Development of Extended Release Matrix Tablets of Felodipine Through Solid Dispersions for Better Drug Release Profile by a 3^2 Factorial Design

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ABSTRACT

Felodipine extended release matrix tablets with slow initial release and long action are suitable for once daily administration and might be good substitutes for immediate acting calcium channel blockers to minimize the risk of myocardial infarction. The aim of the present study are to prepare felodipine extended release matrix tablets through forming solid dispersions of the drug followed by wet granulation technique and also to study the influence of polymers on the release rate of the drug. The drug excipients compatibility was confirmed by Fourier transmission infrared spectroscopy and Differential Scanning Calorimetry studies. The solid dispersions, with an enteric polymer Eudragit L 100, and then the matrix tablets with hydroxypropyl methyl cellulose K4M were prepared. Here, a 3^2 factorial design of response surface method was employed to study the influence of the two polymers at 3 levels by design of experiments. The influence on the release rate constant was studied by response surface plots and Analysis of Variance. The drug release pattern from formulation F8, with a release of 87.84 % after 8 hrs, was complied with the dissolution criteria of test 2 of USP 35 and NF 30. The results of dissolution kinetics indicated that the selected model and the factors were significant at polynomial quadratic order.

Key words: Felodipine, Solid dispersion, Matrix tablet, Design of Experiments, Analysis of Variance.

INTRODUCTION

Felodipine is a calcium channel blocking agent used mainly in the treatment of hypertension. The main mechanism of calcium channel blockers is to inhibit the calcium mediated slow channel component of action potential in smooth/cardiac muscle.[1] The most important action of calcium channel blocker is smooth muscle relaxation. Direct extensions of the therapeutic action of these drugs results in excessive inhibition of calcium channel leads to the cardiac depression, cardiac arrest, bradycardia, atrioventricular block and finally heart failure.[2] Retrospective case control studies reported that immediate acting calcium channel blocker (nifedipine) results in the increased risk of myocardial infarction in patients with hypertension due to decrease of the vascular selectivity.[3] Hence slow release and long acting vaso-selective calcium channel blockers are well tolerated.[4] Felodipine has greater vascular selectivity, larger tissue distribution and longer $t_{1/2}$. The extended release (ER) preparation is a suitable dosage form for felodipine.[5-6] The ER dosage forms with zero–order drug release are always superior to first–order drug release as the former can maintain uniform plasma drug concentrations with minimal fluctuations.[7] Vinod J *et al*[8] developed film coated extended release matrix tablets of felodipine formulated with various grades of methocel.

Hence from the pharmaco dynamics and pharmacokinetics of felodipine, it is understood that the extended release formulation is the well tolerated dosage form.[9] Felodipine is prone for first pass metabolism, so to minimize this, its initial release

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should be low. Basing on these principles, the extended release dosage form of felodipine with as less as possible release in the first 1-2 hrs and with zero–order release kinetics is an ideal dosage form. So, the main objectives of the present investigation are lies with the i) preparation of solid dispersions of Felodipine with an enteric polymer Eudragit L100, ii) formulation and preparation the extended release (ER) tablets of the Felodipine solid dispersions with Eudragit L 100 as carrier and hydroxypropyl methyl cellulose (HPMC) K4M as the rate retarding material and iii) characterization of the ER tablets to understand the kinetics and release mechanisms.

MATERIALS AND METHODS

Materials

Felodipine was purchased from Sigma Aldrich, Mumbai. Eudragit L 100, HPMC K4M and Methanol were obtained from Merck Specialists Pvt. Ltd., Mumbai. Lactose, Talc, Hydrochloric acid, Magnesium stearate, Tween 80 and Acetone were obtained from S.D fine chemicals Ltd., Mumbai.

METHODS

As the felodipine is light sensitive drug, all the processes which include the drug were performed in dark rooms, where there is no direct entry of sunlight; and all the glassware including dissolution vessels used were of amber colored.

Fourier transmission infrared (FT-IR) analysis

The physicochemical compatibility between Felodipine & polymers (HPMC K4M and Eudragit L100) used in the research were carried out by subjecting to IR spectral studies using Perkin Fourier Transform infrared Spectrophotometer, Shelton, USA. The samples were prepared by mixing the drug with the maximum amounts of polymers used in the formulations. These samples were scanned under diffuse reflectance mode and plotted the graph by KBr pellet method and spectra were recorded in wave length region between 4000 cm^{-1} to 400 cm^{-1}. The spectra obtained for pure drug was compared with that of the physical mixtures of the drug with polymers.

Preparation of Felodipine solid dispersions

Solid dispersions (SDs) of Felodipine were made with Eudragit L 100 at two ratios of drug to polymer viz. 1:0.25 and 1:0.5 by solvent evaporation with some modifications to the methods reported.[10-12] 5 ml of acetone was taken in a china dish, to this the polymer was added and mixed to dissolve. Then the corresponding amount of felodipine was added and mixed until it dissolved. Then the mixture was stirred slowly and then set to drying in hot air oven at 45^{0}C for about 20 min to get the solvent evaporated completely. Then the obtained solid dispersion was scratched, sieved through mesh #80 and stored in desiccators for further use.

Evaluation of Felodipine SDs

Percentage yield

Percentage yield was calculated according to the following formula

$$\text{Percentage yield} = \quad \times 100$$

Differential scanning calorimetry (DSC) studies

DSC studies were performed on pure Felodipine and its SDs with Eudragit L100 using differential scanning calorimeter (DSC 60, Schimadzu) previously calibrated using indium. The samples of 6 to 8 mg were accurately weighed onto solid aluminum pans with seals and crimped. Reference pan was an empty sealed aluminum pan. The measurements were obtained at a heating rate of 100^{o}C/min with purging of dry nitrogen at a constant rate of 20 mL/min.

Estimation of drug content

50 mg drug equivalent solid dispersion, calculated according to the ratios, was taken and added to 1 % w/v polysorbate 80 solution in a conical flask, stirred to dissolve and kept in orbital shaking incubator for 24 hrs at 25^{o}C. Then the volume was adjusted to 100 ml in a volumetric flask. The solution was filtered, the filtrate was sufficiently diluted with 1 % w/v polysorbate 80 and checked for the absorbance in UV-Visible spectrophotometer at 360 nm.

Preparation of ER matrix tablets of Felodipine

The tablets were prepared by wet granulation method by employing HPMC K4M as the rate controlling polymer. Different ER tablets of felodipine were prepared to study the effect of two variables which were physical form of the drug and the amount of rate controlling polymer at three levels each. The accurately weighed quantities (as shown in Table 1) of the drug or its SD, lactose and HPMC K4M were screened (through #80) and taken in a mortar, and were mixed thoroughly. Then wet mass was prepared by employing water as the granulating fluid and then the mass was passed through sieve #20 to obtain the granules. The granules were dried in hot air oven at 50^{o}C. Then the dried granules were sieved and mixed with the previously weighed and screened (through #80) extra–granular excipients

such as magnesium stearate and talc and then they were compressed in 12 stage rotary tablet press (SHAKTHI Tablet Press 1 GMP) as each tablet weighed 150 mg. The prepared tablets were properly stored in desiccators until further use.

Experimental design

Response surface quadratic model[13] was selected to optimize the amount of polymers in solid dispersion and in the final tablet. The design was developed with Stat – ease® Design Expert 7 software. Here, two factors viz. percentage of Eudragit L 100 in the solid dispersion (as factor A) and percentage of HPMC K4M in the final tablets (as factor B) were studied at three levels. Experiment was done with 9 different combinations and 10 runs (Table 2) according to the directions of the design. The release rate constant was taken as the response variable (R_1). The equation for the response variable was given as

$$R_1 = 0.27–0.052*A–0.14*B+0.024*A*B+4.214e^{-003}*A^2+0.051*B^2$$

Characterization studies

Micromeritic properties of the granules

The granules of all the formulations were subjected to various microscopic studies such as bulk density, packed bulk density, angle of repose, Carr's index and Hausner's ratio.

Physical evaluation tests of the Felodipine ER tablets

The prepared tablets of all the formulations were subjected to various physical characterization tests like hardness, tensile strength and friability to evaluate the physical strength of the tablets.

Assay

Five tablets were powdered in a mortar. From this, powder equivalent to 50 mg of drug was taken in a 100 ml standard volumetric flask. It was diluted with 20 mL of methanol and made up to the mark with methanol, filtered and the filtrate was made up to the mark in a 100 mL volumetric flask with methanol. Further appropriate dilutions were made and the absorbance was measured at 360 nm by using double beam UV Visible spectrophotometer (Schimadzu).

In vitro drug release studies and kinetics of drug release

These studies for Felodipine ER matrix tablets were performed according to the USP35 NF30 in 1 % w/v polysorbate (tween) 80 buffer of 500 ml as medium using dissolution rate test apparatus (DISSO 800–LAB INDIA) with a paddle stirrer at 100 rpm.[14] The dissolution medium was maintained at a temperature of 37 ± 0.5°C and samples were withdrawn at regular time points, filtered and measured at a wavelength of 360 nm using double beam UV-Visible spectrophotometer (Schimadzu). The obtained dissolution profile was checked for acceptance according to the Test 2 of USP35 and NF30, which was shown in table V. The obtained data was also subjected to kinetic analytical models like zero–order, first–order, Higuchi's and Korsemeyer–Peppas to understand the kinetics and mechanism of drug release.

Design of Experiment (DoE) validation and Analysis of Variance (ANOVA)

All the 9 combinations of factors were taken in a single block with one centre point per block (so, 10 runs) in the 3 level factorial design of response surface method. The response parameter was evaluated by polynomial order of quadratic model. The observed and predicted values of the response were compared and graphs were also plotted. The normal plot of residuals between % probability and internally studentized results were plotted. ANOVA was performed to identify whether the selected factors were significant or not individually and combinely and at exponential level also.

RESULTS AND DISCUSSION

Drug excipients compatibility studies

Compatibility studies of drug and polymer were conducted by employing FTIR spectral studies. FTIR spectra of pure Felodipine and the physical mixtures of drug-HPMC K4M; drug-Eudragit L 100; and drug-HPMC K4M-Eudragit L 100 were shown in Figure 1–4. The characteristic peaks of the Felodipine at 3371.04, 3098.45, 1308.75 and 1277.74 cm^{-1} corresponding to the N-H of secondary amine group, C-H (aromatic) and C=O of carboxyl group respectively, were observed with the spectra of pure Felodipine as well as with the physical mixtures. As the identical principal peaks were observed in all the cases, it was confirmed that no interaction was exist in between the drug and polymers (individually and combinely).

Studies on Felodipine solid dispersions

The prepared solid dispersions of felodipine were studied for the effectiveness of the method. The results of percentage yield, which was around 86–89 %, indicated that the employed method, solvent evaporation, was well suitable for the preparation of solid dispersions even with hydrophobic carriers. This might be attrib-

Table 1: Formulae of 9 different combinations of Felodipine ER matrix tablets

S. No.	Name of the Ingredient	Quantities in mg per 1 tablet								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Felodipine	10	-	-	10	-	-	10	-	-
2.	Felodipine SD (1:0.25)	-	12.5	-	-	12.5	-	-	12.5	-
3.	Felodipine SD (1:0.5)	-	-	15	-	-	15	-	-	15
4.	HPMC K4M	7.5	7.5	7.5	15	15	15	22.5	22.5	22.5
5.	Magnesium stearate	3	3	3	3	3	3	3	3	3
6.	Talc	3	3	3	3	3	3	3	3	3
7.	Lactose	126.5	124.0	121.5	119.0	116.5	114.0	111.5	109.0	106.5
	Total weight	150	150	150	150	150	150	150	150	150

Table 2: Factor combinations according to the selected design

Formulation code	Factor Levels		Run
	A	B	
F1	–1	–1	8
F2	0	–1	5
F3	1	–1	9
F4	–1	0	10
F5	0	0	2
F5 (r)	0	0	4
F6	1	0	3
F7	–1	1	7
F8	0	1	6
F9	1	1	1
Factors	Factor levels in actual terms		
	–1	0	1
A: % w/w of Eudragit L100 in SDs	0	20	33.3
B: % w/w of HPMC K4M in tablets	5	10	15

Table 3: Dissolution kinetic parameters of Felodipine ER matrix tablets

S. No.	Formulation	Regression co–efficient			Release rate constant (%dose/min)	Korsemeyer–Peppas 'n' value
		Zero–order	First–order	Higuchi's		
1	F1	0.984	0.887	0.935	0.546	0.877
2	F2	0.958	0.943	0.933	0.468	0.860
3	F3	0.959	0.835	0.885	0.383	0.830
4	F4	0.974	0.917	0.908	0.318	0.782
5	F5	0.976	0.800	0.893	0.261	0.754
6	F5 (r)	0.983	0.809	0.907	0.265	0.751
7	F6	0.984	0.870	0.876	0.241	0.748
8	F7	0.993	0.874	0.859	0.213	0.739
9	F8	0.989	0.886	0.864	0.185	0.725
10	F9	0.995	0.825	0.861	0.144	0.707

Table 4: Results of ANOVA studies

Source	Sum of Squares	df	Mean Square	F value	p-value Prob>F	
Model	0.15	5	0.029	149.81	0.0001	significant
A-Eudragit L 100	0.016	1	0.016	81.38	0.0008	
B-HPMC K4M	0.12	1	0.12	623.10	<0.0001	
AB	$2.209x10^{-3}$	1	$2.209 x10^{-3}$	11.30	0.0283	
A^2	$4.144 x10^{-5}$	1	$4.144 x10^{-5}$	0.21	0.6692	
B^2	$6.120 x10^{-3}$	1	$6.120 x10^{-3}$	31.30	0.0050	
Residual	$7.821 x10^{-4}$	4	$1.955 x10^{-4}$			
Lack of Fit	$7.741 x10^{-4}$	3	$2.580 x10^{-4}$	32.36	0.1285	not significant
Pure Error	$8.000 x10^{-6}$	1	$8.000 x10^{-6}$			
Cor Total	0.15	9				
The Model F-value of 149.81 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.						
Values of "Prob > F" less than 0.0500 indicate model terms are significant.						
Values greater than 0.1000 indicate the model terms are not significant.						
The "Lack of Fit F-value" of 32.26 implies the Lack of Fit is not significant relative to the pure error. There is a 12.85% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good.						

* df–degrees of freedom; Prob–Probability.

uted to the efficiency of the selected solvent, acetone, which could dissolve both the drug and polymer, and could easily be evaporated. The results of percentage drug content, which was around 97-98 %, indicated that the drug was completely and uniformly mixed and/or entrapped in the polymer matrix, this might be because of the freely soluble tendency of the drug and polymer in the solvent employed.

Felodipine and its solid dispersion were subjected to DSC studies (shown in Figure 5) and the obtained spectra indicated that there was no physical interaction between the drug and Eudragit L100 even after preparation of solid dispersion as the endotherm obtained in case of solid dispersion was found to be at the same temperature (≅148^0C) as that in the case of pure felodipine.[15] This indicated that the solvent evaporation method was found to be suitable and effective.

Studies on pre-compression blend

Granules of Felodipine SDs were prepared by wet granulation technique. These granules were evaluated for various derived properties such as bulk density, tapped density and flow properties such as angle of repose, Hausner's ratio and Carr's index. The difference in the bulk densities, before (0.50-0.52 g/cc) and after (0.58-0.61 g/cc) a suitable tapping procedure, indicated that the granules were having good compressibility and packageability.[16] The results of the flowability studies were found to be the angles of repose of 13.1–19.3, the Carr's indices of 9.8-13.5 and the Hausner's ratios of 1.1-1.2 indicated that the granules of all the formulations were having good to excellent flow properties. These studies combinely indicated that the granules of all formulations were efficient for the compression into tablets.

Studies on compressed Felodipine ER matrix tablets

The tablets of all batches were subjected to different physical evaluation tests and the results obtained were found to be within the limits of US Pharmacopoeia. The tablets weighed in between 148.6-150.8 g with an average weight of 149.7 g, with hardness of 4.25–4.75 $kg.cm^{-2}$ and friability of 0.53–0.71 %. The results of hardness and friability indicated that the tablets were sufficiently hard enough to resist the external pressures during handling, packaging and transportation. This might be attributed to excellent adhesive characteristics of the binding agent i.e., HPMC K4M. The results of assay were found to be 97.9–101.5 % with an average of 99.1 %.

In vitro drug release studies: Comparison based on the physical nature of the drug

The results of the dissolution studies of sets formulations, F1 to F3, F4 to F6 and F7 to F9 (shown in Table 3 and Figure 6) indicated that upon increasing the concentration of Eudragit L 100 in the solid dispersions, the dissolution rate constant was decreased, i.e. more

controlled release was achieved. This might be attributed to the increasing hydrophobicity and more effective entrapment of the drug at higher concentrations of enteric polymer Eudragit L 100. Unlike reported in the works of other authors (Vinod J *et al*, the best formulation and the marketed tablet had a release of 28.4 % and 20.8% respectively after 1 hr, followed by first–order kinetics) the initial burst release was well controlled mainly in the formulations F7 to F9. This further might cause the device to follow perfect zero–order drug release kinetics, which are superior to first–order kinetics.

These results also indicated that the drug release followed zero order kinetics (shown in Table 4). The drug release mechanism was found to be non-Fickian diffusion (anomalous transport) from the regression coefficient of Higuchi's plots and Korsemeyer-Peppas 'n' value (dissolution exponent). It was also observed that the degree of irregularity in drug release mechanism was decreased upon increasing the concentration of Eudragit L 100, which was evidenced by the decrease in the 'n' values in the order of F1 to F3. This might be attributed to the more efficient dispersion of the drug in the polymer and there by consistent diffusion from the polymer matrix upon increasing the concentration of Eudragit L 100.

In vitro drug release studies: Comparison based on the concentration of HPMC K4M

The results of the dissolution studies of sets formulations, "F1, F4 & F7", "F2, F5 & F8" and "F3, F6 & F9" indicated that upon increasing the concentration of HPMC K4M as a binding agent or rate retarding agent, the dissolution rate was found to be was decreased, i.e. more controlled release was achieved. This might be attributed to the increased adhesive nature of the polymer, increased viscosity and diffusion path length of gel formed[17] and, more stringent entrapment of the drug or solid dispersion in the polymer matrix.

These influences of polymers on the release rate constant were illustrated by the response surface model graphs (Figure 7a & 7b). The two predictor variables i.e. concentrations of two polymers were taken on x–axis and y–axis; and the response variable was represented by either a wireframe surface (in 3d surface plot) or the response values were represented by contour lines (in contour plot). Upon increase in the concentration of either of the polymers, the response was changing from red to blue color indicating that the release rate constant was decreased. The release profile of formulation F8 was found to be complied with dissolution criteria of test 2 of USP35 and NF30 for extended release matrix tablets of felodipine.

DoE validation and ANOVA

The observed and the predicted responses were compared and, it was found that the prediction error was varied between-3.33 % and 6.33 % only. The observed responses showing excellent goodness of fit with the predicted responses which was evidenced by the linear plot drawn between them (Figure 8). The normal residual plot indicated that nearly uniform and random scatter. The results of the ANOVA (shown in Table 4) indicated that the model and the model terms of the selected response surface quadratic model were significant.

CONCLUSION

The concentrations of Eudragit L100 and HPMC K4M were found to influence the rate and mechanism of drug release individually and combinely. Solid dispersions of felodipine with Eudragit L100 were found to be effective in controlling the initial drug release, in achieving zero order kinetics from the extended release matrix tablets that were prepared with HPMC K4M as rate controlling polymer and also to obtain the desired release profile that complies with compendial requirements.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

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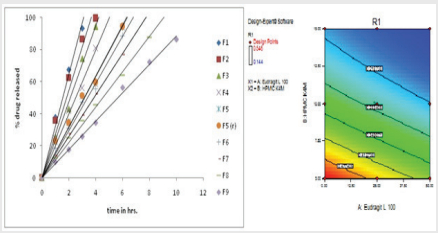
PICTORIAL ABSTRACT



ABBREVIATIONS USED

USP: United States Pharmacopoeia; **NF:** National Formulary; **ER:** Extended Release; **HPMC:** hydroxypropylmethyl cellulose; **FT-IR:** Fourier Transmission Infra-Red; **SD:** Solid Dispersion; **DSC:** Differential Scanning Calorimetry; UV: Ultraviolet; **DoE:** Design of Experiment; **ANOVA:** Analysis of Variance.

SUMMARY

- The concentrations of Eudragit L100 and HPMC K4M were found to influence the rate and mechanism of drug release individually and combinely that was evidenced by ANOVA.
- Solid dispersions of felodipine with Eudragit L100 were found to be effective in controlling the initial drug release as it is an enteric polymer
- The extended release matrix tablets of felodipine prepared through solid dispersions were found to show zero order drug release kinetics.
- This mode of preparation of extended release matrix tablets of felodipine were found to effective in obtaining the desired release profile that complies with compendial requirements.

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Grandhi Srikar: Is an assistant professor in University college of Pharmaceutical Sciences at the Acharya Nagarjuna University, Guntur, India. He has done his masters in Pharmaceutics specialization and interested in research mainly in the fields of development of oral controlled drug release products and particulate systems for targeted drug delivery. He is currently doing his doctoral research on development of nanoparticles for liver targeting.