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Preparation and Evaluation of Agar Spherules of Felodipine

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The main objective of the present study is to prepare solid dispersions and controlled drug delivery systems of felodipine, a poorly water soluble drug. With a view to improve the dissolution rate and promote uniform absorption and enhance bioavailability. In the current work, an attempt was made to prepare solid dispersion (common solvent method) by using PEG-6000 in the ratio of 1:1,1:2,1:3,1:4 and 1:9 drug polymer ratio. The complexes were studied for the in-vitro drug release. The dissolution profile shows 1:9 drug-polymer ratio complex gave higher dissolution rate. Further, the complex (1:9) was used to prepare agar spherules in the ratio of 1:5 and 1:10 drug/complex: agar ratio. These prepared spherules were studied for in-vitro drug release pattern. The in-vitro drug release data were plotted according to zero order, first order and Higuchi's diffusion model. The former did not yield linear plot. The data were subjected to linear regression analysis and correlation co-efficient values for Higuchi's plots are nearly approaching unity and hence it can be said that, the drug release in agar spherules occurs by diffusion through the hydrophilic matrix.

Keywords: Agar spherules, Felodipine, Drug delivery system.

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. Hence, an attempt was made to improve dissolution rate of poorly soluble drugs. felodipine is almost completely absorbed after oral administration. But extensive first pass metabolism results in an oral bioavailability of only 20%. Peak plasma levels are reached in 2.5 to 5 hours. Peak plasma concentration-time curve (AUC) increases with increasing doses. The mean peak and trough plasma concentrations after a 10mg dose of felodipine in an immediate release form were 20 and 0.5 nmol/l respectively. The dose for half-maximum reduction of blood-pressure (ED50) is 4-6nmol/l. In hypertensive patients, 20mg dose of felodipine an extended release formulation gives mean peak and trough steady state plasma concentrations of 23 and 7nmol/l respectively. Hence, an attempt was made to maximizing therapeutic utility of the dose administered [2&3]. Further controlled drug delivery system of felodipine provide the convenience of once a day dosage regimen instead of twice daily dosage as in the case of conventional tablet formulation[4].

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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 Pharmacopoeial 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 4h 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.

Table 1.

S.No.	Fromulation	Code
1.	Felodipine: agar spherules (1:5)	A1
2.	PEG-6000solid disperion (1:9)**:** agar spherules (1:5)	A2
3.	Felodipine: agar spherules (1:10)	A3
4.	PEG-6000solid disperion(1:9) **:** agar spherules (1:10)	A4
5.	Commercial tablet (FELOGARD-10 mg., CIPLA)	CF

Preparation of Solid Dispersion

Solvent evaporation method was used for the preparation of solid dispersion. Drug:carrier ratio1: 4 was 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° under vacuum. The solid dispersion were pulverized and shifted (# 40) and stored in a desiccator [5-9].

Preparation of Agar spherules[10]

1.5 gms of powdered agar-agar was dissolved in 25ml of water at 95° in a water bath. The colloidal solution was gradually cooled to 80° and mixed with 300mg of felodipine drug. The dispersion was transferred quickly into 200ml of liquid paraffin which was maintaining at 55±2° in a water bath. The contents were stirred for 5 min with the help of stirrer to form fine dispersion spherules. The mixture was cooled in a ice bath to 10° for rigidization of spherules. Then the prepared spherules were filtered through mesh # 40 and wash thrice (100ml each) with petroleum ether until the adhering liquid paraffin was totally removed. The felodipine agar spherules were dried at room temperature in vacuum desiccators.

Agar spherules of felodipine: PEG-6000 solid dispersion was prepared by using above procedure. All the formulas are tabulated in Table 2.

Drug Content Estimation of Agar spherules

30 mg of agar spherules were taken with 5ml of water and the contents were heated 90 to 95° to dissolved the agar. Then it was shaken with 30ml of methanol for 30minutes to extract the drug. Then volume was adjusted to 50ml with methanol and filtered. 1ml of filterate was taken, dilute to 10ml with methanol and absorbance was measured at 238 ηm using 90% methanol as a blank[11]. The mean % drug content estimation of agar spherules was shown A1-12.0 ± 0.1233, A2-12.0±0.133, A3-10.01±0.133 and A4-1.93± 0.060.

Table 2. Values showing the regression formula, correlation coefficient and slope for zero order kinetics (when plotted cumulative % drug released versus time for all formulated agar spherules and commercial formulation)

S. No.	Formulation Code	Regresion formula Y=A+Bx	Correlation coefficient'r'	Slope
1.	CF	Y = -1.4481 + 0.0893x	0.9140	0.0893
2	A1	Y = - 1.4937 + 0.1326x	0.9352	0.1326
3	A2	Y = -1.6173 +0.1049x	0.9352	0.1049
4	A3	Y=-1.0890 +0.1739x	0.9439	0.1739
5	A4	Y=-1.0460 +0.1412x	0.9795	0.1412

Average particle size determination of agar spherules by microscopic method:

The average particle size of the agar spherules were determined by microscopic method using eye piece and stage micrometer. The average particle size of agar spherules were A1-2116.06, A2-109.72, A3228.53 and A4 – 221.18 µm.

Dissolution rate studies

Felodipine, pure drug, and all its solid dispersions and its agar spherules 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 (simulated gastric fluid) containing pH 1.2 ± 0.2% SLS to (pH 1.2) 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 and also K values were obtained by plotting log cumulative percent drug undissolved against time, the results are shown in Fig. 1 & 2. further the results were plotted % of drug released v/s square root of time to know the pattern of drug release. The plots were shown in Fig 3.

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.

The in-vitro dissolution study of various solid dispersions of felodipine was repeated after 90 days using simulated gastric fluid containing pH 1.2 ± 0.2% SLS to maintain sink condition.

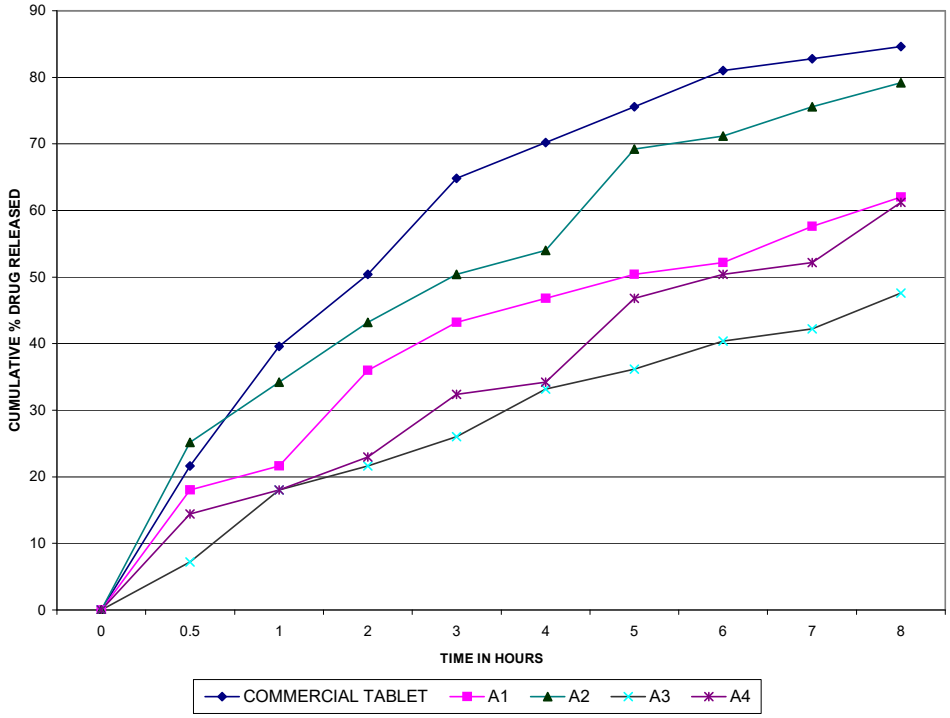

Fig. 1. Plot of cumulative percent drug released v/s time for all formulated agar spherules and commercial tablet

It was found that there is no much difference in the drug release rates. The *in vitro* drug release data were plotted according to zero-order kinetics, first-order kinetics and Higuchi's diffusion model, the former did not yield linear plot as shown in the Figs. 1, 2 & 3. Further, the data were subjected to linear regression analysis and correlation coefficient values for Higuchi's plots are nearly approaching unity and hence it can be said that the drug release in agar spherules occurs by diffusion through the hydrophilic matrix. Values showing the regression formula, correlation coefficient and slope were shown in Table 3,4 and 5.

Table 3. Values showing the regression formula, correlation coefficient and slope for first order kinetics (when plotted cumulative percent drug released versus time for all formulated agar spherules and commercial formulation)

S. No.	Formulation Code	Regresion formula Y=A+Bx	Correlation coefficient 'r'	Slope
1.	CF	Y = 18.66 - 9.697x	0.9837	-9.697
2.	A1	Y = 40.43 - 20.782x	-0.9764	-20.782
3.	A2	Y = 24.02 - 12.374	-0.9869	-12.374
4.	A3	Y=59.42 - 30.094	-09838	-30.094
5.	A4	Y=41.98 - 21.213	-0.9890	-21213

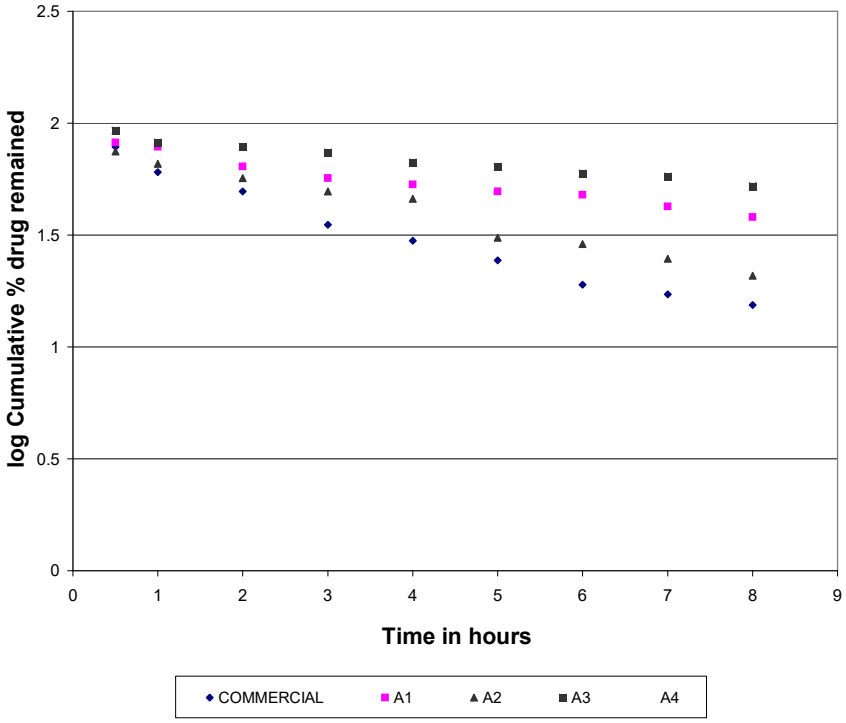

Fig. 2. Plot of cumulative %drug remained v/stime

Table 4. Values showing the regression formula, correlation coefficient and slope for higuchi's plot (when plotted cumulative percent drug released versus time for all formulated agar spherules and commercial formulation)

S. No.	Formulation Code	Regresion formula Y=A+Bx	Correlation coefficient 'r'	Slope
1.	CF	Y = -0.0937 + 0.03145x	0.9867	0.03145
2.	A1	Y = -0.0802 + 0.04593x	0.9932	0.04593
3.	A2	Y = 0.0974 + 0.03610x	0.9922	0.03610
4.	A3	Y=0.11115 + 0.05837x	0.9938	0.05837
5.	A4	Y=0.15728 + 0.04641x	0.9874	0.04641

RESULTS

Four agar spherules formulations of felodipine and felodipine solid dispersion were prepared using two different drug: carrier ratios and were subjected to in-vitro drug release study over a period of 8 h. Out of all four formulations, formulation A_2 has released about 79% of drug over the period of 8 hours, whereas commercial formation has released about 85% over the same period. Hence, from the studies carried out it can be concluded that, Improvement in the dissolution profile of poorly soluble drug felodipine is achieved through the preparation of PEG solid dispersion. PEG-6000 solid dispersion in a drug carrier ratio 1:9 (S_{10}) shows the highest dissolution rate among all the solid dispersion prepared ($t_{70\%}$ = 5 minutes and DE_{30min} = 77.30%). There are no appreciable changes in the drug content and drug release rates of the solid dispersion after aging for 90 days at room temperature. Among the agar spherules formulation A_2 is showing promising results as extended release formulation of felodipine. Further studies in this context are required to obtain a overall drug release profile similar to that of commercial formulation. When in-vitro drug release data were plotted according to zero-order kinetics, first-order kinetics and Higuchi's diffusion model, the former did not yield linear plot as shown in the Fig. 1, 2 & 3. Further, the data were subjected to linear regression analysis and correlation coefficient values for Higuchi's plots are nearly approaching unity and hence it can be said that the drug release in agar spherules occurs by diffusion through the hydrophilic matrix.

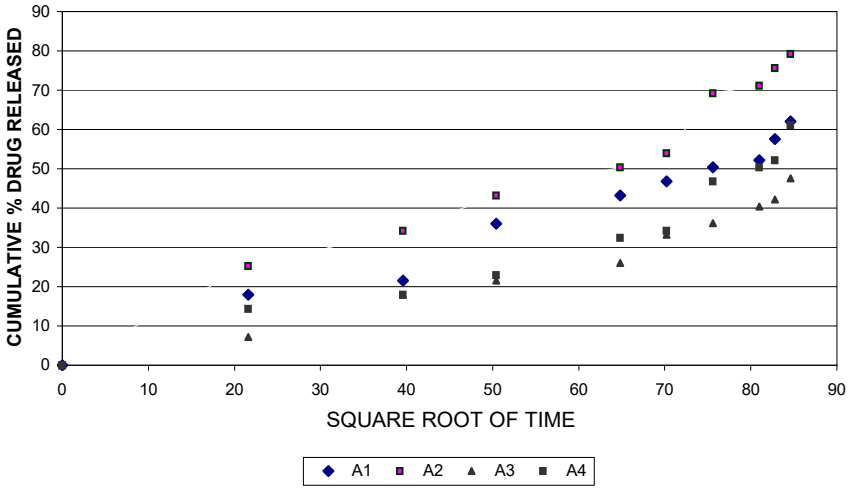

Fig.3. Plot of % Drug released V/s square root of time

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