

Formulation and Evaluation of Polymeric Nanoparticles of Felodipine

Abdul Hasan Sathali A^{1*}, Manikkavasagan A², Umamaheswari D³, Prabhu R³

¹M.Pharm., Ph.D., Principal, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai, Tamilnadu, India

²Post Graduates Scholar, Department of pharmaceutics, COP, MMC, Madurai, Tamilnadu, India

³Assistant Professor, Department of Pharmaceutics, COP, MMC, Madurai, Tamilnadu, India

DOI: [10.36348/sjmpps.2022.v08i02.001](https://doi.org/10.36348/sjmpps.2022.v08i02.001)

| Received: 23.12.2021 | Accepted: 02.02.2022 | Published: 06.02.2022

*Corresponding author: Abdul Hasan Sathali A

M.Pharm., Ph.D., Principal, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai, Tamilnadu, India

Abstract

Objective: The objective of the present study was to formulate and evaluate polymeric nanoparticles of Felodipine by Nano precipitation technique using EudragitL100 and EudragitS100 as a polymers. The nanoparticles were characterized for particle size, poly-dispersity index, entrapment efficiency (EE), zeta potential, solubility, morphological study, *invitro* study, *Ex vivo* intestinal permeability studies and stability studies. Infrared studies showed that there was no drug excipients interaction. Negative values of zetapotential indicated the good stabilization of the prepared nanoparticles. Solubility measurement studies revealed that the solubility of nanoparticles was increased to ten times than the pure drug. The entrapment efficiency was found in between $29.72 \pm 3.27\%$ – $63.95 \pm 3.50\%$. The *in-vitro* drug release was extended maximum up to 12 hrs with Eudragit L100. The curve fitting data shows that the drug release followed first order kinetics, Higuchi's plots stated non-fickian diffusion controlled. The intestinal permeability of formulated nanoparticles were found to be more than pure drug. SEM shows that nanoparticles were found spherical in structure without aggregation and uniform distribution of the drug within the nanoparticles. Accelerated stability studies were also carried out following ICH Guidelines.

Keywords: EudragitL100, EudragitS100, Felodipine, Nanoprecipitation, Polymeric nanoparticles.

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I. INTRODUCTION

Hypertension is one of the most common disorders throughout the world. Managing hypertension continues to be challenging with the currently available drugs, since they have poor bioavailability by oral route and due to toxicity at higher doses. The solubility and dissolution behavior of a drug is the key determinant to its oral bioavailability. Improvement of oral bioavailability of poor water soluble drugs remains to be one of the most challenging aspects of drug development. Nanoparticulate drug delivery system is one of the best approaches to enhance the dissolution rate and solubility of drugs suffers from oral bioavailability problems. Polymeric nanoparticles are the colloidal drug delivery system with a particle size of 10 – 1000 nm that potentially delivers the therapeutic agent in the systemic circulation in a controlled manner [1]. Nanonization process which reduces the particle size of active pharmaceutical ingredient (API) down to the sub-micron range is a popular technique in

pharmaceutical field for the delivery of poorly water soluble drugs [2]. Felodipine is a BCS class II drug which has poor solubility and high permeability. It is a dihydropyridone calcium channel blocker which acts by decreasing smooth muscle contractility and subsequent vasoconstriction by inhibiting influx of calcium ions through voltage gated L-type calcium channels. Inhibition of initial influx of calcium decreases the contractile activity of smooth muscle cells and results in vasodilation, leading to overall decrease in blood pressure [3]. Felodipine is used in the management of hypertension. The oral bioavailability of felodipine very low, nearly just 15% due to its limited solubility and high first pass metabolism [4]. The present study was aimed to improve the solubility of felodipine by formulating a nanoparticle using eudragit L 100 and eudragit S 100 as a polymer along with stabilizers pluronic F 68 and polyvinyl alcohol.

2. MATERIALS AND METHODS

2.1 MATERIAL

Felodipine was obtained as a Gift sample from Shasun Pvt. Ltd, Pondicherry, India. Eudragit L 100, Eudragit S 100 were obtained as Gift samples from Edict Pharmaceuticals, Chennai and Pluronic F68, Polyvinyl alcohol were also obtained as gift samples from Madras Pharmaceuticals, Chennai, India & Shasun Pvt. Ltd, Pondicherry, India. All other chemicals and solvents used were of analytical grade.

2.2 METHODS

2.2.1 Fabrication of polymeric nanoparticles

Felodipine loaded polymeric nanoparticles were prepared using nanoprecipitation technique. The details of compositions for felodipine nanoparticles as shown in table 1A&1B. A known weight of felodipine (10 mg), polymers (Eudragit L 100, Eudragit S 100) of different ratios (1:10,1:20,1:30,1:40,1:50,1:60&1.70) were dissolved well in 20 ml of methanol, forms an organic phase. An aqueous phase which comprises of 40ml of water containing different concentrations of stabilizers 1% Pluronic F68 & 1% Polyvinyl alcohol. The organic phase was slowly injected on to the aqueous phase under continuous stirring. Nanoparticles form instantaneously by precipitation of the polymer in narrow window of composition, after which the organic solvent was removed by evaporation under continuous stirring for 3- 4 hours. The plain (drug free) nanoparticles were prepared using the same procedure by omitting the drug [5, 6].

3. CHARACTERIZATION OF FELODIPINE POLYMERIC NANOPARTICLES

3.1. Fourier Transform Infrared Spectroscopic analysis (FT-IR)

FT-IR Spectra of Felodipine and Eudragit L 100/ Eudragit S 100 polymeric nanoparticles were recorded using FT-IR Spectrophotometer (Shimadzu, Japan) to investigate any interaction between Felodipine and polymers in formulated nanoparticles. The prepared pellets were scanned over the wave number range from 4000 to 400 cm^{-1} with resolution of cm^{-1} [7, 8].

3.2. Determination of Particle Size, Polydispersity Index and Zeta potential :

The particle size, polydispersity index (PDI) & zeta potential of prepared polymeric nanoparticles were achieved by using Zetasizer 3000 (Malvern Instruments, UK). All the samples were diluted with aqueous phase of the formulation to get optimum measurements. Average particle size in nanometers, polydispersity index and zeta potential were measured [9, 10].

3.3. Determination of % Entrapment efficiency

The amount of felodipine loaded polymeric nanoparticles (entrapped drug) were separated from the aqueous medium by ultracentrifugation method

(Eppendorf Centrifuge, 5417R, Germany) at 14,000 rpm for 90 min at 4°C. Then, the supernatant layer was taken and further diluted with the help of buffer solution. The concentration of free drug present in the supernatant layer was determined by UV-spectrophotometer (shimadzu, Japan). The % entrapment efficiency (EE) was calculated by using the given equation [11].

$$\text{Entrapment efficiency} = \frac{\text{Drug content} - \text{unentrapped drug}}{\text{Drug content}} \times 100$$

3.4. *In vitro* drug release study

The *in vitro* release studies of felodipine from polymeric nanoparticles were performed using dialysis membrane. The nanoparticle equivalent to 10 mg of felodipine was placed in the dialysis bag (donor) and the receptor compartment was filled with 100 mL of 0.1N HCL with 0.1% SLS acid buffer for a period of 2 hours and then it was at pH 6.5 with 0.1% SLS phosphate buffer for the next 10 hours (50rpm at 37°C±2°C). The samples were withdrawn at an interval of 15 minutes for the first 2 hours and 30 minutes interval for the next 10 hours. Fresh medium was replaced each time to maintain constant volume. Samples were analyzed by UV Visible spectrometer [7].

3.5. *In vitro* release kinetics

The mechanism of drug release from polymeric nanoparticles can be reported by studying the drug release kinetic models (zero order, first order, Higuchi's, Hixon-Crowell and Korsmeyer-peppas). The best fitted release kinetic model selected on the basis of regression analysis [5].

3.6. Lyophilization of nanosuspensions

Felodipine nanosuspensions were lyophilized by using freeze dryer (Lyodel-Delvac Pumps Pvt. Ltd, USA) to enhance the chemical stability of polymeric nanoparticles. The freshly prepared nanosuspensions were lyophilized with cryoprotective agent (mannitol). And were rapidly cooled down to -50°C for 2 hours followed by primary drying at 1.03 mbar and secondary drying at 0.001 mbar [12].

3.7. Solubility measurement studies

The solubility of the felodipine loaded polymeric nanoparticles and pure drug in distilled water and phosphate buffer pH 6.5 with 0.1% SLS using mechanical shaker. A known weight equivalent to (10 mg) of felodipine (pure drug) and prepared nanoparticles were separately introduced in to the 25 ml stoppered conical flasks and agitated for 24 hrs. An aliquot was filtered and diluted suitably and analysed by UV-spectrophotometer [13].

3.8. Surface Morphology

This study was performed by scanning electron microscopy (SEM, S-4800, Hitachi

Technologies Corporation, Japan). The nanoparticles were kept on the sample holder and the scanning electron micrographs were taken [14, 15].

3.9. *Ex vivo* intestinal permeability studies

Ex vivo permeation study of felodipine polymeric nanoparticles were carried out on rat intestine (Institutional Animal Ethical Committee Ref. No: IAEC/127/KMCP/261211303/2013-14) using 12 male Wistar albino rats of either sex, were fasted for 18 – 20 hours and followed by anaesthetized. The intestinal segments were isolated and washed with pH 7.4 phosphate saline buffer with 0.1% SLS to remove any mucous and lumen contents. One end of the segment was tied with suture thread and the selected felodipine polymeric nanoparticles and pure drug (equivalent to 10 mg) were injected separately in three parts of the intestinal segments with the help of syringe and other end of intestine was tied with the help of suture thread. The tied intestinal segments was placed in beaker containing 100 ml of pH 7.4 with 0.1% SLS phosphate saline buffer continuously bubbled with 95% O₂ and 5% CO₂ with constant stirring at 100 rpm and maintained at 37°C±2°C. An aliquot sample was withdrawn at time intervals of 15, 30, 60, 90 and 120 minutes. Fresh medium was replaced each time to maintain constant volume. Samples were analyzed by UV Visible spectrometer at 362nm [16].

3.10. Stability Studies

Stability studies were carried out for the selected polymeric nanoparticles formulation (F7) as per the modified ICH guidelines. The formulations were divided into 3 sets of samples and stored at 4°C ± 2°C and 40°C ± 2°C/ 70% ± 5% RH for the period of 1 month. The drug content and entrapment efficiency of all samples were estimated periodically [17].

4. RESULTS AND DISCUSSION

4.1. Fourier Transform Infrared (FT-IR) Analysis

The FT-IR spectra of pure drug (felodipine), excipients and physical mixture of the drug were given in Fig (1-4). After spectral analysis, no significant difference was observed in the characteristic peaks of pure drug felodipine and felodipine loaded polymeric nanoparticles.

4.2. Determination of Particle size, Polydispersity Index & Zeta potential

The particle size of the formulations (F7, F14, F21 & F28) were found to be 192.4nm, 238.7nm, 210.3nm & 298.4nm. The formulations in terms of drug / polymer ratios, surfactant concentration as well as the volume of external phase resulted in significant differences in particle size and good entrapment efficiency. The polydispersity index is a measure of dispersion homogeneity and ranges from 0 to 1, values close to 0 indicates a homogenous dispersion while those greater than 0.3 indicate high heterogeneity. The polydispersity index of formulations

(F7, F14, F21 & F28) were found to be 0.132, 0.165, 0.159 & 0.172, which showed a relative homogenous dispersion. Zeta potential of formulations F7, F14, F21, F28 showed negative charge (-19.4mV, -12.1mV, -16.2mV & -10.9mV) may be due to the presence of terminal carboxylic groups of polymers. High potential values should be achieved in order to ensure a high energy barrier and favor a good stability.

4.2. Determination of entrapment efficiency

The drug entrapment efficiency of all the formulations were in the range of 29.72% to 63.95% as shown in table 2A&2B. Drug entrapment efficiency was found to be maximum (63.95%) in 1: 7 drug: polymer ratio (F7 with Eudragit L100) which was found to be increase with increase in polymer concentration.

4.3. *In vitro* release study

The cumulative % drug release for all the formulations (F1-F28) were shown in Fig (5-8) The drug-polymer composition influences the *in vitro* drug release rate from nanoparticles. The smaller size nanoparticles prepared with lower amount of Eudragit L100 & Eudragit S100 exhibited higher drug release rate, this might be due to the increased nanoparticle surface resulting in larger drug fraction exposed to the dissolution medium and also the higher amount of drug loading. Among that, formulation F7 possessing higher entrapment efficiency 63.95% and least burst release profile 15.71% than the rest of the formulations and *in vitro* drug release of the formulation F7 was found to be 55.37% in 12 hours.

4.4 Kinetics of drug release

The regression coefficient (r²) and n values for all formulations were shown in table 3A&3B. It was found that the *in vitro* drug release of the prepared nanoparticles were best fitted with first order Kinetics and Higuchi model followed by non-fickian diffusion mechanism.

4.5. Solubility measurement studies

The results of solubility studies of pure drug and optimized formulation F7 was shown in table 4. From the results it was observed that the optimized formulation showed better solubility than pure drug in both distilled water and phosphate buffer pH 6.5 with 0.1% SLS may be due to progressive reduction of particle size, increased the solubility of drug.

4.6. Surface Morphology

The SEM Photograph of the selected best formulation F7 Eudragit L 100 with 1% Pluronic F68 were shown in Fig (9). The results indicated that the formulated nanoparticles revealed almost spherical in shape with relative smooth surface.

4.7. *Ex vivo* intestinal permeability studies

Ex vivo permeation studies (diffusion studies) were carried out for pure and optimized formulation

(F7) using intestinal segments like duodenum, jejunum and ileum region. The intestinal permeability of optimized polymeric nanoparticle formulation (F7) showed better permeability than the pure drug and shown in table 5.

4.8. Stability studies

It was confirmed that the formulated felodipine polymeric nanoparticle F7 remained more stable at $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ than $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $70\% \pm 5\%$ RH as per ICH guidelines and the observation was given in Table 6.

Table 1A: Composition of Felodipine loaded polymeric nanoparticles

Formulation Code	Drug: Polymer Ratio	Weight of Drug	Eudragit L 100	Concentration of Pluronic F68	Concentration of Polyvinyl Alcohol
F1	1:10	10mg	100mg	1%	-
F2	1:20	10mg	200mg	1%	-
F3	1:30	10mg	300mg	1%	-
F4	1:40	10mg	400mg	1%	-
F5	1:50	10mg	500mg	1%	-
F6	1:60	10mg	600mg	1%	-
F7	1:70	10mg	700mg	1%	-
F8	1:10	10mg	100mg	-	1%
F9	1:20	10mg	200mg	-	1%
F10	1:30	10mg	300mg	-	1%
F11	1:40	10mg	400mg	-	1%
F12	1:50	10mg	500mg	-	1%
F13	1:60	10mg	600mg	-	1%
F14	1:70	10mg	700mg	-	1%

Table 1B: Composition of Felodipine loaded polymeric nanoparticles

Formulation Code	Drug: Polymer Ratio	Weight of Drug	Eudragit S 100	Concentration of Pluronic F68	Concentration of Polyvinyl Alcohol
F15	1:10	10mg	100mg	1%	-
F16	1:20	10mg	200mg	1%	-
F17	1:30	10mg	300mg	1%	-
F18	1:40	10mg	400mg	1%	-
F19	1:50	10mg	500mg	1%	-
F20	1:60	10mg	600mg	1%	-
F21	1:70	10mg	700mg	1%	-
F22	1:10	10mg	100mg	-	1%
F23	1:20	10mg	200mg	-	1%
F24	1:30	10mg	300mg	-	1%
F25	1:40	10mg	400mg	-	1%
F26	1:50	10mg	500mg	-	1%
F27	1:60	10mg	600mg	-	1%
F28	1:70	10mg	700mg	-	1%

Table 2A: Entrapment Efficiency of Felodipine loaded polymeric nanoparticles

S. No	Formulation Code	Entrapment Efficiency (%) \pm Sd*
1	F1	30.05% \pm 3.53
2	F2	29.72% \pm 3.27
3	F3	31.90% \pm 3.20
4	F4	33.65% \pm 3.60
5	F5	45.66% \pm 1.05
6	F6	57.86% \pm 3.07
7	F7	63.95% \pm 3.50
8	F8	30.81% \pm 2.88
9	F9	31.46% \pm 0.58
10	F10	34.99% \pm 0.63
11	F11	39.42% \pm 3.31
12	F12	43.37% \pm 3.82
13	F13	51.07% \pm 3.33
14	F14	59.38% \pm 1.34

Table 2B: Entrapment Efficiency of Felodipine loaded polymeric Nanoparticles

S. No	Formulation Code	Entrapment Efficiency (%) \pm Sd*
15	F15	31.55% \pm 3.63
16	F16	32.02% \pm 0.82
17	F17	33.05% \pm 1.38
18	F18	35.75% \pm 2.27
19	F19	44.77% \pm 2.07
20	F20	50.22% \pm 2.22
21	F21	58.02% \pm 2.24
22	F22	30.45% \pm 0.15
23	F23	31.90% \pm 1.72
24	F24	34.12% \pm 2.89
25	F25	34.28% \pm 2.48
26	F26	40.48% \pm 1.51
27	F27	46.02% \pm 2.26
28	F28	54.47% \pm 1.24

Table 3A: Kinetics release studies of Felodipine loaded polymeric nanoparticles

Formulation code	Zero order Kinetics		First order Kinetics		Higuchi Model		Korsmeyer-Peppas model		Hixson Crowell	
	R ² value	K ₀ (h ⁻¹)	R ² value	K ₁ (h ⁻¹)	R ² value	K _H (h ⁻¹)	R ² value	n value	R ² value	K _{HC} (h ^{-1/3})
F1	0.988	5.582	0.981	-0.042	0.981	22.77	0.994	0.701	0.991	-0.122
F2	0.99	5.275	0.983	-0.038	0.98	21.46	0.996	0.676	0.993	-0.111
F3	0.982	5.074	0.987	-0.035	0.987	20.72	0.995	0.68	0.992	-0.107
F4	0.984	4.889	0.986	-0.033	0.984	19.9	0.994	0.663	0.992	-0.101
F5	0.979	4.713	0.989	-0.031	0.988	19.23	0.995	0.661	0.992	-0.096
F6	0.985	4.475	0.986	-0.029	0.98	18.23	0.991	0.673	0.99	-0.089
F7	0.984	4.182	0.99	-0.026	0.982	17.00	0.995	0.647	0.993	-0.081
F8	0.982	5.558	0.975	-0.043	0.982	22.59	0.995	0.646	0.987	-0.124
F9	0.984	5.439	0.98	-0.041	0.983	22.13	0.996	0.658	0.99	-0.119
F10	0.986	5.157	0.983	-0.037	0.981	20.95	0.995	0.649	0.991	-0.11
F11	0.985	4.988	0.984	-0.035	0.982	20.29	0.996	0.656	0.991	-0.104
F12	0.986	4.738	0.984	-0.031	0.98	19.29	0.995	0.679	0.99	-0.096
F13	0.986	4.588	0.987	-0.03	0.981	18.68	0.995	0.673	0.992	-0.092
F14	0.986	4.327	0.99	-0.027	0.981	17.59	0.995	0.657	0.993	-0.085

Table 3B: Kinetics release studies of Felodipine loaded polymeric nanoparticles

Formulation code	Zero order Kinetics		First order Kinetics		Higuchi Model		Korsmeyer-Peppas model		Hixson Crowell	
	R ² value	K ₀ (h ⁻¹)	R ² value	K ₁ (h ⁻¹)	R ² value	K _H (h ⁻¹)	R ² value	n value	R ² value	K _{HC} (h ^{-1/3})
F15	0.980	5.659	0.978	-0.044	0.987	23.06	0.996	0.655	0.989	-0.127
F16	0.985	5.493	0.979	-0.041	0.982	22.34	0.996	0.655	0.99	-0.121
F17	0.987	5.258	0.978	-0.038	0.979	21.35	0.995	0.653	0.989	-0.113
F18	0.986	4.999	0.988	-0.035	0.983	20.33	0.995	0.65	0.993	-0.104
F19	0.985	4.903	0.988	-0.033	0.985	19.95	0.994	0.649	0.994	-0.102
F20	0.987	4.504	0.99	-0.029	0.983	18.33	0.995	0.664	0.994	-0.09
F21	0.985	4.397	0.991	-0.028	0.983	17.89	0.996	0.658	0.994	-0.087
F22	0.98	5.612	0.978	-0.044	0.987	22.86	0.997	0.651	0.989	-0.126
F23	0.98	5.528	0.984	-0.042	0.988	22.51	0.996	0.645	0.992	-0.123
F24	0.983	5.408	0.984	-0.04	0.986	22.05	0.996	0.669	0.992	-0.118
F25	0.983	5.039	0.985	-0.035	0.984	20.49	0.996	0.65	0.991	-0.106
F26	0.986	4.993	0.986	-0.035	0.983	20.30	0.996	0.652	0.993	-0.104
F27	0.988	4.658	0.988	-0.03	0.98	18.94	0.995	0.664	0.993	-0.094
F28	0.989	4.411	0.986	-0.028	0.976	17.93	0.993	0.672	0.991	-0.087

Table 4: Solubility studies

Time (Hrs)	Solvent Used	Solubility ($\mu\text{g/ml}$)	
		Pure Drug	Formulation F7
4 hrs	Distilled water	29.91 $\mu\text{g/ml}$ \pm 3.218	117.23 $\mu\text{g/ml}$ \pm 3.215
	Phosphate buffer pH 6.5 with 0.1% SLS	43.89 $\mu\text{g/ml}$ \pm 3.207	260.58 $\mu\text{g/ml}$ \pm 3.210

n=3*

Table 5: *Ex vivo* intestinal permeability studies

Small intestinal segments	Cumulative amount of drug permeated (mg) \pm SD	
	Pure drug	Formulation F7
Duodenum	0.2219 \pm 0.001	0.8592 \pm 0.001
Jejunum	0.2533 \pm 0.008	0.8975 \pm 0.016
Ileum	0.2329 \pm 0.011	0.8743 \pm 0.001

n=3*

Table 6: Stability studies of optimized formulation (F7)

Evaluation parameter	Storing temperature	0 day	1 month
% Drug content	4°C	92.51% \pm 0.10	90.01% \pm 0.05
	40°C /70%RH	92.51% \pm 0.10	87.88% \pm 1.11
% Entrapment efficiency	4°C	62.82% \pm 1.34	60.79% \pm 1.07
	40°C /70%RH	62.82% \pm 1.34	58.81% \pm 1.92

n=3*

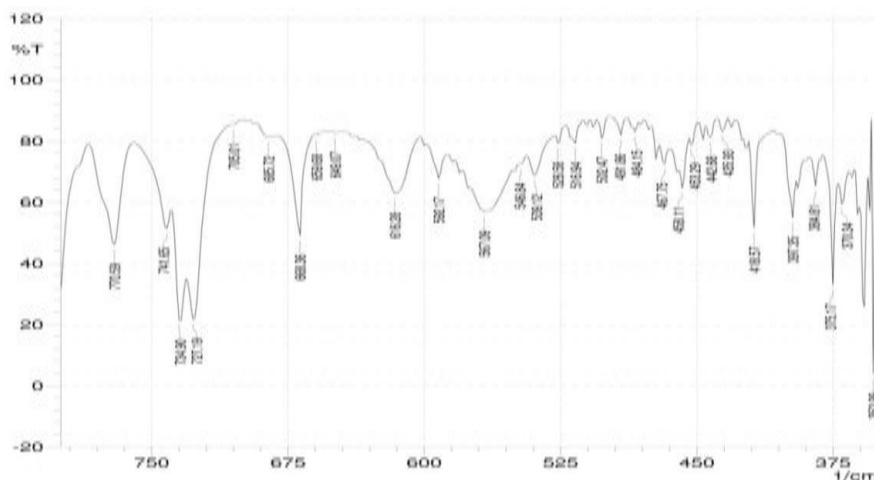


Figure 1: FT- IR spectra of pure Felodipine

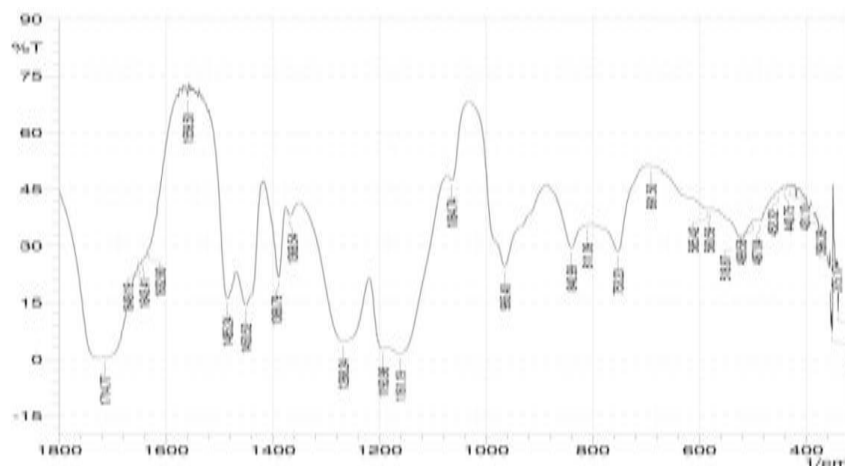


Figure 2: FT- IR spectra of Eudragit L 100

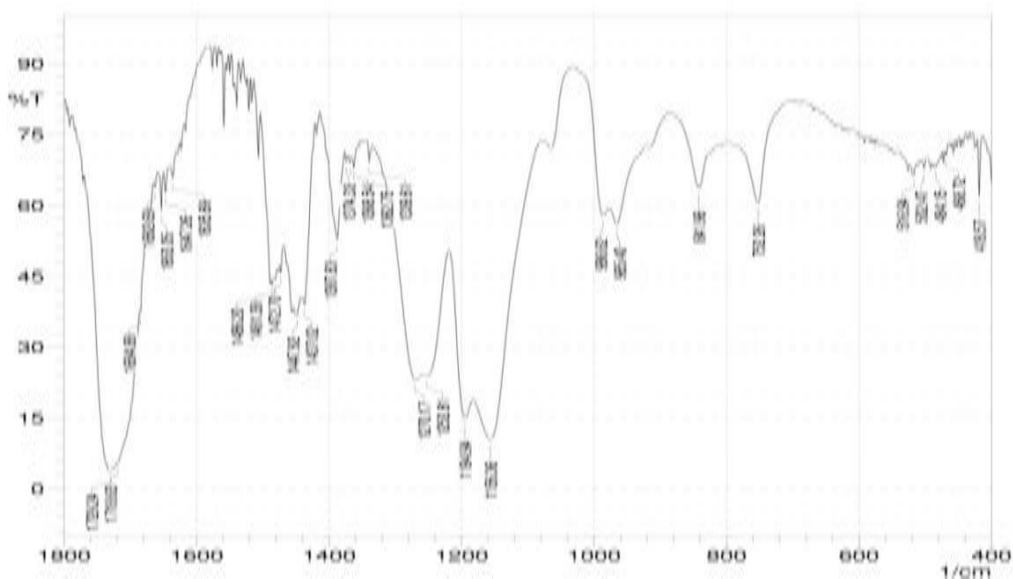


Figure 3: FT- IR spectra of Eudragit S 100

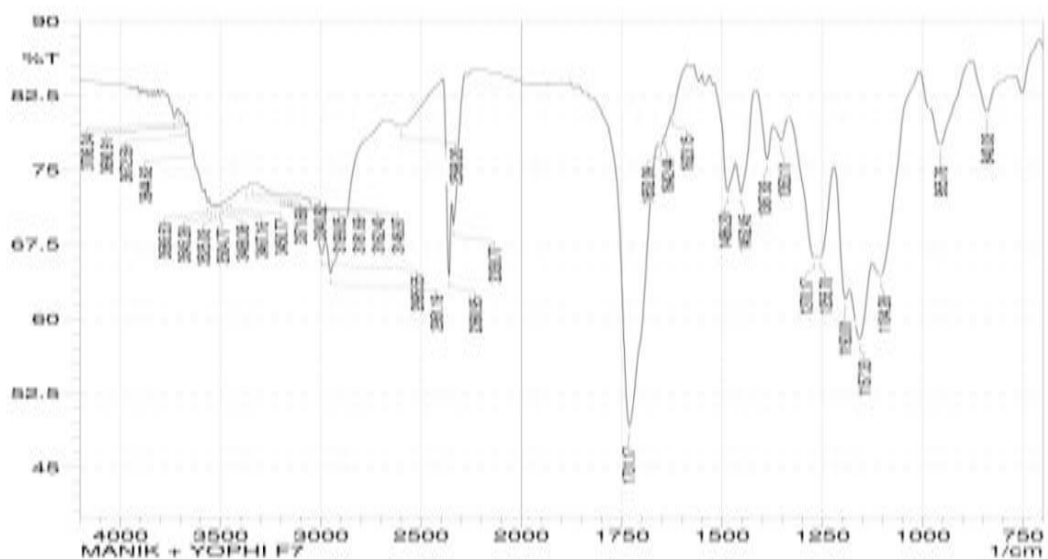


Figure 4: FT- IR spectra of optimized polymeric nanoparticles formulation F7

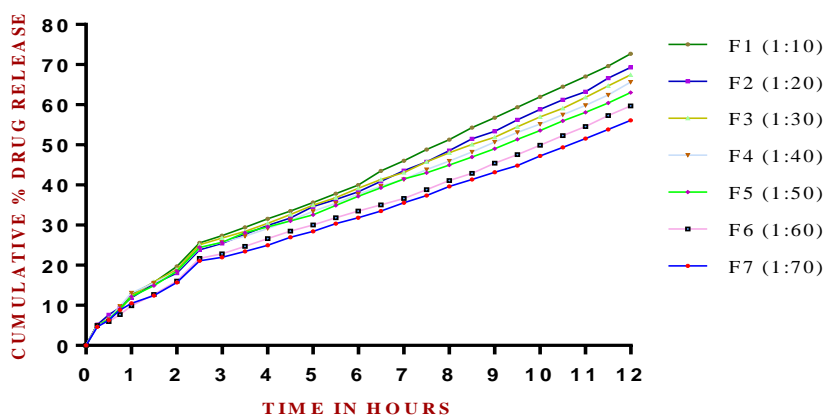


Figure 5: Cumulative % drug release of formulations (F1 –F7)

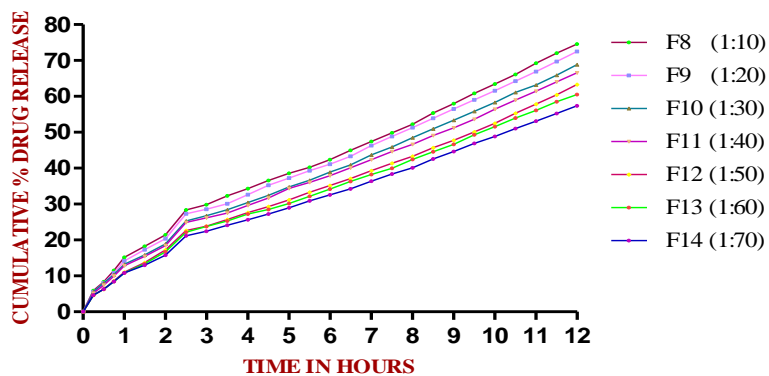


Figure 6: Cumulative % drug release of formulations (F8 –F14)

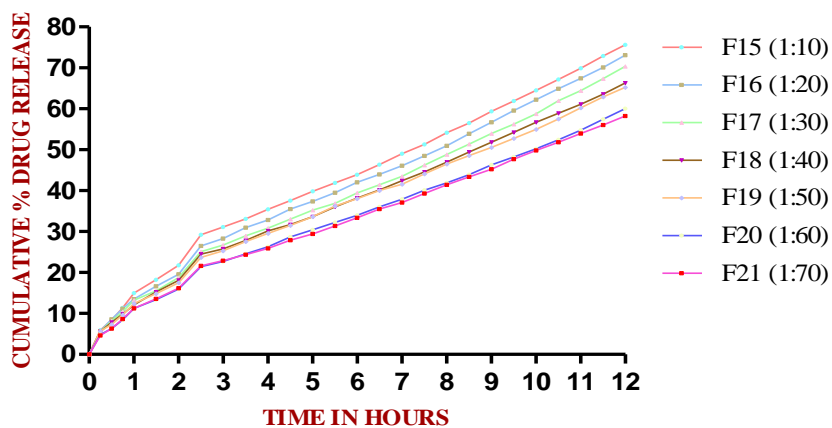


Figure 7: Cumulative % drug release of formulations (F15–F21)

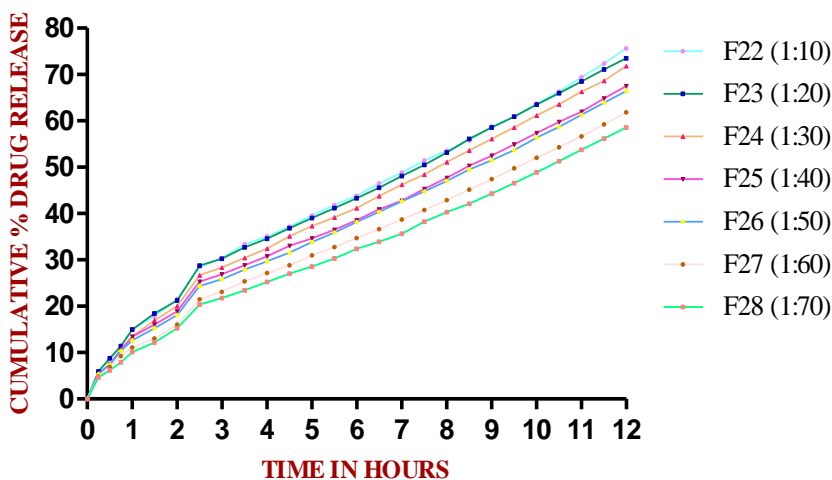


Figure 8: Cumulative % drug release of formulations (F22–F28)

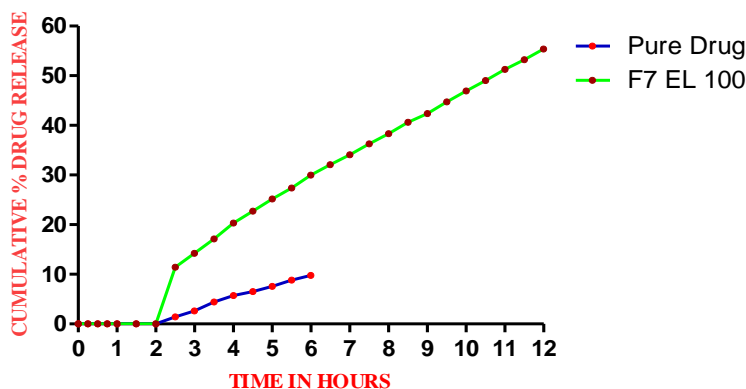


Figure 8: Cumulative % drug release of pure drug and formulation F7

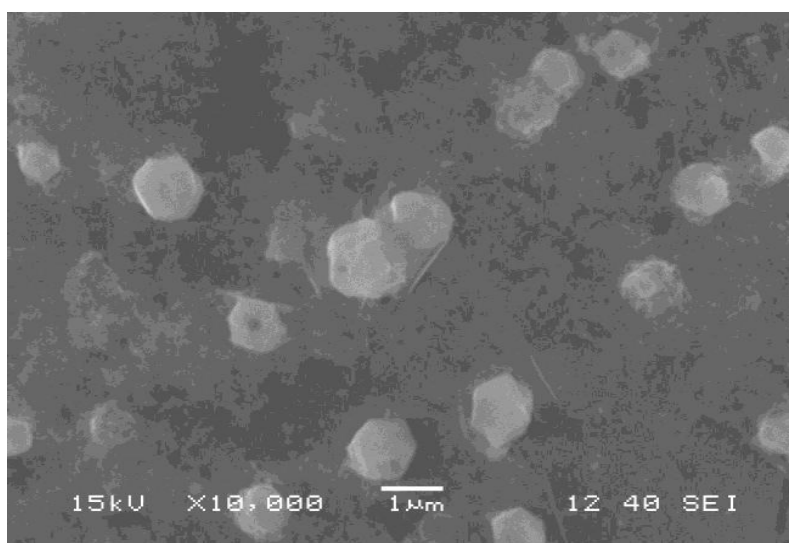


Figure 9: SEM analysis of optimized formulation F7

CONCLUSION

Felodipine loaded polymeric nanoparticles were prepared by Nano precipitation technique. Drug-polymer excipient comparability was confirmed by FT-IR studies. The method resulted in consistent production of smaller size nanoparticles with narrow size distribution and good entrapment efficiency. The solubility and *ex vivo* intestinal permeability studies suggested that the formulated polymeric nanoparticles can improve the bioavailability of felodipine. The formulated polymeric nanoparticles showed slow release of drug with the reduced burst release than pure drug. These results may prove to be beneficial for the prolonged utilization of the formulation as an adjuvant anti-hypertensive therapy. Thus, the polymeric nanoparticles may provide an effective drug delivery for poorly water soluble lipophilic drugs.

ACKNOWLEDGEMENT

The authors would like to gratefully acknowledge the Dean Dr. A. RATHINAVEL, M.S, M.Ch, Ph.D. Madurai Medical College, Madurai, for providing the necessary facilities to carry out this research work.

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