study the influence of the formulation factors on the responses (the percentage of felodipine released at different times) three-dimensional response surfaces and histograms were plotted using the Modde 10 – statistical software. The mentioned graphical results are presented in Figure 4. From the plotted histograms (Figure 4 – Y_1A to Y_{11}A) it can be observed that the increase of the PVP:FD ratio in the SD (X_1) from 0.5 to 2 increases the release rate of the FD, the increase in the percent of the polymeric coating (X_2) from 3% to 8% determines a reduction in the release rate of FD and the increase in the percent of pore forming polymer (X_3) from 8 to 22% increases the overall release of the API.

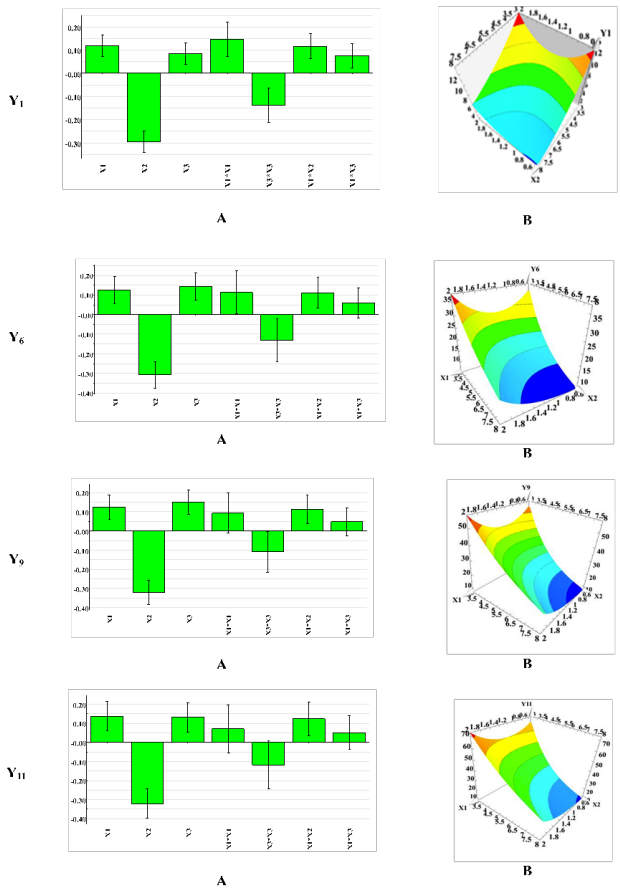

Figure 4.
Influence of the formulation factors over the release rate of FD: **Y_1** – at 0.5 hours; **Y_6** – at 4 hours; **Y_9** – at 8 hours; **Y_{11}** – at 12 hours

The X_1*X_1 interaction shows a non-linear evolution in the experimental domain, observation that is sustained also by the three dimensional plots. The X_1*X_2 interaction meaning is that by increasing the X_1 factor (the amount of PVP in the SD) and by increasing the X_2 factor (the percent of the film coating) results in an increase of the FD dissolution. The response surfaces describe the interactions between two independent variables (the PVP:FD ratio in the solid dispersion – X_1 and the percent of film coating – X_2) on a response and the global influence of the studied formulation factors on the release of FD – the histograms. By analysing the response surfaces (Figure 4 – Y_1B to $Y_{11}B$) for the whole dissolution test it can be observed that the PVP:FD ratio and the film coating ration has a significant importance on the release rate of the API. An increase of PVP in the PVP:FD ratio (X_1) determines an increase in the release rate of the FD. This can be explained by the increased hydrophilicity of the FD in the SD (in the PVP:FD = 2 SD the FD is found in an amorphous state – which is more soluble in comparison with the crystalline one found in the PVP:FD = 0,5 SD). The increase of the film coating on the coated pellets determines a decrease in the FD release rate. The increase of the film coating (X_2) from 3% to 8% causes a longer path through which the dissolution medium/the dissolved drug solution travels within the pellet coating. From the three dimensional response surface it can be observed that in the case of the PVP:FD = 0.5 SD the FD has a good dissolution due to the small amount of PVP in the dissolution, regardless that the FD is found in a crystalline state. Also a good dissolution of the API is observed in the case of the PVP:FD = 2:1 SD where the drug is found under a amorphous state (affirmation sustained by the DSC study data). In all the prepared samples the amount of FD in the dispersion was maintained the same, only the PVP proportion was modified. An inflection point was determined in the case of the PVP:FD = 1.25 SD, from which the FD was dissolved poorly in comparison with the other dispersions. This can be explained as follows: the amount of PVP is 2.5x higher than in the case of the first solid dispersion, PVP gives the SD a higher viscosity and the FD is found in both states in the first two SD (crystalline and amorphous) (Figure 4 – Y_1B to $Y_{11}B$). The results, for the prepared SD, are in accordance with the studied literature. The increase in the amount of the hydrophilic component in the drug SD increases the solubility of the API, due to amorphisation [15, 24]. Also the results for coating composition are in accordance with the literature. An increase in the polymeric loading of the solid pharmaceutical preparations determines a decrease in the release rate of the model drug and the increase in the percent of pore forming polymer in the film coating determines a more porous layer through which the dissolution media/drug solution can permeate enter/quit easier [12-14].

Release kinetics

The results after the data fit of the FD release with the six kinetic release models (Table V.) are: formulation N1, N2, N4, N5, N7, N8, N11, N12, N14 - N17 fitted best with the Peppas model, formulation N3 and N10 fitted best with the Higuchi model, formulation N9 and N13 fitted best with the Baker-Lonsdale model and formulation N6 fitted best with the First order model. The models were chosen based on the values of AIC, values highlighted in Table V. The good correlations with the Peppas model suggests that the FD release from the multi-particulate preparations is based on diffusion processes through the polymeric coating pores and swelling phenomenon of the PVP inside of the pellet, used as SD former. The good correlation with the Higuchi model (N3 - n = 0.5402, N10 - n = 0.4952, values close to 0.5) indicates that the FD release is proportionate with the square root of time, which means that the release is controlled by diffusion processes. The release of FD from N9 and N13 formulations fitted well with the Baker-Lonsdale model, model specific for the spherical preparations and formulation N6 released the FD by First order kinetics.

Because the Peppas models explained well the release kinetics of FD from the majority of the studied pellets, the release constant k was included as studied response in the experimental design.

From the plotted histograms obtained after the experimental data analysis it can be observed that the increase of the PVP ratio in the SD (X_1), increases the release rate constant of FD (Figure 5 – $Y_{12}A$). This can be explained by the increased hydrophilicity of the model drug in the SD, where at higher PVP ratios the FD is found in an amorphous state. The X_1*X_1 interaction indicates that this factor has a non-linear influence over the release constant of the API (Figure 5 – $Y_{12}B$). Another factor that increases the release rate constant is the ratio of pore forming polymer in the coating (X_3) (Figure 5 – $Y_{12}A$). This phenomenon can be explained due to the fact that the film coating is more porous and more permeable in comparison with one that has fewer pores in its composition.

Table V

Results for the kinetic release characterization

	Baker and Lonsdale			Peppas				Hixon and Crowell		
	R	AIC*	k	R	AIC*	k	n	R	AIC*	k
N1	0.9847	49.16	0.0036	0.9960	**33.61**	11.670	0.5755	0.9425	63.46	0.0195
N2	0.9710	52.42	0.0021	0.9972	**26.50**	7.564	0.6745	0.9728	51.72	0.0147
N3	0.9929	-9.64	0.0001	0.9945	-9.20	1.294	0.5402	0.8795	20.85	0.0017
N4	0.9820	26.03	0.0003	0.9974	**7.21**	3.268	0.6362	0.9649	37.82	0.0053
N5	0.9824	54.11	0.0048	0.9950	**38.88**	13.204	0.5806	0.9533	61.01	0.0232
N6	0.9739	69.87	0.0164	0.9965	45.63	22.602	0.5720	0.9902	59.21	0.0516
N7	0.9905	32.22	0.0011	0.9984	**13.80**	6.718	0.5789	0.9303	53.75	0.0103
N8	0.9906	35.03	0.0015	0.9988	**13.21**	7.773	0.5762	0.9327	56.38	0.0120
N9	0.9992	**3.99**	0.0012	0.9991	7.08	8.473	0.4735	0.8401	61.26	0.0105
N10	0.9982	18.21	0.0020	0.9991	12.31	10.357	0.4952	0.8770	64.09	0.0139
N11	0.9451	66.64	0.0053	0.9964	**38.05**	10.826	0.7067	0.9809	55.00	0.0247
N12	0.9926	18.45	0.0004	0.9993	**-4.34**	4.062	0.5804	0.9232	43.77	0.0060
N13	0.9984	**-6.51**	0.0002	0.9984	-4.03	3.592	0.4847	0.8319	43.45	0.0043
N14	0.9676	50.38	0.0014	0.9992	**11.24**	5.909	0.7085	0.9807	44.77	0.0120
N15	0.9834	38.16	0.0010	0.9991	**8.01**	5.835	0.6302	0.9547	49.06	0.0099
N16	0.9834	37.17	0.0090	0.9982	**14.08**	5.647	0.6262	0.9517	48.76	0.0094
N17	0.9791	39.92	0.0090	0.9964	**20.82**	5.471	0.6421	0.9561	47.92	0.0064

	Higuchi			First order			Zero order		
	R	AIC*	k	R	AIC*	k	R	AIC*	k
N1	0.9916	42.52	13.450	0.9549	60.87	0.9549	0.9065	68.60	4.7873
N2	0.9789	48.94	10.538	0.9786	49.11	0.9786	0.9560	56.91	3.8041
N3	0.9932	**-10.09**	1.395	0.8817	20.66	0.0051	0.8750	21.23	0.4935
N4	0.9852	24.44	4.228	0.9527	37.00	0.0164	0.9408	39.41	1.5182
N5	0.9900	48.01	15.365	0.9687	60.39	0.0778	0.9037	49.10	5.1610
N6	0.9924	56.45	25.870	0.9972	**45.35**	0.1859	0.8979	84.44	9.1785
N7	0.9936	27.80	7.792	0.9393	52.27	0.0325	0.9090	56.56	2.7720
N8	0.9944	29.41	8.980	0.9428	54.64	0.0384	0.9080	59.67	3.1910
N9	0.9984	11.81	8.066	0.8573	60.11	0.0333	0.8004	63.64	2.8159
N10	0.9990	**11.40**	10.265	0.8951	62.45	0.0449	0.8327	67.21	3.6026
N11	0.9650	61.58	16.060	0.9851	52.31	0.0826	0.9559	64.06	5.8227
N12	0.9943	15.47	4.725	0.9290	42.94	0.0184	0.9106	45.38	1.6813
N13	0.9982	-5.43	3.491	0.8392	43.00	0.0131	0.8164	44.32	1.2220
N14	0.9745	47.80	8.793	0.9853	41.78	0.0380	0.9679	50.27	3.1884
N15	0.9877	34.93	7.464	0.9612	47.39	0.0311	0.9391	52.23	2.6768
N16	0.9874	34.16	7.167	0.9579	47.27	0.0296	0.9368	51.63	2.5692
N17	0.9834	37.36	7.167	0.9616	46.49	0.0296	0.9431	50.71	2.5733

The increase in the polymeric coating on the pellets (X_2) determines the decrease of the release rate constant by the fact that the dissolution medium has a longer path through which the dissolution medium/the dissolved drug solution travels through the pellet coating (Figure 5 – Y_{12}A).

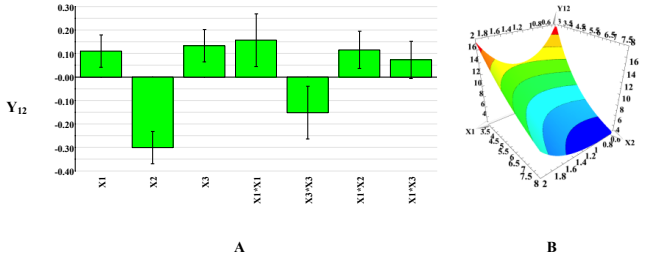

Figure 5.

Influence of the formulation factors over the release kinetics of FD: **Y_{12}** – k Peppas

Scanning electron microscopy (SEM)

The FD SD loaded pellets were analysed by SEM. In Figure 6 are presented the images of the studied pellets (initial pellet – A, pellet loaded with PVP:FD = 0.5SD – B, pellet loaded with PVP:FD = 1.25SD – C, pellet loaded with PVP:FD = 2SD – D) – single pellet, crushed pellet and detail of the crushed pellet.

From these images it can be observed the increase of the solid dispersion layer. This phenomenon appears because the quantity of FD in the SD was maintained the same, only the PVP ratio was modified.

The SEM images of the formulation N6 that released around 90% of the FD content in 12 hours of dissolution testing are presented in Figure 6 – E. In these images it can be observed that the obtained polymeric coating is an even and continuous film that covers the entire drug loaded pellet. In the detailed images of the crushed pellet the solid dispersion layer and the polymeric coating layer can be clearly distinguished.

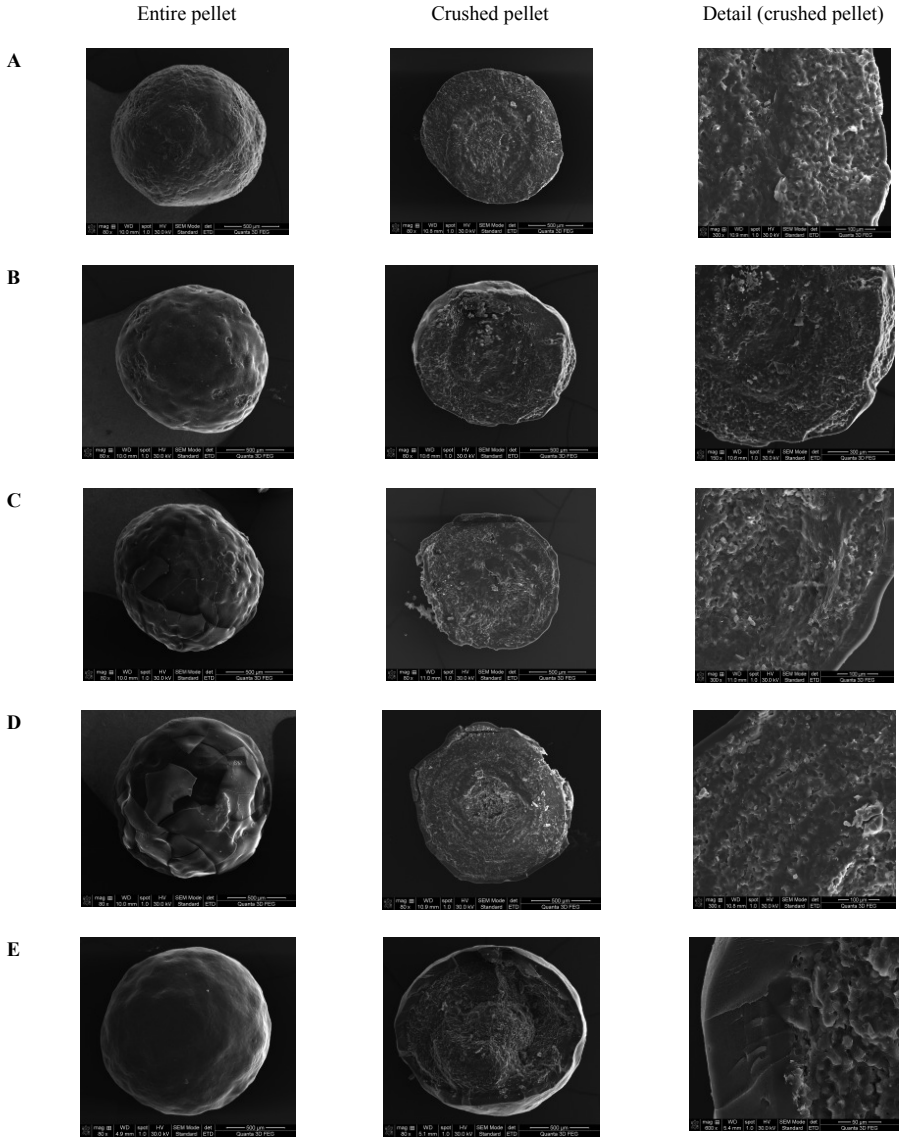

Figure 6.

SEM images of the unloaded pellets (**A**) and the three other FD SD loaded pellets (pellet loaded with PVP:FD = 0.5SD – **B**, pellet loaded with PVP:FD = 1.25SD – **C**, pellet loaded with PVP:FD = 2SD – **D**), formulation N6 (**E**)

Conclusions

A series of novel coated prolonged release pellet formulations containing different FD SDs were prepared based on a central composite experimental design.

The prepared formulations were smoothly and evenly loaded/coated and presented a prolonged release over a 12 hours period or more. The experimental results varied depending on the formulation factors, which indicates a good data fit of the experimental results with the chosen model. The prepared pellets showed that by using the FD as a SD the solubility increased, due to the amorphous state in which the FD is found in the SD, and that the release rate is directly influenced by the nature and the thickness of the film coating and the pore forming polymer. The release kinetics of FD from the coated pellets fitted best the Peppas,

Higuchi, Baker-Lonsdale and First order mathematical equations.

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