

INFLUENCE OF SOME FORMULATION FACTORS ON THE RELEASE OF FELODIPINE FROM EXTENDED RELEASE HYDROPHILIC MATRIX TABLETS

RAREȘ I. IOVANOV*, IOAN TOMUȚA, SORIN E. LEUCUȚA

University of Medicine and Pharmacy „Iuliu Hațieganu”, Faculty of Pharmacy, Department of Pharmaceutical Technology and Biopharmaceutics, 400023, Cluj-Napoca, Romania

**corresponding author: riovanov@umfcluj.ro*

Abstract

In this paper we have studied the influence of some variables on the release of felodipine from extended release hydrophilic matrix tablets. The employed polymers for the extension of the release were: hydroxypropylmethylcellulose (Methocel E4MCR and Methocel K100M) and polyethylene oxide (Polyox WSR Coagulant). For this purpose a reduced experimental design with 3 variables and 2 levels was used. The studied formulation variables were: the percent of polymers, the type of hydroxypropyl-methylcellulose and the ratio between the polymers in the tablet. From the obtained results it was concluded that the most important variable on the release of felodipine was the percent of polymers in the tablet. From the experimental data, an optimal formulation was developed, which has proved to be similar with the dissolution profile of the chosen reference product.

Rezumat

În această lucrare s-a studiat influența unor factori de formulare asupra cedării felodipinei din comprimate cu cedare prelungită de tip matriță hidrofilă. Polimerii utilizați în vederea prelungirii cedării au fost: hidroxipropilmetilceluloză (Methocel E4MCR și Methocel K100M) și polietilen oxidul (Polyox WSR Coagulant). În acest scop s-a folosit un plan experimental redus cu 3 variabile și 2 nivele. Variabilele studiate au fost: procentul de polimeri, tipul de hidroxipropilmetilceluloză și raportul de combinare dintre aceștia. Din rezultatele obținute s-a concluzionat că factorul cu cea mai mare influență asupra cedării felodipinei a fost procentul de polimeri din comprimat. Pornind de la datele experimentale s-a realizat o formulare optimizată, care s-a dovedit a fi similară cu profilul de cedare al produsului de referință ales.

Keywords: matrix tablets; hydroxypropylmethylcellulose; polyethylene oxide; extended release

Introduction

The aim of this study was the preparation of extended release, over 10 hours hydrophilic matrix type tablets containing felodipine. Felodipine (FELO) is used for the excellent anti-hypertension and antianginal properties as a calcium channel blocker drug [2, 5]. The good permeability, the poor water solubility as well as the short biological half-life are

characteristics that recommend this active substance as a good candidate for extended release preparations [10]. The hydrophilic matrix type tablets are a commonly used approach for the extended release formulations [1, 3, 4, 6, 7, 8]. The studied tablets were prepared using two polymers: polyethylene oxide (Polyox) and hydroxypropylmethylcellulose (HPMC).

In order to observe the influence of the formulation variables on the release characteristics of the tablets a reduced experimental design with 3 factors and 2 variables, which needed 10 tablet formulations, was developed [11]. The objective of this study was to see the influence of the different percents of polymers and the ratio between them on the release of felodipine from the experimental tablets in order to obtain an extended *in vitro* release characteristic over a 10 hours period which was followed by an optimization of a formulation in order to obtain a similar *in vitro* release profile of felodipine as from the original product.

Materials and methods

Materials

Felodipine, a yellow crystalline powder with the particle size around 300 μm (supplied by Everlight Chemical Industrial Corporation, Taiwan), was used as model drug. Three hydrophilic polymers were used in this study: one type of Polyox (Polyox WSR Coagulant, supplied by Union Carbide Europe) and two types of HPMC (Methocel E4MCR and Methocel K100M, supplied by Colorcon, UK). Lactose M80 (supplied by DMV, Holland) was used as filler, citric acid and vitamin C (supplied by BASF, Germany) were used as antioxidants. In all tablets formulations fumed silica - Aerosil (supplied by Degussa, Germany) and Magnesium stearate (supplied by Merck, Germany) were used as glidants and lubricants. Sodium lauryl sulfate (supplied by Merck, Germany) was used as a solubility enhancer for the active substance in the dissolution medium.

All the employed materials were used as received.

Experimental design

An experimental design with 3 factors and 2 variables was developed in order to see the influence of some formulation factors on the release of felodipine using Modde 6 statistical software. We have choosed as independent factors: the percent of extended release polymers, the type of HPMC and the ratio between the polymers as they are presented in table I. The characteristics of the experimental design, the studied responses and the matrix of responses are presented in table II, III and table IV, respectively.

Table I

Independent variables

Formulation variables	Symbol	Levels	
Percent of extended release polymers (%)	X1	30	50
Type of HPMC	X2	E4MCR	K100M
Ratio between polymers	X3	0.5	1

Table II

The matrix of experimental design

Exp. No.	X1	X2	X3
1	30	E4MCR	0
2	50	E4MCR	0
3	30	K100M	0
4	50	K100M	0
5	30	E4MCR	1
6	50	E4MCR	1
7	50	E4MCR	0.5
8	30	K100M	1
9	50	K100M	1
10	50	K100M	0.5

Table III

Responses studied

No.	Response	Symbol
1	% released at 0.5 hours	Y1
2	% released at 1 hour	Y2
3	% released at 1.5 hours	Y3
4	% released at 2 hours	Y4
5	% released at 3 hours	Y5
6	% released at 4 hours	Y6
7	% released at 5 hours	Y7
8	% released at 6 hours	Y8
9	% released at 8 hours	Y9
10	% released at 10 hours	Y10

Table IV

Matrix of responses

Exp. Name	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10
N1	10.1	18.17	27.38	35.01	48.28	61.37	73.13	82.56	89.11	96.34
N2	3.59	6.07	9.22	12.24	18.45	25.32	31.27	38.78	51.38	65.08
N3	4.78	10.32	16.3	23.66	36.48	48.61	58.1	67.11	80.14	92.61
N4	0.99	1.16	1.3	1.51	2.27	3.76	6.03	9.41	17.3	25.28
N5	1.5	2.8	5.74	8.24	20.51	38.51	53.52	67.1	82.2	98.33
N6	1.01	0.99	1.12	1.56	3.78	9.64	17.89	26.66	48.82	74.63
N7	2.79	1.33	1.28	1.59	4.3	10.43	19.83	30.75	53.13	81.09
N8	1.64	2.99	6.2	12.04	28.57	47.89	66.4	80.92	93.96	98.27
N9	0.97	1.28	2.49	5.43	14.44	28.56	40.11	54.95	79.75	99.14
N10	1.02	1.11	1.54	3.08	7.93	15.46	26.99	39.9	67.5	94.77

Tablet preparation

All the materials for the tablet preparation - FELO 10 mg/tablet, polymers between 30% and 50% (as shown in Table II), antioxidants (citric acid 0.5% and vitamin C 1%), glidant 0.25% and lubricant 0.5%, were mixed in Erweka planetary mixer type PRS for 10 minutes. The powder mix was sieved through a 500- μ m sieve and then mixed again for 5 minutes in the same apparatus. Tablets with 210 mg weight were prepared by direct compression using an EK-0 Tablet press (Korsch, Germany) equipped with

8 mm diameter punch and dies. The tablet hardness was between 6-8 kg force and the friability under 1%.

***In vitro* evaluation**

Dissolution testing was performed according to an adapted method from the USP 30th Edition [12]. The test was conducted at $37 \pm 0.5^\circ$ in the PharmaTest PT-DT7 apparatus equipped with the no. 1 apparatus (basket) at 50-rpm rotation speed. The dissolution media consisted of 500 ml phosphate buffer with pH=6.5 and 1% sodium lauryl sulfate. A 2 ml sample was taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 hours. The drug assay was performed at 240 nm using a HPLC Agilent 1100 series apparatus equipped with a Zorbax SB-C18, 5 μ m x 4.6 x 250 chromatographic column, mobile phase: acetonitrile: phosphoric acid 0.1% in water = 75:25 at a flow of 1.5 ml/minute and 3 minutes retention time.

Results and discussion

***In vitro* release of felodipine**

FELO was slowly released over 10 hours from all the experimental formulations. In USP 30 [12] there are presented the release profile acceptance criteria for felodipine extended release tablets. These are: for 2 hours - between 10% - 30%, for 6 hours between 42% - 68% and for 10 hours not less then 75%. Studying the matrix of responses and the release profiles of the experimental formulations (Table IV and Fig. 1) we can observe that felodipine was released in conformity with the USP provision as follows: for 2 hours – formulation 1, 2, 3 and 8; for 6 hours – formulation 1, 3, 5, 8 and 9; for 10 hours – formulation 1, 3, 5, 7, 8, 9 and 10. Overall, only the formulation 1, 3 and 8 are in conformity with the foresight of USP 30.

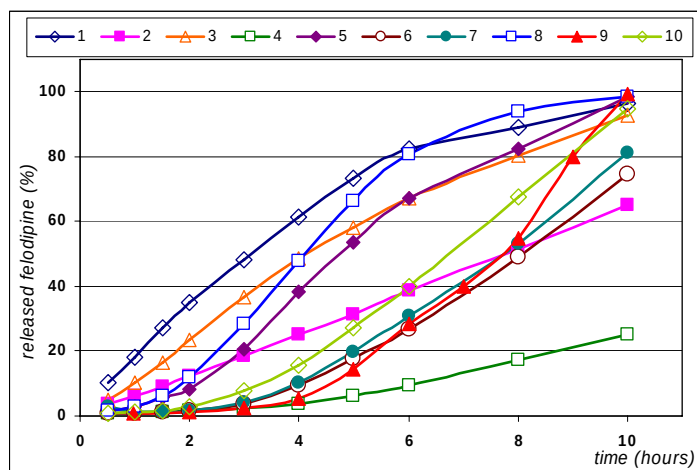


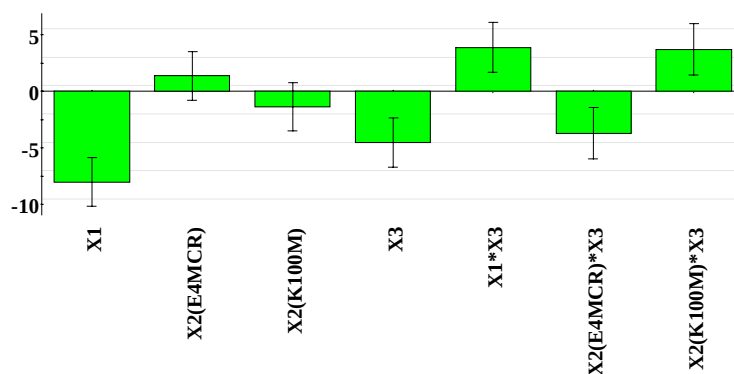
Figure 1

Release profiles of the experimental formulations (the studied extended release)

Influence of the formulation factors on the release characteristics of FELO

In fig. 2 and 3 are presented the influence of the formulation factors on the release of felodipine at different time intervals (2, 4, 6 and 8 hours). We can observe that the most important formulation variable is the percent of polymers (**X1**); by increasing the percent of polymers from 30 to 50%, regardless if the tablet is composed only HPMC or polymer blend, a reduced release of the drug was observed in all formulations and at all studied time intervals (Fig. 1, Fig. 2, Fig 3 and Table II). Another important formulation variable is the ratio between the polymers (**X3**). The increase of the polymer ratio from “0” (only HPMC) to “1” (1:1 ratio blend of HPMC and Polyox) determines the occurrence of a 2 hours lag time in the release of felodipine (Fig. 1 and Fig. 2 – Y_4). This can be observed in all the tablets that contain polymer blends (formulations 5 – 10).

Y_4



Y_6

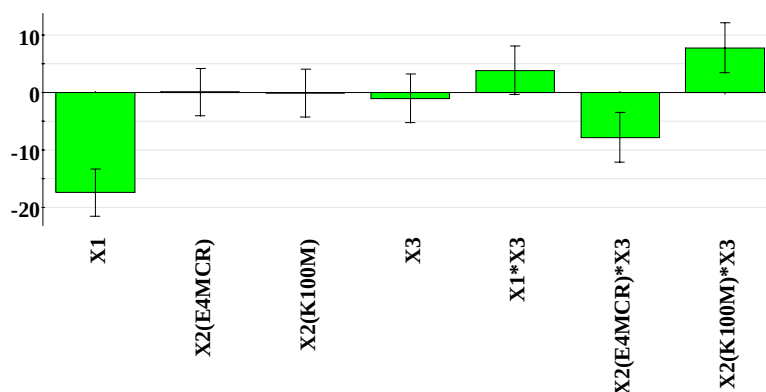
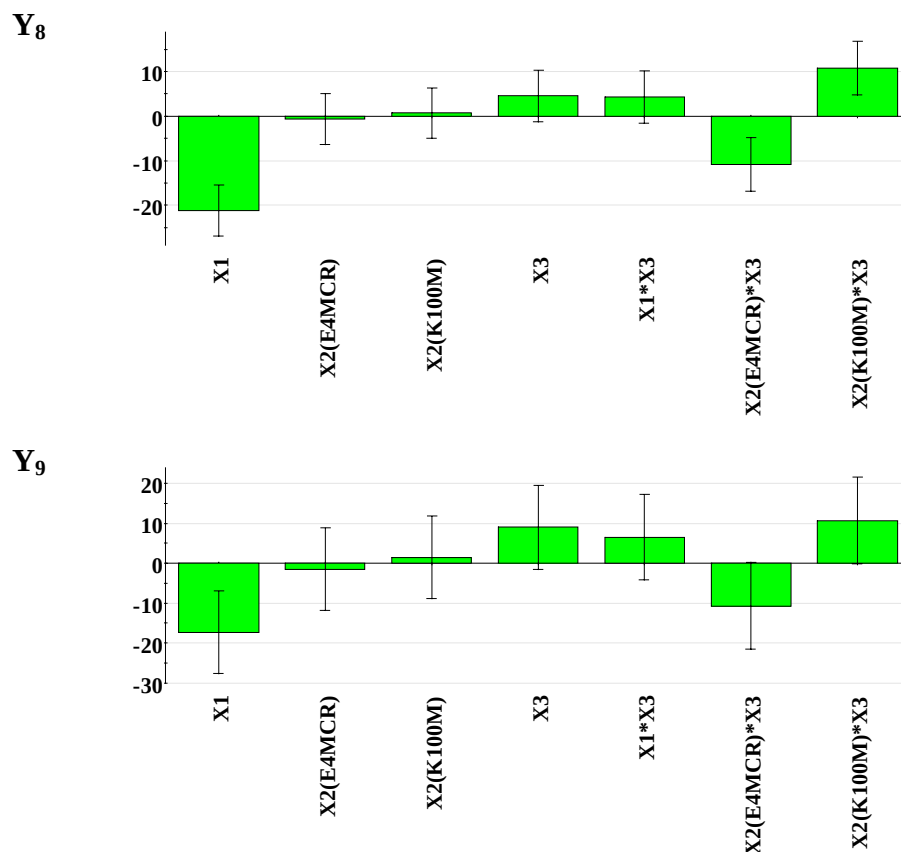


Figure 2

Influence of the formulation factors over the release of felodipine:
 Y_4 – at 2 hours; Y_6 – at 4 hours

**Figure 3**

Influence of the formulation factors over the release of felodipine:

Y₈ – at 6 hours; Y₉ – at 8 hours

The determination of the optimum formula

The optimal formulation was generated with the help of Modde 6 statistical software based on the experimental data. The optimal formulation contained 41.7% HPMC E4MCR extended release polymer. The dissolution profile of this formulation was compared with the release characteristics of a reference product, in our case – Plendil[®] 10 mg from Pfizer (Fig. 4) and the similarity factor was also determined. If the value for the similarity factor (f_2) is in the range of 50 – 100, the global differences in the release profiles at all the dissolution time intervals are less than 10% [9] that means that the two products have similar release profiles. The similarity factor (f_2) in our case was 68.28 and from this we can conclude that optimized formulation is similar to the reference product.

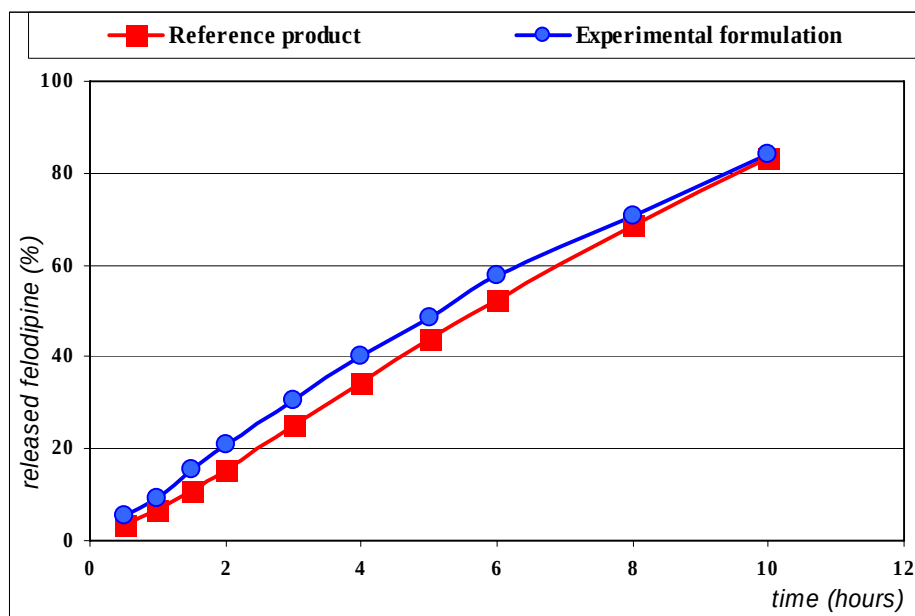


Figure 4
Release profiles of felodipine from the original formula
and the experimental optimized formula

Conclusions

We have developed an experimental design to determine the influence of some formulation factors over the release of felodipine from direct compression prepared tablets. The most important factor is: the percent of hydrophilic polymers (HPMC and Polyox) in the tablet, which means that the increase of the polymer percent has a significant influence on the release prolongation of felodipine from the tablet. The addition of Polyox WSR Coagulant in the tablets determines a 2 hours lag time in the release of the model drug.

We have prepared an optimal formulation that proved to be similar to the reference product concerning the *in vitro* drug release on a 10 hours period.

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