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Original Article

DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM USING NOVEL SOLUBILIZERS FOR ANTIHYPERTENSIVE DRUG

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ABSTRACT

Objective: The objective of present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of felodipine, based on chronopharmaceutical approach for management of hypertension.

Methods: The strategy adopted was to improve solubility of felodipine by using novel solubilizers like Sepitrap 4000 and Sepitrap 80 in different ratios. Core tablets (CR) of felodipine were prepared by direct compression method using optimum ratio of felodipine and solubilizers. CR tablet was then press coated using different grades of HPMC like E5, E15 and E50 in varying ratios. Pulsatile tablets were evaluated for pre-compressional and post-compressional parameters. Swelling studies and water uptake studies were also carried out to select optimum concentration of polymer that could provide desired lag time.

Results: CR tablet formulated with Sepitrap 4000 and Sepitrap 80 (1:1 ratio) showed 100.16±2.06% release in 15 and 30 min respectively. On the basis of *in vitro* release profile it was found that the optimized formulation F6showed the lag time of about 7.5h which showed compliance with chronotherapeutic objective of hypertension. A direct correlation between swelling and lag time was observed from swelling index and water uptake studies. Solid state characterization (FTIR, XRD studies) indicated that there was decrease in crystallinity of the drug with no interaction between drug and excipients.

Conclusion: Pulsatile drug delivery system is capable of delivering the drug when and where it is required. Drug is released as a burst after a lag time (during peak morning hours) giving relief from morning surge hypertension effect.

Keywords: Chronotherapy, Lag time, Felodipine, Sepitrap, Press-coated tablets, Pulsatile delivery.

INTRODUCTION

Oral route of drug delivery is typically considered the favoured and the most preferable having the highest degree of patient compliance. There are many conditions and diseases where sustained release formulations do not show good efficiency such conditions demand the release of drug after a lag time ie form of pulse. If the timing of dosage regimen is adjusted according to cyclic rhythm of diseases effective management can be achieved [2, 3].

Felodipine is a dihydropyridine derivative, calcium channel blocker used in treatment of hypertension and angina. It is completely absorbed from the gastrointestinal tract; however, extensive first-pass metabolism through the portal circulation results in a low systemic availability of 15% it belongs to BCS class II [4, 5].

The main objective of the work was to improve solubility of felodipine using novel solubilizers and then formulate into bilayered pulsatile releasetablet.Heart rate and blood pressure follows a circadian rhythm it increases in early morning hours and declines in night, such marked rise in blood pressure is called the morning or "a.m." surge. Pulsatile delivery system shows burst release of drug after an optimal lag time which would be effective in treating morning surge hypertension with minimum side effects [6, 7].The system consists of a core tablet containing novel solubilizers and coated with different grades of hydroxyl propyl methylcellulose to produce burst release after predetermined lag time [8, 9].

MATERIALS AND METHODS

Materials

Felodipine was obtained as a gift sample from Cipla, Mumbai, India. Sepitrap 4000, Sepitrap 80 were gifted by Seppic, Mumbai, India.Hydroxypropylmethylcellulose (HPMC E5, E15, and E50) were obtained as gift samples from Colorcon Asia Pvt.Ltd. Mumbai, India. Microcrystalline cellulose was a kind gift from Signet Chemicals Mumbai, India. Magnesium stearate and talc were obtained from S.D. Fine Chemicals Pvt Ltd, Mumbai, India. All other chemicals and reagents used were of analytical reagent grade.

Preparation of physical mixtures

Felodipine is practically insoluble in water; inorder to improve its solubility novel solubilizers sepitrap 4000 and sepitrap 80 were used. Physical mixtures were prepared by grinding felodipineand individual solubilizers in a mortor (the ratio of felodipine to solubilizer used was 1:1) [4].

Saturation solubility studies

Solubility studies were performed for physical mixtures by taking dose equivalent amount of physical mixtures of sepitrap in a glass vial containing 5 mL of 0.1N HCl.Then vials were covered with cellophane membrane to avoid any loss of solvent and then kept in rotary shaker for 48 h at 37± 0.5 °C. Samples were filtered and measured by HPLC at 239 nm after appropriate dilution with methanol. Three determinations were carried out for each sample to calculate the solubility of felodipine.

Preparation of rapid release core tablets (RRCT)

Felodipinecore tablets were prepared by direct compression method [Table 2]. Two types of core tablets were prepared one containing solubilizersepitrap 4000 and other containing sepitrap 80 (C1 and C2 respectively) for producing burst release from final coated tablet [6, 7]. The average weight of core tablet was found to be 100 ± 0.12 mg.

Preparation of pulsatile release tablets (PRT)

Best fast release core tablet was used for preparation of pulsatile release tablets and dry coating of it was done by using different grades of HPMC (E5, E15 and E50) at different concentrations [Table 3] [10]. Press coated tablet was prepared by placing 50% of polymer in 11mm die and core tablet was placed on it. Further remaining quantity of polymer was added finally compressed by using 16-

station tablet punching machine (Cadmach) [11-14]. The average weight of pulsatile release tablet was 340 ± 0. 12 mg.

Table 1: Formulation of physical mixtures (PMS)

Formulation	Ratio	Drug (mg)	Sepitrap 4000 (mg)	Sepitrap 80 (mg)
PM1	1:1	5	5	-
PM2	1:1	5	-	5

Table 2: Formulation of rapid release core tablets of felodipine

Formulation	PM1 (mg)	PM2 (mg)	Microcrystalline cellulose (mg)	Magnesium stearate (mg)	Talc (mg)
C1	10	-	87	1.5	1.5
C2	-	10	87	1.5	1.5

Table 3: Composition of pulsatile release tablets of felodipine

Formulation	Core tablet weight (mg)	HPMC E5 (mg)	HPMC E15 (mg)	HPMC E50 (mg)
F1	100	240	-	-
F2	100	-	240	-
F3	100	-	-	240
F4	100	300	-	-
F5	100	-	300	-
F6	100	-	-	300

Table 4: Physical evaluation of powder blend

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
C1	20±1.29	0.321	0.402	20.15	1.252
C2	21.66±1.13	0.318	0.339	20.301	1.254

Physical characterization

The physical characteristics such as thickness, hardness, friability,content uniformity and weight variation tests were evaluated for all the formulations according to the Indian Pharmacopoeia [15].

***In vitro* release profile of felodipine**

The release rate of felodipine from physical mixtures as well as from press coated tablet systems were carried out using USP dissolution apparatus type II in 0.1N HCl (900 ml) at 37 ± 0.5ºC. The speed of rotation was maintained at 50 rpm [15]. Aliquots of dissolution medium were withdrawn at predetermined time interval and content of felodipine was determined by using UV spectrophotometer at 239 nm. The dissolution studies were conducted in triplicate.

Swelling index and water uptake studies

The swelling index of best PRT was compared with other PRTs with same concentration as that of optimized PRT by using USP dissolution apparatus type I. In this study six tablets were placed in the basket of dissolution apparatus by using 0.1N HCl as dissolution medium at 37±0.5ºC. Tablets were withdrawn at each time intervals and blotted with tissue paper to remove excess water and weighed on the analytical balance [10, 16, 17]. Swelling index was calculated by using the following formula

$$\text{Swelling Index (\%)} = \frac{Wt - Wi}{Wi} \times 100$$

Where, Wt is the weight of wetted tablet at each time interval and Wi is the initial dry weight of the tablet.

The increase in weight (uptake) due to absorbed liquid (A) was calculated at each time point from,

$$\text{Water uptake (\%)} = \frac{Wt - Wf}{Wf} \times 100$$

Where Wf is the weight of the dried tablet or partially eroded tablet at each time interval.

Solid state characterization

X-Ray Diffraction(XRD)

X- ray diffraction studies were carried out for pure felodipine, Sepitrap 4000, Sepitrap 80 and core tablets (C1 and C2)were analyzed using an X'Pert PRO MPD diffractometer(PANalytical, Almelo, the Netherlands) with a copper anode (Cu K radiation = 0.15406 nm, 45 kV, 40 mA). The diffraction patternwas measured with a step size of 0.017° and a dwell time of 45 s at each step between 3 and 5º 2 at ambient temperature [6, 10].

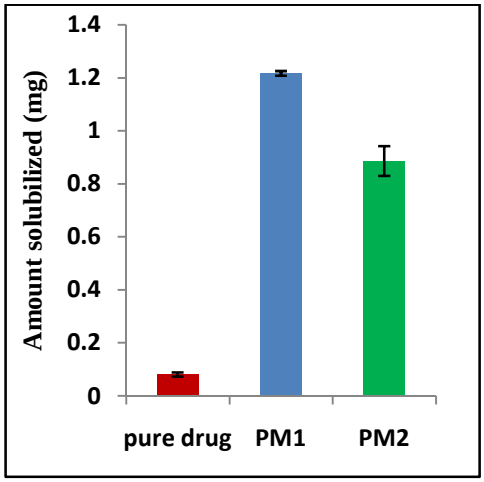

Fig. 1: Saturation solubility studies

Fourier Transform Infrared Spectroscopy (FTIR)

IR spectroscopy of the pure felodipine, solubilizers such as sepitrap 80, sepitrap 4000 and best formulationwere conducted using an FTIR Spectrophotometer (IR Prestige 21 Shimadzu model) which was employed to characterize the possible change in physical state of drug using physical mixture of solubilizer. Samples were prepared using KBrdisk method.Samples of about 2mg werelightly ground and mixed with 200 mg IR grade dry potassium bromideand then compressed at 10 tonnes in a hydraulic press to form discs. The

spectrum was recorded in the range of 4000– 450 cm^{-1} at room temperature. Analyse were performed at room temperature.

RESULTS AND DISCUSSION

Saturation solubility studies

Saturation solubility studies reveal that the use of novel solubilizers sepitrap 4000, sepitrap 80increased the solubility of drug.

Note: PM1: Physical mixture of sepitrap 4000, PM2: Physical mixture of sepitrap 80

Characterization of pre-compression blend

Powder blends of all formulations were characterized with respect to angle of repose, bulkdensity, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 25º and Carr's index values were less than 23 for the granules of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.3 for both the batches indicating good flow properties.

Evaluation of tablets

The results of hardness, thickness, friability, uniformity of weight and drug content of the tablets are given in Table 5.All the tablets of different batches compiled with the official requirements of uniformity of weight as their weights varied within the limits. The hardness of the tablets ranged from 2.3 to 6.1 kg/cm^2 and the friability values were less than 0.52% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.2 to 4.72 mm. All the formulations satisfied the content of the drug as they contained 97.4 to 100.5 % of felodipine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control.

Table 5: Physical evaluation of prepared tablets

Formulation code	Hardness (kg/cm^2)*	Weight variation (mg)***	Thickness (mm)*	Friability (%)**	Drug Content (%)*
C1	2.9 ± 0.9	100.82 ± 1.2	2.3 ± 0.9	0.38 ± 0.5	99.9 ± 1.2
C2	2.8 ± 0.8	100.32 ± 0.9	2.2 ± 0.9	0.523 ± 0.06	97.4 ± 1.9
F1	5.3 ± 0.8	339.3 ± 2.5	3.9 ± 0.2	0.4 ± 0.08	98.6 ± 1.9
F2	5.6 ± 0.2	341 ± 3.6	3.72 ± 0.8	0.32 ± 0.7	97.4 ± 0.9
F3	6.1 ± 0.5	343.9 ± 1.1	4.0 ± 1.0	0.27 ± 0.4	100.5 ± 0.4
F4	5.5 ± 0.7	401 ± 1.58	4.72 ± 0.7	0.4 ± 0.08	96.2 ± 0.2
F5	5.9 ± 0.8	400 ± 0.86	4.67 ± 0.8	0.33 ± 0.04	98.6 ± 0.6
F6	6.1 ± 0.2	399.5 ± 1.3	4.5 ± 0.11	0.32 ± 0.1	98.57± 0.9

*All values represent mean ± standard deviation (SD), n=3
** All values represent mean ± standard deviation (SD), n=6
*** All values represent mean ± standard deviation (SD), n=20

In vitro release profiles

From the results it is evident that the release from the core tablet depends on the nature of the solubilizers. Formulation C1 showed complete drug release within 15min and found to be suitable for formulating into pulsatile release tablets.

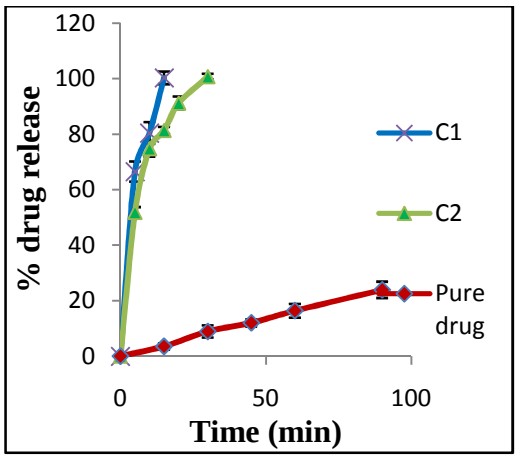

Fig. 2*: In vitro* release of felodipine from core tablets

Six formulations were designed to have different tablet release profiles by changing weight of coating layers with low viscosity grades of HPMC (F1, F2, F3 with 240 mg coating and F4, F5, F6 with 300mg coating). Consequently, differences in tablet release profiles were noted in the *in vitro* testing as seen in Figure 3.

As the coated tablet was placed in the medium, it was observed that the hydrophilic polymeric layer started swelling, which underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually starts to erode up to a limiting thickness. After this stage, a rupture of the shell was observed under the pressure applied by the swelling of the core tablet releasing drug from core tablets. All of this process corresponded to a lag time capable of exhibiting a pulsatile release of the drug. The profiles relevant to the coated tablet showed that a lag phase was allowed by the quick delivery of the active agent. The delayed duration clearly depended on the kind and amount of hydrophilic polymer which was applied on the core [18, 19]. The lag time of the tablet coated with 300mg of HPMC E50 (F6) was found to be 7.5 h.

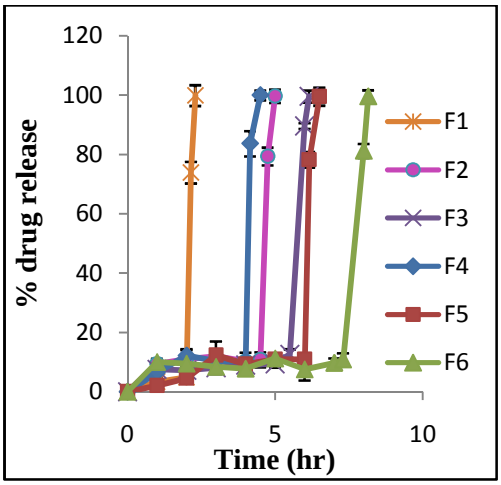

Fig. 3: *In vitro* release of felodipine from pulsatile release tablets

Swelling and water uptake studies*:*

The swelling behaviour of optimized PRT containing HPMC E50 was compared with other PRTscontaining HPMC E5 and HPMC E15 at same concentration i.e. 300 mg.

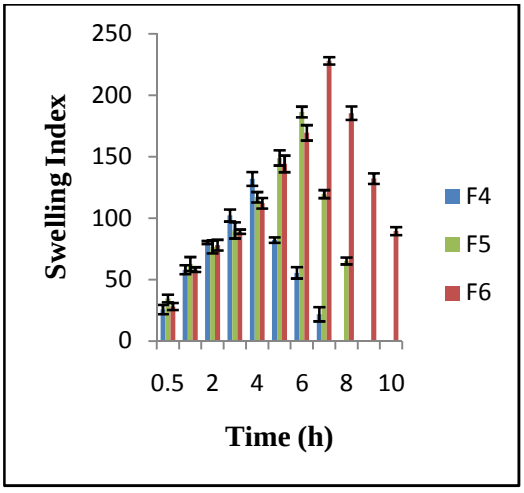

Fig. 4: Swelling indices for PRT with 300 mg of HPMC E5, E15 and E50.

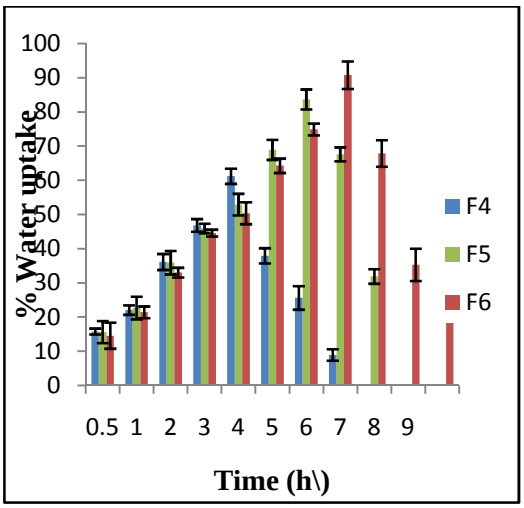

Fig. 5: Water uptake studies for PRT with 300 mg of HPMC E5, E15 and E50

The obtained results showed that the swelling front erodes faster for PRTs with HPMC E5 and the swelling fronterosion was comparably slower in PRTs with HPMC E15 and E50 due to their marked viscosity properties. In swelling index study, an increase in thickness of rubbery layer of PRT with HPMC E50 was higher as compared with PRTs with HPMC E5 and HPMC E15. This result may be attributed to complete penetration of solvent and high viscosity of the HPMC E50. A direct correlation between swelling and lag time was observed and found that the formulation having maximum swelling indices showed higher lag time [10]. Similarly formulation having higherwater uptake showed higher lag time.

At '0' h the pulsatile tablet is intact. Tablet swells at its maximum in first 3h. At 4h and 5h blue colour of core can be seen from outer press coat. After 6h press coat is completely removed and core tablet can be seen intact. After 7h core tablets starts disintegrating and it release its contents completely after 7.5h.

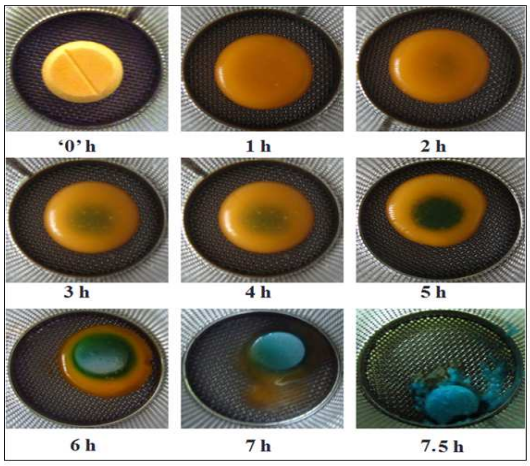

Fig. 6: Morphological changes of optimal formulation during swelling studies

Powder X-ray diffraction:

Polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability. On the other hand, the importance of polymorphism on the therapeutic effectiveness of a drug and the pharmaceutical implication of the presence of metastable crystalline forms in the bulk powder are well recognized. Transformation from crystalline state to amorphous state favours the faster dissolution of drug there by improved solubility and dissolution rate as later contains high internal energy and improved thermodynamic properties compared to pure crystalline drug.

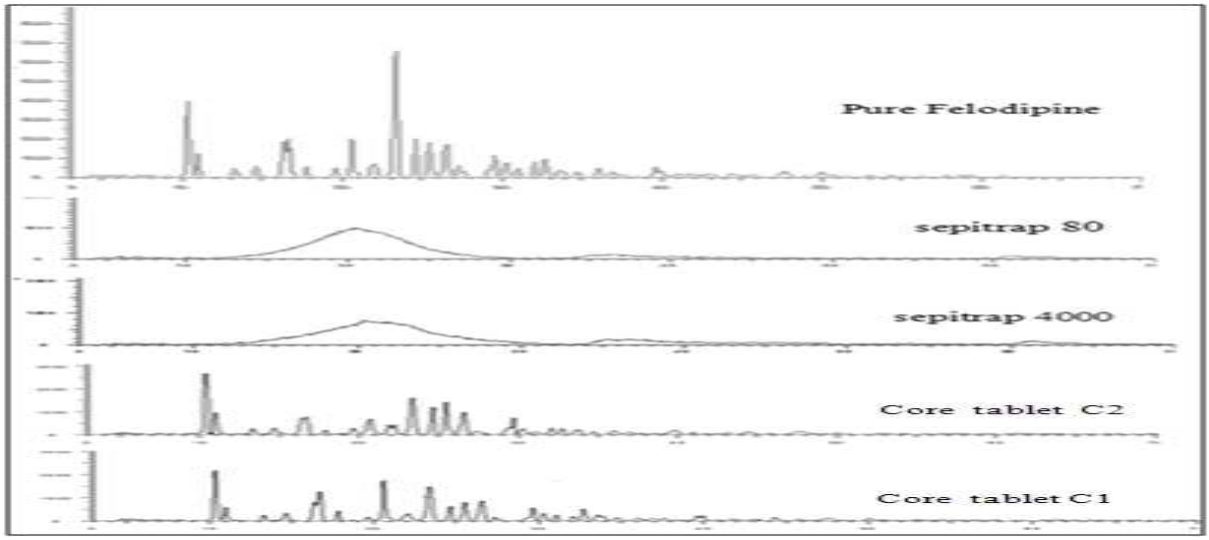

Fig. 7 : X-ray diffractograms

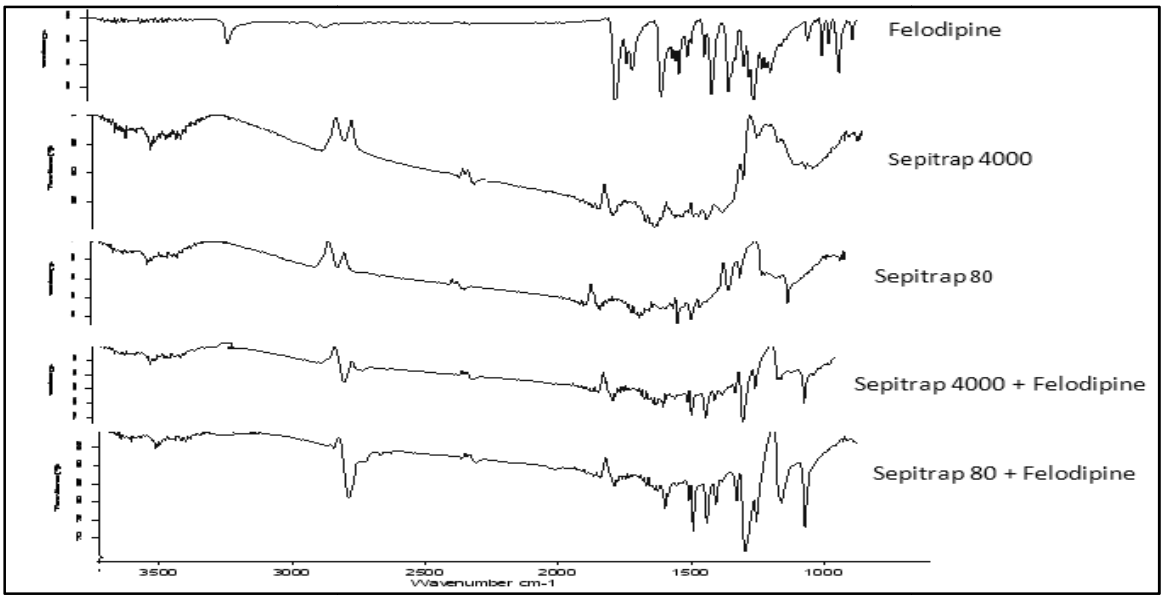

Fig. 8: FTIR Spectra

Powder X-ray Diffraction scans of pure drug; solubilizers and core tablet mixture were conducted to understand the crystallinity of pure drug and any loss or modification of pure drug crystallinity after its formulation into mixture. The X-ray diffractograms of pure felodipine showed sharp distinct characteristic peaks at 2 theta diffraction angles of 10º and 22º due to its crystalline nature.Surfactants (Sepitrap 4000 and Sepitrap 80) showed only broad peak at 2 Theta of 20º due to its amorphous nature and no peak was seen at 2Theta of 10º. Optimized core tablet formulation showed characteristic peak at 10º of 2 theta scale with low intensity for both Sepitrap 4000 and Sepitrap 80. But the intensity of peak reduction was more with Sepitrap 4000 as compared to Sepitrap 80. There might be change of physical state of drug from crystalline form to slightly amorphous form due to which the crystallinity of drug peak is reduced but still prominent peak of drug can be observed from the spectra.

Fourier Transform Infrared Spectroscopy

FTIR studies were done for pure drug (felodipine), solubilizers (sepitrap 4000, sepitrap 80), and physical mixtures to determine compatibility between drug and excipients.If the drug and excipients interact, the peaks corresponding to the functional groups in the drug FTIR will shift to different wavenumbers compared to spectra of the pure drug and pure excipients. The characteristic peaks of felodipine and solubilizers (sepitrap 4000, sepitrap 80)were observed in physical mixture. This suggests that there is no significant interaction between the drug and carrier.

CONCLUSION

A chronotherapy based pulsatile release tablets of felodipine was successfully developed. Taking into consideration the chronotherapy of hypertension, pulsatile release tablet with 300 mg concentration of HPMC E50 in coating layer and sepitrap 4000 in core tablet (formulation F6) gave satisfactory release lag time of 7.5 h followed by drug release within 15 min. Hence this formulation can be helpful for the patients with morning surge. From this, it can also be said there is a chance for decrease in dose of the drug. Solid state characterization (FTIR, XRD studies) indicated that there was decrease in crystallinity of the drug with no interaction between drug and excipients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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