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Preparation and evaluation of solid dispersion of felodipine

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ABSTRACT

The main objective of the present study is to improve the dissolution rate of felodipine. In the present work an attempt was made to prepare solid dispersion (common solvent method) by using PEG_{4000} and PEG_{6000} in the ration of 1:1, 1:2, 1:3, 1:4, 1:9 drug polymer ratio. The complexes were studied for the dissolution, the dissolution profiles shows that the drug excipient ratio of 1:9 gives higher dissolution rates than all the other ratios. Further PEG_{6000} gave faster dissolution rates of felodipine than the PEG_{4000} and obeys first order kinetics. The TLC of pure drug and PEG complexes had shown comparable Rf values and absence of additional spots. The IR spectrum of drug and solid dispersion found that in the functional group region except for peaks at 3300cm^{-1} wherein -OH and -NH of drug and PEG_{4000}have merged to give a broad peak. The C=O peak of the drug has remained unchanged indicating the no change in the nature of the drug during formulation with $PEG_{4000}$and also with PEG_{6000}.

Key words: Preparation and evaluation, solid dispersion of felodipine.

INTRODUCTION

The Felodipine is an anti-hypertensive drug[1]. It is practically insoluble in water and its absorption is dissolution rate limiting step. Felodipine is a highly lipid soluble and its pharmacokinetics fits in to the pattern of kinetics for lipid soluble drugs. The drug is completely absorbed from GIT[1]. Hence, an attempt was made to improve dissolution rate of poorly soluble drugs, the preparation of solid dispersion has often proved to be successful[2-6], In solid dispersion the drug is dispersed in an inert water-soluble carrier at solid state. Several water-soluble carriers such as mannitol, polyethylene glycols (PEGs), citric acid, Succinic acid polyvinyl pyrrolidone are used as carriers for preparing solid dispersions. In the present work an attempt was made to prepare solid dispersion (common solvent method) by using PEG_{4000} and PEG_{6000} in the ration of 1:1, 1:2, 1:3, 1:4, 1:9 drug polymer ratio. The complexes were studied for the dissolution; the dissolution profiles shows that the drug excipient ratio of 1:9 gives higher dissolution rates than all the other ratios. Further PEG_{6000} gave faster dissolution rates of felodipine than the PEG_{4000} and obeys first order kinetics.

MATERIAL AND METHODS

Felodipine was obtained from Cipla Ltd, Bangalore, PEG_{4000} and PEG_{6000} purchased from Sd fine Chemicals. All the carriers and solvents used were of analytical or pharmacopeial grade.

Solubility studies of pure drug in different solvents

Excess amount of felodipine was added to stoppered conical flasks containing 10ml of solvent (media) and placed on a rotary flask shaker. The flasks were removed from shaker after 4 h and kept aside for 24 h at a constant temperature to attain equilibrium condition. Suitable aliquots were

withdrawn from the filtered solutions and analyzed for the drug content. The results are given in Table-1.

Preparation of Solid Dispersion

Solvent evaporation method was used for the preparation of solid dispersion. Five different drug; carrier ratios (1:1, 1:2, 1:3, 1:4 and 1:9) were used. The respective amounts of carrier were dissolved in 2ml of Chloroform and 2ml of acetone and felodipine was added in parts with continuous stirring. The solvent was then removed by evaporation at 40^0 under vacuum. The solid dispersion were pulverized and shifted (# 40) and stored in a desiccator[7-13].

Dissolution rate studies

Felodipine, pure drug, and all its solid dispersion were subjected to dissolution test using In-vitro dissolution rate apparatus of USP XXIII dissolution rate test apparatus (Electro-lab electronics) employing paddle stirrer.

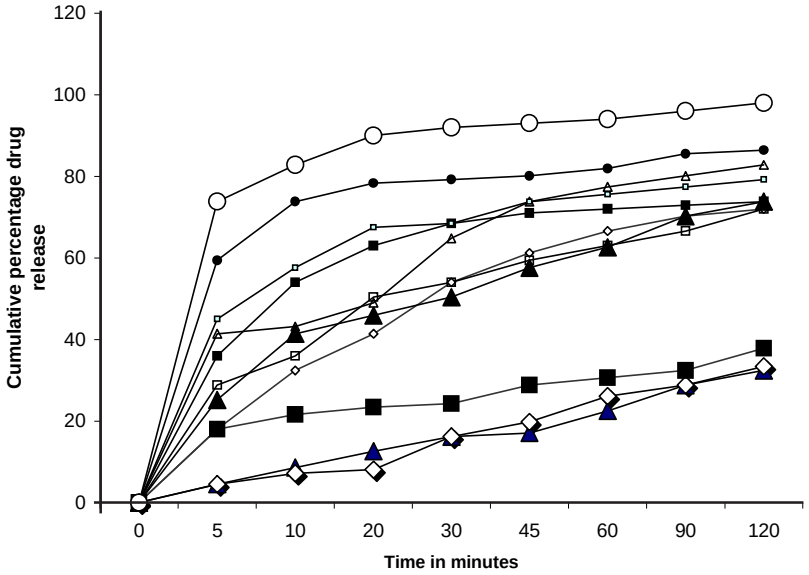
This test was performed using 900ml of dissolution medium (stimulated gastric fluid) containing pH 1.2 ± 0.2% SLS to (pH1.2) containing 0.2% SLS was used to maintain the sink condition. And a sample equivalent to 10mg of felodipine was taken in a hard gelatin capsule and used for the test. The stirrer was adjusted to rotate at 50 rpm and a temperature of 37° ±0.5° was maintained throughout the experiment. A 5ml aliquot of dissolution medium was withdrawn at different time intervals. It was suitably diluted and assayed spectrophotometrically by measuring absorbance at 239nm. The percentage of drug dissolved at various time intervals was calculated and plotted against time. The $T_{50\ min.}$ $T_{90\ min}$ values were calculated from plots also K values were obtained by plotting log cumulative percent drug undissolved against time, the results are shown in figure-1. All solid dispersions were subjected to Thin Layer Chromatography (TLC) studies using ethyl acetate (40ml) and cyclohexane (60ml) as a solvent system. The spot is detected by placing in a chamber containing iodine crystals. The Rf values were calculated and the results are shown in Fig. 2.

All solid dispersions were kept in an evacuated desiccator. The drug content estimations were repeated after 90 days. No appreciable change was found in the drug content estimation. The results are tabulated in Table 2.

Table 1: Solubility studies of felodipine at room temperature

S. No.	Solvent (Media)	Saturation Solubility (mcg/ml)*
1	Distilled water	4.7
2.	Distilled water+ 10% methanol	7.2
3.	Distilled water+ 20% methanol	13.5
4.	Distilled water+ 30% methanol	48.8
5.	pH 1.2 buffer	6.8
6.	pH 1.2 buffer +10%methanol	7.7
7.	pH 1.2 buffer +20%methanol	15.0
8.	pH 1.2 buffer +30%methanol	62.5
9.	pH 1.2 buffer +0.1% SLS	60.0
10.	pH 1.2 buffer +0.2% SLS	110.0
11.	pH 7.4 buffer	5.0
12.	pH 7.4 buffer+ 10% methanol	6.8
13.	pH 7.4 buffer+ 20% methanol	12.5
14.	pH 7.4 buffer+ 30% methanol	25.0
15.	pH 7.4 buffer+ 0.1% SLS	58.0
16.	pH 7.4 buffer+ 0.2% SLS	113.0

*Average of three determinations.



S- pure Felodipine (-Δ-), S1-Felodipie PEG4000 (1:1)(-◊-), S2-Felodipie PEG4000 (1:2)(-◊-), S3-Felodipie PEG4000 (1:3)(-Δ-), S4-Felodipie PEG4000 (1:4)(-Δ-), S5-Felodipie PEG4000 (1:9)(-´-), S6-Felodipie PEG6000 (1:1)(- %-), S7-Felodipie PEG6000 (1:2) (- -), S8-Felodipie PEG6000 (1:3)(– -), S9-Felodipie PEG6000 (1:4)(- -), S10-Felodipie PEG6000 (1:9)(-O-)

Fig. 1: *In vitro* dissolution of Felodipine in pure form and Solid dispersions prepared with Felodipine: PEG 4000 and PEG6000 in various ratios(n=3)

The in-vitro dissolution study of various solid dispersions of felodipine was repeated after 90 days using stimulated gastric fluid containing pH 1.2 ± 0.2% SLS to maintain sink condition. It was found that there is no much difference in the drug release rates.

IR spectral studies

The IR spectrum of the drug felodipine was recorded in Nujol, which was shown a peak at 3370cm^{-1} for NH, and 1696 cm^{-1} for C=O and 1559 cm^{-1} for C=C absorptions. These are the characteristic peaks of the drug.

When drug was taken with the PEG_{4000} and the spectra of formulated mixture was recorded. The IR spectrums are shown in the Fig. 3.

RESULTS AND DISCUSSION

All solid dispersions were found to be fine and free flowing powders. All solid dispersions of

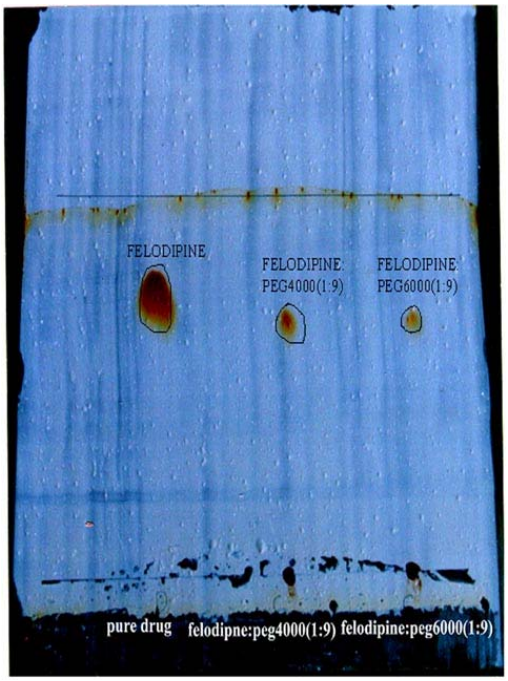


Fig. 2: Thin layer chromatography plate

Table 2: Drug content estimation of formulation before and after storage at room temperature for 90 Days

Formulations	Drug: PEG ratio	Drug content estimation		Drug content estimation after storage at room temp. for 90 Days	
		Mean % drug content ± SD	Wt. equiv. to 10 mg of Felodipine	Mean % drug content ± SD	Wt. equiv. to 10 mg of Felodipine
PEG_{4000} S1	1:1	48.5±0.156	20.62	47.95±0.311	20.86
S2	1:2	34.01±0.352	29.40	33.9 ±0.280	29.50
S3	1:3	26.51±0.101	37.72	25.88±0.185	38.64
S4	1:4	21.60±0.254	46.30	21.43±0.076	46.66
S5	1:9	10.50±0.245	95.24	10.45±0.266	95.69
PEG_{6000}					
S6	1:1	52.50±0.350	19.05	52.58±0.213	19.11
S7	1:2	34.14±0.248	29.29	33.78±0.364	29.60
S8	1:3	24.50±0.243	40.82	24.33±0.331	41.10
S9	1:4	21.49±0.117	46.53	21.3±0.257	46.95
S10	1:9	10.51±0.090	95.15	10.23±0.325	97.75

felodipine gave a single spot in TLC studies and same Rf values were obtained for pure felodipine and its solid dispersions. The IR spectrum of drug and solid dispersion found that in the functional group region except for peaks at 3300cm^{-1} wherein –OH and –NH of drug and PEG_{4000} have merged to give a broad peak. The C=O peak of the drug has remained unchanged indicating the no change in the nature of the drug during formulation with PEG_{4000} and also with PEG_{6000}.

Dissolution rate of felodipine from all its solid dispersions has compared to the pure felodipine and physical mixture was found to have increased. Dissolution profile of all the solid dispersions was dependent on drug-excipient ratio. As the proportion of excipient in the solid dispersion increases then the dissolution rate also increases. A comparison of t_{50} %, t_{90} % and dissolution efficiency at 30 minutes ($DE_{30min.}$) shows that the drug-excipient ration of 1:9 gives higher dissolution rates than all the other drug-excipient ratios. Further PEG_{6000} gave faster dissolution rates of felodipine than the PEG_{4000}. The K values of first order rate constants, obtained showed that all the dispersions followed first order kinetics, as K values of solid dispersions were more than that of the pure drug.

The results of interaction studies using TLC and melting point analysis the absence of any chemical interactions the drugs and the carriers indicating the compatibility. The solid dispersions were stored in a desiccator after 90 days repeated drug content analysis and dissolution shown no marked change. The solid dispersion of felodipine with PEG_{4000} and PEG_{6000} found to be enhances the bioavailability of the drug and suitable for the formulation.

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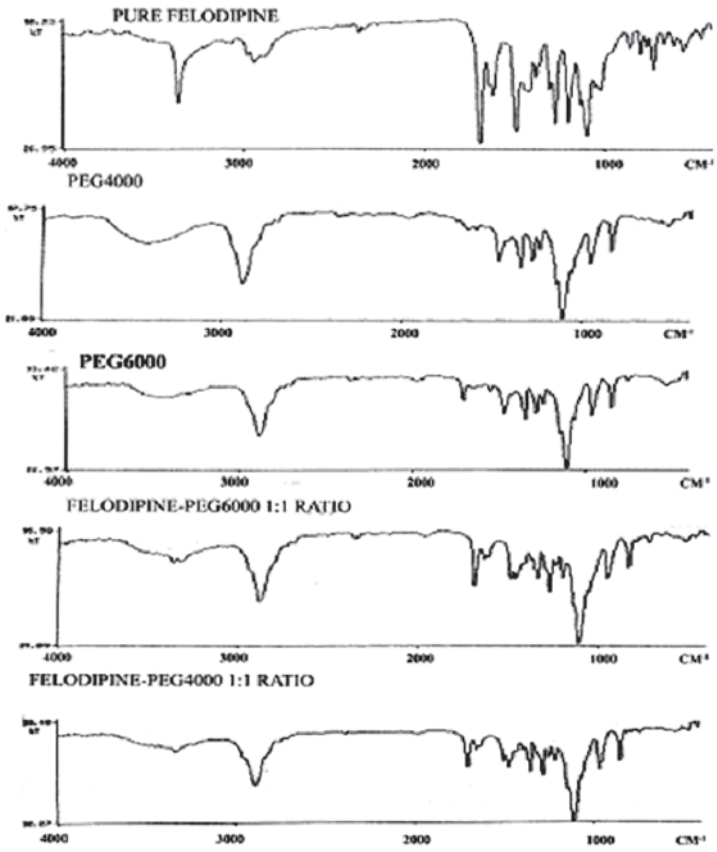

Fig. 3: Infrared spectrum of felodipine and solid dispersion of Felodipine with PEG-4000 and 6000

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