DEVELOPMENT OF A RESERVOIR TYPE PROLONGED RELEASE SYSTEM WITH FELODIPINE VIA SIMPLEX METHODOLOGY

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Abstract

Background and aims. Felodipine is a dihydropyridine calcium antagonist that presents good characteristics to be formulated as prolonged release preparations. The aim of the study was the formulation and in vitro characterization of a reservoir type prolonged release system with felodipine, over a 12 hours period using the Simplex method.

Methods. The first step of the Simplex method was to study the influence of the granules coating method on the felodipine release. Furthermore the influence of the coating polymer type, the percent of the coating polymer and the percent of pore forming agent in the coating on the felodipine release were studied. Afterwards these two steps of the experimental design the percent of Surelease applied on the felodipine loaded granules and the percent of pore former in the polymeric coating formulation variables were studied. The in vitro dissolution of model drug was performed in phosphate buffer solution (pH 6.5) with 1% sodium lauryl sulfate. The released drug quantification was done using an HPLC method. The release kinetics of felodipine from the final granules was assessed using different mathematical models.

Results. A 12 hours release was achieved using granules with the size between 315–500 μm coated with 45% Surelease with different pore former ratios in the coating via the top-spray method.

Conclusion. We have prepared prolonged release coated granules with felodipine using a fluid bed system based on the Simplex method. The API from the studied final formulations was released over a 12 hours period and the release kinetics of the model drug substance from the optimized preparations fitted best the Higuchi and Peppas kinetic models.

Keywords: felodipine, prolonged release, reservoir type preparation, multiparticulate preparations, Simplex method

Background and aims

The coating of the solid pharmaceutical preparations (tablets, pellets, granules, capsules, etc) is used mainly for two reasons depending on the coating characteristics [1]. The first use is a cosmetic one (non-functional) in order to improve the visual characteristics of the product and to distinguish it from others similar preparations and the second one is functional [1,2]. The functional coating can be used: to protect the active pharmaceutical ingredient (API) from degradation (especially in the acidic part of the gastro-intestinal tract – in the stomach) or from interactions between some ingredients in the formulation, to mask some disagreeable organoleptic characteristics (bad smell, bad

taste) or to modify the release characteristics of the API in order to obtain a prolonged, sustained or pulsed release [1,2].

The multi-particulate preparations (granules or pellets) are frequently coated with different types of polymers in order to obtain prolonged release formulations and they are in general formulated as hard gelatin capsules or tablets [3-6]. In comparison with the monolithic preparations, the multi-particulate preparations offer some important advantages: uniform spreading in the gastro-intestinal tract, less irritation in the stomach or intestine due to lower drug concentrations per pharmaceutical unit and constant release of the API, release that determines constant plasmatic drug concentrations with constant therapeutic effect and with less side effects [3,5,6]. Because the entire drug content is distributed in many units they are less susceptible for dose dumping due to film imperfections (burst-effect) [3,7,8].

The release of the drug substance from the reservoir type preparations is influenced by the polymeric film coating thickness or the polymeric loading percent and the properties of the polymeric coating [3,5,9].

The multi-particulate prolonged release reservoir type preparations combine the advantages of the multi-particulate preparations with the drug release modulation capabilities offered by the polymeric coated of reservoir type preparations [3,10,11].

The Simplex method is a step-by-step optimization method. The results obtained for the initial series of experiments are used to define the next series of experiments in order to find the optimal, optimal that was set at the start of the experiment [12,13].

Felodipine (FD) was chosen as model drug substance for this study. It is a 2nd Biopharmaceutical Class drug substance with high permeability and low solubility; good characteristics for a prolonged release formulation. This is a selective calcium blocker with direct cardiac effects used in the treatment of arterial hypertension and pectoral angina [14-17].

The aim of the study was the development of a multi-particulate preparation with FD in the form of coated granules with insoluble but permeable polymers in order to release the FD over a 12 hours period. Using the Simplex method, step-by-step, the influence of the coating method, the coating polymer type, the percent of loaded polymer and the percent of pore former in the polymeric coating on kinetic release profile was studied and optimized. The release kinetics of felodipine was assessed using different mathematical models for the formulations that released the API over a 12 hours period.

Materials and methods
Materials
Felodipine (Nivedita Chemicals PVT Ltd, India); lactose monohydrate (LM) (Pharmatose 80M and Pharmatose 200M, DMV International, Holland) and microcrystalline cellulose (MC) (Vivapur 101 and Vivapur 102, JRS Pharma, Germany) were used as diluents; polyvinylpyrrolidone – PVP (Kollidon K30, BASF, Germany) was used as binder; aqueous dispersion of ethyl acrylate and methyl methacrylate (Eudragit NE 40D, Evonix, Germany), acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups (Eudragit RS 30D, Evonix, Germany), aqueous ethyl-cellulose dispersion (Surelease E719040, Colorcon, UK) were used as film forming polymers and low viscosity hydroxipropylmethylcellulose; HPMC (Methocel E5LV, Colorcon, U.S.A.) was used as a pore forming agent in the polymeric coating; triethyl citrate; TEC (Merck, Germany) was used as plasticizer in the polymeric coating. All the other substances used in this research were analytic grade from Merck, Germany.

Methods
Preparation of granules loaded with FD
The FD loaded granules were prepared in the Aeromatic Strea 1 fluid bed coating system (Aeromatic, Switzerland) using the top-spray method (Figure 1a). The compositions of the FD loaded granules are presented in Table I. The API was dissolved in alcohol and in the drug solution was added the PVP to obtain a 10% binder solution. In this solution the FD was completely dissolved. The binder and FD solution was sprayed on the LM and MC mixture. At the beginning of the granulation process the powders were mixed and heated for two minutes and at the end of the granulation process the granules were dried for 5 minutes at 32°C in the same apparatus. The granulation process parameters for the two types of granules were: inlet air temperature 32-40ºC, outlet air temperature 26-28ºC, fan air 4-6 m³/min, atomizing pressure 0.5 atm, spray rate 12-20 g/min, filter cleaning pressure 5 atm and the nozzle diameter of 0.8 mm.
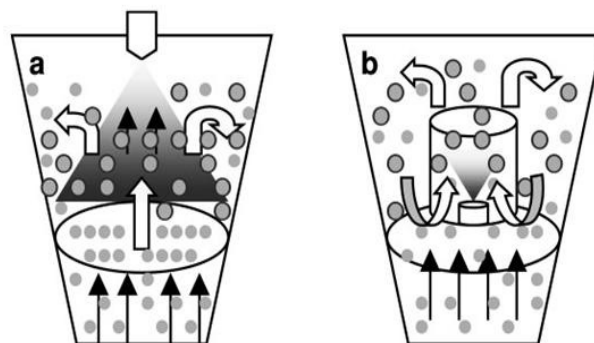

Figure 1. Top-spray method (a), bottom-spray method (b) [18].

Table I. The compositions of the FD loaded granules.

	per dose (mg)	%	Laboratory charge of 200 grams
Lactose monohydrate	119.25	68.14	136.29
Microcrystalline cellulose	39.75	22.71	45.43
Felodipine	10	5.71	11.43
Polyvinylpirrolidone	6	3.43	6.86
Alcohol*	60	0,00	0,00
Total	175	100.00	200.00

*not found in the final product

The Simplex method

Figure 2 presents the experimental design used in this study to develop multi-particulate prolonged release system in order to release the FD over a 12 hours period and to study the effect of the formulation factors on the FD release. In the first step of the experimental design the influence of the coating process was studied. The second step focused on the influence of the coating polymer type, the percent of loaded polymer and the percent of pore former in the polymeric coating. The last step was to study the influence of the percent of Surelease loaded on the FD granules and the percent of pore former in the polymeric coating.
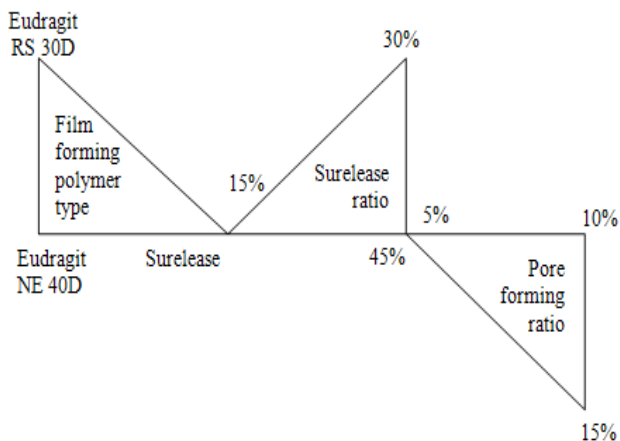

Figure 2. The Simplex experimental design.

The coating of FD loaded granules

In order to study the influence of the coating method (top-spray and bottom-spray method), the coating polymer type (Eudragit RS 30D, Eudragit NE 40D and Surelease E719040), the percent of loaded polymer (between 10 and 25%) and the percent of pore former in the polymeric coating (between 0 and 25%) the 100-150 μm sized FD loaded granules were used. These were prepared using Pharmatose 200M and Vivapur 101 and from these granules the above mentioned fraction was selected. The nine studied formulation are presented in Table II.

Table II. The coated granules formulations based on the 100-150 μm FD granules.

	Surelease E719040	Eudragit RS 30D	Eudragit NE 40D	HPMC
Exp 1	25	-	-	0
Exp 2	17.5	-	-	12.5
Exp 3	10	-	-	25
Exp 4	-	10	-	25
Exp 5	-	17.5	-	12.5
Exp 6	-	25	-	0
Exp 7	-	-	10	25
Exp 8	-	-	17.5	12.5
Exp 9	-	-	25	0

To study the influence of the percent of Surelease loaded on the FD granules (between 15 and 45%) and the percent of pore former in the polymeric coating (between 5 and 15%) the 315-500 μm sized loaded granules were used. These were prepared using Pharmatose 80M and Vivapur 102 and from these granules the above mentioned fraction was selected. The six studied formulations are presented in Table III.

The coating of the FD granules was done in the same apparatus as the granulation process using the bottom-spray method (with Würster insert) (Figure 1 b) or the top-spray method. The coating compositions based on Eudragit RS 30D and Eudragit NE 40D also contained 30% talcum (as lubricant), 10% titanium oxide - TiO_2 (as opacifier), 15% plasticizer – triethyl citrate (TEC) for the Eudragit RS 30D based coating and HPMC as pore forming polymer in different ratios.

The coating parameters are presented in Table IV. At the beginning of the coating procedure the drug loaded granules were heated for 2 minutes and at the end of the coating process they were dried for 5 minutes in the same apparatus (at 32°C for the Eudragit based coatings and at 54°C for the Surelease coating).

Table III. The coated granules formulations based on the 315-500 μm FD granules.

	Surelease E719040	HPMC		Surelease E719040	HPMC
Exp 10	15	-	Exp 13	45	5
Exp 11	30	-	Exp 14	45	10
Exp 12	45	-	Exp 15	45	15

Table IV. Preparation condition for the coated FD loaded granules.

	Eudragit RS 30D	Eudragit NE 40D	Surelease E719040 (top-spray)	Surelease E719040 (buttom-spray)
Inlet air temperature (ºC) (set/real)	34	38	54	58
Outlet air temperature (ºC)	26	29	44	34
Fan air (m3/min)	5/6	5/6	6	4/5
Atomizing pressure (atm)	0,5	0,5	0,5	1,4
Spray rate (g/min)	9	10	8	8
Filter cleaning pressure (atm)	5,2	5	5,5	5
Nozzle diameter (mm)	0,8	0,8	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±0.5º in the PharmaTest PT-DT7 dissolution equipment using the no. 2 apparatus (paddle) at a 50 rpm rotation speed. The dissolution medium consisted of 500 ml phosphate buffer pH=6.5 with 1% sodium lauryl sulfate. 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 autosampler, 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. All the tested prolonged release coated granules contained an equivalent of 10 mg FD and all the determinations were done in triplicate and the results are the mean of the three determinations.

Release kinetics

The release characteristics of FD from the prolonged release coated granules was determined using several mathematical models (Table V), such as Baker-Lonsdale [19] Peppas [20,21], Hixon and Crowell [22], Higuchi [23,24] and first order [25,26]. The dissolution data obtained after the *in vitro* testing was fitted using the above mentioned kinetic models, 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. In order to distinguish which mathematical model describes better the release of FD, the AIC was used. A lower value for this criterion indicates a better fit and the chosen mathematical model describes with the greatest accuracy the release profile of chosen model drug.

Table V. The studied mathematic 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	$Q_0 1/3 - Q_t 1/3 = K_s t$
Higuchi	$Q_t/Q_8 = K_h t^{0.5}$
First order	$Q_t/Q_8 = K_1 t$

Results

The influence of the coating method (bottom-spray and top-spray method) on the FD release

Figure 3 presents the release profiles for FD from 25% Surelease coated granules (Exp 1) prepared via the two different coating methods.

The influence of the type of coating polymer on the FD release

The graphical results for the *in vitro* release profiles of FD from the Eudragit RS 30D, Eudragit NE 40D and Surelease coated granules are presented in Figure 4.

The influence of the Surelease ratio on the FD release

Because the initial parameters were not capable to prolong for 12 hours the release of FD, the study focused

on the 315-500 μm granules coated with different ratios of Surelease.

Figure 5 presents the dissolution profiles of coated 315-500μm FD loaded granules with Surelease without pore forming polymer.

Influence of the pore forming polymer ratio on the FD release

The influence of the pore forming polymer in the 45% Surelease coated granules on the FD release is shown in Figure 6.

Release kinetics from the prolonged release coated granules

The release kinetics of FD was determined for the 45% Surelease coated granules with different proportions of pore forming polymer. Table VI presents the statistical results for the release kinetics data fit, the best values being highlighted.
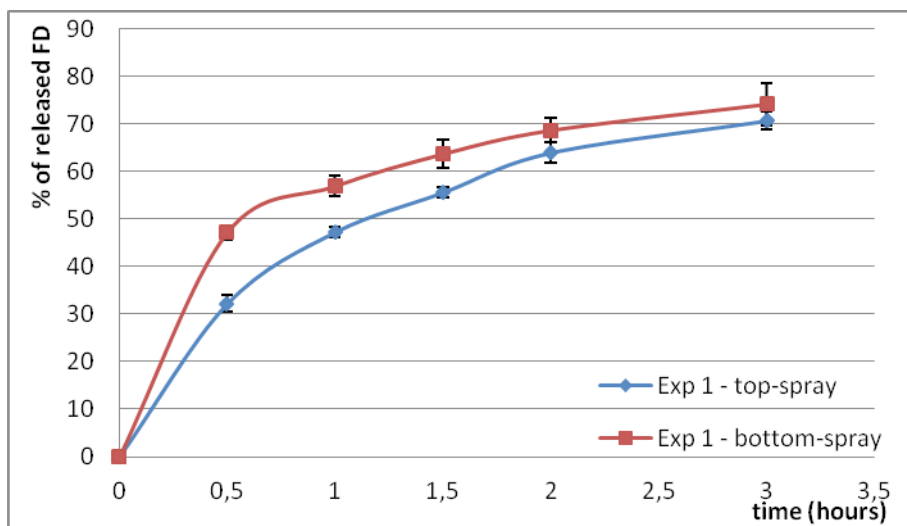

Figure 3. The release profiles of FD from the coated granules using the bottom-spray and top-spray method.
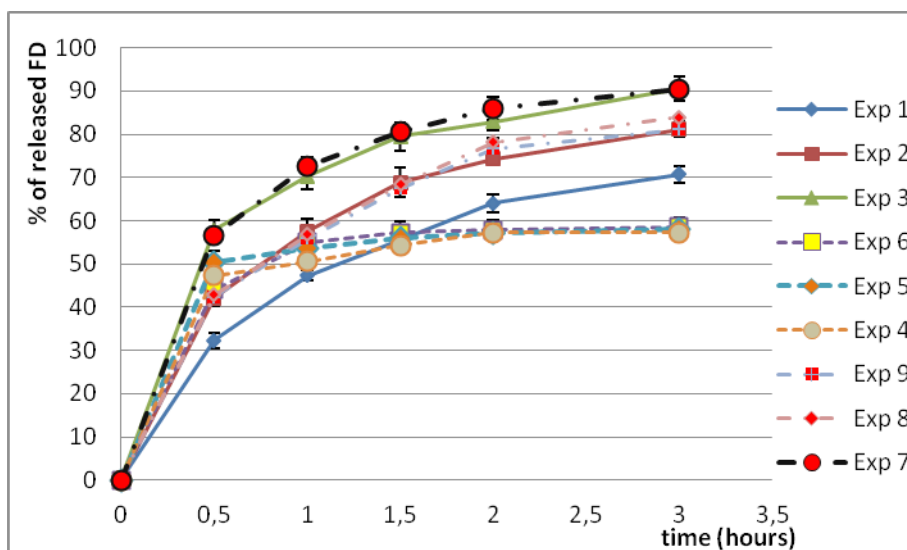

Figure 4. The release profiles of FD from coated granules with different coating polymers.
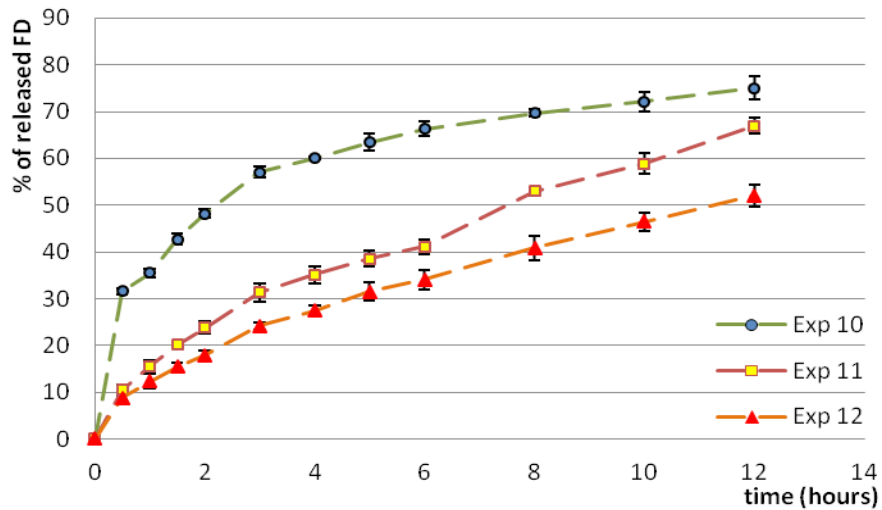
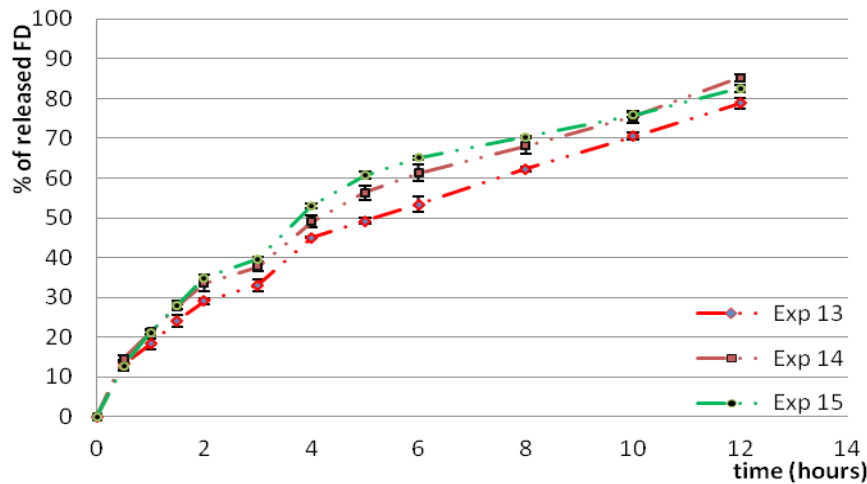**Figure 5.** The release profiles of FD from the coated granules using high proportions of Surelease.

Figure 6. The release profiles of FD from the 45% Surelease coated granules using different pore forming polymer ratios.

Table VI. Release kinetics from the prolonged release coated granules.

		Exp 13	**Exp 14**	**Exp 15**
Baker and Lonsdale	R	0,9823	0,9823	0,9788
	k	0,0107	0,0127	0,0148
	AIC	67.31	66.91	67.44
Peppas	R	0,9988	0,9970	0,9911
	k	20,1820	22,0915	23,9693
	n	0,5500	0,5378	0,5268
	AIC	**39.15**	**46.07**	61.86
Hixson and Crowell	R	0,9426	0,9454	0,9491
	k	0,0402	0,0449	0,0501
	AIC	72.70	75.19	77.23
Higuchi, Square Root Time	R	0,9959	0,9952	0,9901
	k	21,9663	23,5512	25,0794
	AIC	51.90	48.63	**60.03**
First Order	R	0,9680	0,9729	0,9782
	k	0,1400	0,1583	0,1786
	AIC	64.67	66.05	66.25

Discussion

The influence of the coating method (bottom-spray and top-spray method) on the FD release

In this part of the study the influence of the coating method of the granules on the FD release was studied. The Exp 1 formulation was coated via the top-spray method and the bottom-spray method in order to see the differences between the two coating processes. From the analysis of FD dissolution profiles it can be observed that in the first 30 minutes the granules prepared via top-spray method released 33% FD in comparison of the 48% FD from the granules prepared via the bottom-spray method. These differences can be observed at all dissolution points. This can be explained probably by the fact that the top-spray method determines a more uniform coating in comparison with the one obtained via the bottom-spray method.

The results are in concordance with other researches mentioned in the literature. In the case of silicone elastomeric coating the coating procedure influenced significantly the release of the API from coated tablets [27].

Based on these results the top-spray method was selected as method of coating FD granules in order to obtain a multi-particulate prolonged release system.

The influence of the type the coating polymer on the FD release

In the next step the study focused on the influence of the type of the coating polymer. To better understand the influence of this formulation variable the selected coating polymers were used in three concentrations with or without pore forming polymer in the coating composition.

The ethyl-cellulose based polymeric coating (Exp 1 – Exp 3) influences in a significant manner the release of the FD. It can be observed that in the case of the 10% Surelease and 25% pore forming agent coated granules are releasing almost 60% of the active substance in the first 30 minutes in comparison with the 25% Surelease coated granules that are releasing only 33% in the same period of time and after 3 hours the FD released percentage increases to 70%.

From the dissolution profiles of Eudragit RS 30D coated granules (Exp 4 – Exp 6) it can be observed that more than 40% of FD is released in the first half-hour. Even when the applied coating proportion is increased from 10% to 17.5% and 25% and the pore forming polymer is decreased from 25% to 12.5% and 0%, the differences between the release percentages of FD are not significant. This can be explained due to initial size of the FD loaded granules and the high permeability of the coating, which means that the dissolution media can penetrate easier through the coating to dissolve the API.

In the case of the Eudragit NE 40D coated granules (Exp 7 – Exp 9) the FD is released in a fast manner, more than 40%, in the first 30 minutes of the dissolution test. The explanation for this behavior is similar with the one in the case of the Eudragit RS 30D coated granules. The contact surface between the granules and the dissolution media is high due to the small sized granules and the high coating permeability factors that determine fast release of the API.

Taking in consideration all of the above results, the Surelease coating polymer was chosen in the next part of the study. This conclusion is based on the fact that this polymer allowed around 33% of the FD to be released in the first 30 minutes of the dissolution test, less than in the case of the two Eudragit coatings.

According with the obtained results a burst effect was observed in the first 30 minutes of the dissolution test. In order to avoid the dose dumping or to reduce the API release an increase of the coating polymer and a reduction in the contact surface of the granules with the dissolution media is needed.

The influence of the Surelease ratio on the FD release

The study continued with the formulation of FD loaded granules with the size of 315-500 μm, coated with three proportions of Surelease in order to determine the influence of this parameter on the FD release.

From the release profiles of the Surelease coated granules it can be observed that the FD presented a prolonged release over a 12 hours period or more (after 12 hours 76% of FD was released for Exp 10, 68% for Exp 11 and 50% for Exp 12). The Surelease percent increase in the coating ratio from 15% to 45% determines a decrease in the release rate of the FD from 76% to 51% after 12 hours of dissolution testing.

The 45% Surelease coated granules were chosen in the next part of the study because in this case the FD was released in a constant (desired) manner over a 12 hours period (without a significant initial release – less than 10% released in the first 30 minutes).

The obtained results are in accordance with the literature as shown in the case of glucose release prolongation via the increase of the Surelease coating ratio from 12.5% to 25% [28].

Influence of the pore forming polymer ratio on the FD release

In the last part of the study the influence of the pore forming polymer ratio on the 45% Surelease coated formulation was studied. Based on these results three 45% Surelease coated granules were formulated, each containing a different pore forming polymer ratio (5, 10 or 15%). From these formulations minimum 80% of the FD was released in a prolonged manner over a 12 hours period. This can be explained by the fact that the incorporated pore forming polymer determined a more permeable coating through which the API was released in a constant manner. The obtained results are in accordance with the results found in the literature. In the case of Kollicoat IR used as pore forming polymer a more permeable film is obtained with the increase of Kollicoat IR ratio in the coating [3].

The step by step approach of the Simplex method

used in this study produced prolonged release reservoir type multi-particulate preparation which released the FD over a 12 hours period.

Release kinetics of FD from the prolonged release coated granules

The values obtained after the kinetic analysis of the release data indicates that formulation Exp 13 and Exp 14 fitted best the Peppas kinetic and formulation Exp 15 fitted best the Higuchi models.

The correlation with the Higuchi model indicates that the FD release is proportionate with the square root of time, which means that the release of the API through the polymeric coating is controlled by diffusion processes.

The correlation with the Peppas model is justified by the fact that from this model the Higuchi model is derived. Also the values for "n" varies between 0.5286 to 0.5500, values close to 0.5, value characteristic for the Higuchi model. The values close to 0.5 are indicating that the FD release is controlled by diffusion processes though the polymeric coating.

Conclusions

A novel coated prolonged release granules containing FD were developed via a fluid bed granulation system, in order to release the FD over a 12 hours period, via Simplex design. The first step of this approach determined that the top-spray coating method produced a more uniform coating in comparison with the bottom-spray method as seen in the release differences of the FD. The second step determined that regardless of the coating type of the polymer, the proportion of polymers applied and the pore forming ratio in the coating; the FD is released too fast due to the high contact surface of the granules and the increase in the granule size and the coating ratio is needed to prolong the FD release. The third step determined that the use of 45% Surelease with three different ratios of pore former determined a prolonged FD release over a 12 hours period. The FD release from the prepared multi-particulate preparations is controlled by diffusion through the polymeric coating, a phenomenon explained by Higuchi and Peppas kinetic models.

Acknowledgements

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