Journal of Current Pharma Research
(An Official Publication of Human Journals)
An International Peer Reviewed Journal For Pharmacy, Medical & Biological Science
DOI: 10.25166 CODEN: JCPRD6 NLM ID: 101744065
ISSN: Print: 2230-7834 Online: 2230-7842
SJIF Impact Factor: 6.913

Human Journals
Research Article
August 2023 Vol.:18, Issue:3

Development of Lipidic Drug Delivery System for Bioavailability Improvement of Poorly Water-Soluble Antihypertensive Drug

Journal of Current Pharma Research
(An Official Publication of Human Journals)
An International Peer Reviewed Journal For Pharmacy, Medical & Biological Science
DOI: 10.25166 CODEN: JCPRD6 NLM ID: 101744065

Rakesh Chander Joshi[1*], Aarti Kori [2], Shivanand Patil[3]

M. Pharm, Department of Pharmaceutics, Shri Dev Bhoomi Institute of Education and Sciences and Technology, Pondha Rd, Majhaun, Dehradun, Uttarakhand, 248001, India.

Associate Professor, Department of Pharmaceutics, Shri Dev Bhoomi Institute of Education and Sciences and Technology, Pondha Rd, Majhaun, Dehradun, Uttarakhand, 248001, India.

Submitted: 01 August 2023
Accepted: 21 August 2023
Published: 25 August 2023

HUMAN JOURNALS
www.jcpr.humanjournals.com

Keywords: Lipidic Drug Delivery System, Bioavailability, Antihypertensive Drug

ABSTRACT

Felodipine nanosponges were prepared successfully by using two different polymers, namely hydrophobic polymers (ethyl cellulose, Eudragit) by an emulsion solvent diffusion technique. This production method has been found to be simple, requires no special equipment and is scalable. Preformulation studies were performed to determine the solubility of felodipine. The average particle size of formulations F2 was 5112 nm. The Zeta potential values of the nanosponge showed that the prepared nanosponges are stable. The amount of drug trapped in the nanosponges was calculated and it was found that all prepared nanosponges have high blocking efficiency. From the in vitro release data of the diffusion method, it was found that formulation F2 showed the best release of 40.87% at the end of 12 hours. An increase in drug release as a function of the drug to polymer ratio was observed. It was observed that drug release decreased with increasing amounts of polymer in each formulation. This is because the newly developed nanosponges probably have a core-shell structure with a hydrophobic core formed by ethyl cellulose (F1-F3) and Eudragit (F4-F6) and a hydrophilic shell formed by PVA macromolecules. For drug release, the effect of polymer type and drug: polymer ratio on the drug release from formulated felodipine nanosponges was investigated. The type of polymer was found to have no significant effect on the drug release pattern, while the drug: polymer ratio had a significant effect on the drug release pattern. As the ratio of drug to polymer increases, drug release from the nanosponges decreases. Data obtained from the in vitro release study were fitted to models used to elucidate the release mechanism of felodipine from the nanosponges. The in vitro release model best fits the Korsemeyar-Peppas model. The range of r2 values for these models is 0.994. It is found that formulation (F2) followed the anomalous behavior of non-Fickian diffusion. Felodipine nanosponges can be prepared by a cost-effective and simple emulsion solvent diffusion method using hydrophobic polymers such as ethyl cellulose and Eudragit. The formulated felodipine nanosponges can be used in the treatment of hypertension and produce the drug continuously, which in turn reduces the dose, frequency and side effects.

INTRODUCTION

Oral administration is still the preferred method for most prescriptions. Some drugs have the expected good absorption through the GI tract, while other drugs can cause problems. The U.S. Food and Drug Administration (FDA) introduced classifications for biopharmaceuticals in 1995. [1], which classifies drugs according to their solubility (dissolution rate) and intestinal permeability. There is an increasing number of new drugs in Class II-IV, and many of them have differential effects on the human GI tract. [2]. On the other hand, the poor bioavailability of oral intake materials makes them difficult to manufacture. Aqueous solubility, chemical permeability, dissolution rate, first-pass metabolism, pre-system metabolism and sensitivity of flow mechanisms are some of the factors that affect oral bioavailability. Poor solubility and permeability are the common causes of oral bioavailability problems. One of the most important factors in reaching the desired drug concentration in the body system and obtaining the desired drug response is solubility. Poorly water-soluble drugs often require injection to reach plasma concentrations after oral administration. [3]. Low water solubility is a major problem in new drug products and new formulations. At the point of absorption, all drugs to be absorbed must be in the form of an aqueous solution. Water is mostly preferred solvent for liquid formulations. Most chemicals have low water solubility and are weakly acidic or basic. [4]. Hypertension is a heart disease that causes high blood pressure. High blood pressure was responsible for 45 percent of ischemic heart disease deaths and 51 percent of stroke deaths in 2008, according to the World Health Organization in Geneva. While 600 million people had high blood pressure in 1980, this number increased to 1 billion in 2008, making treatment more difficult. Many studies have shown that the incidence of hypertension has increased in India in the past. In their research, Kearney et al. [5] anticipated that the burden of hypertension in India will quadruple from 118 million in 2000 to 213.5 million in 2025. CVD risk increases from an SBP level of 180 mm Hg in a straight line to the often-neglected DBP value of 105 mm Hg. A 20 mm Hg increase in SBP and a 10 mm Hg increase in DBP are associated with an increased risk of death from stroke, heart disease, or other vascular diseases. Higher SBP and DBP have been associated with an increased risk of CVD, angina, myocardial necrosis (MI), heart failure (HF), stroke, peripheral vascular disease and gastric aortic aneurysm in younger adults. SBP is reliably linked to increased CVD [6]. Although there are many types of antihypertensive drugs, most of them do not treat high blood pressure due to water insolubility, resulting in a lack of bioavailability (BA). Some antihypertensive drugs are substrates of P-gp and cause

first-pass metabolism, resulting in decreased bioavailability. Antihypertensive drugs have other disadvantages such as short half-lives and frequent use. Designing a release model is a process that addresses many drug-related issues. In this case, nanomedicine or nanotherapy opens up new avenues to deliver therapeutic drugs to diseased areas and keep them there longer. Nanomedicine also inhibits hepatic first-pass metabolism, P-gp-mediated efflux and target specificity, allowing long-term therapy. Various innovative drug delivery techniques, such as buccal [7], gastroretentive [8], osmotic controlled, solid dispersion, and liquid solid compacts, were developed in the early 2000s [9].

Materials and methods Drugs and chemicals:

Felodipine, Polyvinyl alcohol, Ethyl Cellulose, Eudragit RS 100, Dichloromethane, Potassium

Dihydrogen Orthophosphate, Sodium hydroxide pellet, Methanol, Disodium hydrogen phosphate, Nitrocellulose membrane

Methods:

Preformulation Studies:

Preformulation testing is the study of the physical and chemical properties of a drug substance alone and when mixed with excipients. The overall goal of preformulation testing is to generate data useful for developing a stable and bioavailable formulation.

Physical characteristics:

The drug sample was evaluated for its physical characteristics like colour, odour, taste and appearance and the results were recorded.

Solubility test:

Felodipine powder of about 1gm was taken in a test tube and solubility in ethanol, DMSO, DMF, water, and dichloromethane was tested.

Melting point:

The melting point of felodipine samples was determined by the open capillary method. The device was calibrated prior to examination and immediately afterward, the felodipine sample was placed in a vessel each 6 mm long and 1 mm in diameter. The capillary is supplied

vertically to the device and heated at 10 °C per minute. Readings were made three times. The melting point of the drug was recorded and compared with the standard used by the Indian Pharmacopoeia.

Determination of Absorbance maximum (λ_{max}):

Scan the sample solution in the 200-400nm range on a UV spectrophotometer using methanol, 0.1N HCl, pH 6.8 phosphate buffer as a blank. The maximum absorbance was observed as 364 nm. The maximum absorption of felodipine at 238 and 361 nm was recorded and compared with the ʎmax value of the standard specified in Indian Pharmacopoeia.

Preparation of Calibration medium:

Phosphate buffer pH 6.8:

As per I.P. standard 50ml of 0.2M potassium dihydrogen phosphate and 22.4ml of 0.2M sodium hydroxide solution were taken in a volumetric flask and made up to 200ml.

Preparation of 0.2M Potassium Dihydrogen Phosphate:

Weigh 27.218 gm of potassium dihydrogen phosphate and take in into the volumetric flask containing distilled water dissolve thoroughly finally make up to 1000ml**.**

Preparation of 0.2M NaOH:

Weigh 8gm of sodium hydroxide pellets taken to the volumetric flask containing distilled water dissolve thoroughly makeup to 1000ml.

Preparation of stock solution:

The weight of pure Felodipine (100 mg) is transferred to a 100 ml container by preparing a standard stock of Felodipine. Dissolve the drug in phosphate buffer and dilute to 100 ml with buffer to obtain a stock solution of 1000µg/ml.

Construction of Calibration Curve of Felodipine:

For initial dilution, pipette 10 ml of the stock solution into a 100 ml flask and dilute to 100 ml with buffer to obtain a 100 µg/ml solution. Take 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10ml of stock solution as in a 10ml container and use pH 6.8 phosphate buffer to maintain volume to achieve a concentration range of 10-100µg/ml, the absorbance of these solutions is, measured

at 364 nm using a UV spectrophotometer. Phosphate buffered saline pH 6.8 was used as blank. Plot the calibration curve of the concentration and absorbance.

Drug Excipient Compatibility Studies:

Record the FT-IR spectrum of the solution using an FT-IR spectrophotometer. Diffuse reflection technology is used in the mid-infrared 4000-400 cm-1 spectral region. The process is to disperse the sample in KBr using a mortar, grind the material into a fine powder bed using a manometer, and place it in a holder. The pressure is about 5 tons for 5 minutes. Place the object in the light path and record the spectrum. The peak properties of functional groups are described. FT-IR spectra were recorded for felodipine, the polymer ethylcellulose and Eudragit. The spectra of formulations containing felodipine, polymers and copolymers were also recorded to check their compatibility.

Formulation of Felodipine Nanosponges

Felodipine-loaded nanosponge was prepared using the appropriate polymer emulsion solvent diffusion method. The dispersed phase contains the specified drug and the polymer dissolved in 20 ml of dichloromethane. The aqueous phase has an indication that polyvinyl alcohol is dissolved in 100 ml of water. The dispersed phase was added dropwise to the aqueous phase with stirring at 2000 rpm for 2 hours on a magnetic stirrer. The resulting nanosponges were collected by filtration and dried in an oven at 40°C for 24 hours. They were then placed in a vacuum desiccator to remove residual solvent. Production of felodipine nanosponges using ethylcellulose and Eudragit polymers.

TABLE 1: FORMULATION OF FELODIPINE NANOSPONGES

S.No	Drug	Formulation Code	Polymer	Drug: Polymer Ratio
1	Felodipine	F1	Ethylcellulose	1:2
2		F2		1:4
3		F3		1:6
4		F4	Eudragit	1:2
5		F5		1:4
6		F6		1:6

CHARACTERIZATION OF NANOSPONGES:

Particle Size Determination:

The average mean diameter and size distribution of loaded nanosponges is found by the dynamic scattering method using Malvern Zetasizer at 25°C. the dried nanosponges were dispersed in water to obtain proper light scattering intensity for felodipine nanosponges.

Determination of Zeta Potential:

The zeta potential is a measure of the surface charge. The number of nanosponges can be determined using a zetasizer (Malvern Instruments) with a zeta cell, a polycarbonate cell with a gold-plated electrode, and water as the sample preparation medium.

Determination of percentage yield:

Felodipine-loaded Nanosponge was weighed after drying. Percentage yield was calculated by

$$\% \text{ yield} = \frac{\text{Practical weight of nanosponges obtained}}{\text{Theoretical weight (drug + polymers)}} \times 100$$

Determination of Entrapment Efficiency:

The amount of felodipine encapsulated in the nanosponge was separated from the aqueous medium by ultracentrifugation at 8000 rpm for 10 min at 4°C, then the supernatant was suitably diluted with no chemicals and measured with a UV spectrophotometer at 364 nm Absorbance. The amount of entrapped drug was calculated from the equation.

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

Drug content:

The prepared nanosponge formulations of felodipine were tested for their drug content. Then a quantity of powder equivalent to 5mg was triturated properly mixed with phosphate buffer pH 6.8 and the total content was analyzed at 364nm by using UV spectrophotometer.

$$\text{Drug Content} = \text{Sample Absorbance} \times 100 \text{ Standard absorbance}$$

Scanning Electron Microscopy:

SEM analysis was performed to determine the microscopic properties (shape and morphology) of the prepared felodipine nanosponges. The nanosponges were properly prepared and dried to remove moisture and images were taken at different magnifications using an electron microscope (CARL ZEISS, BRUKER). Put the sample on a glass slide stored in a vacuum, and then use a connected electric machine running at high speed, such as 15kv, to heat the sample.

X-ray powder diffraction:

The crystal form of the felodipine nanosponges was recorded using an X-ray diffractometer. The X-ray diffraction pattern (XRD) study of felodipine nanosponge will be performed using an X-ray diffraction meter with Cu as the target filter, voltage/current 40KV/40Ma and scanning speed 1○/min. The sample will be examined over a 2θ angle of 4° to 90°.

Thermal analysis:

Thermal analysis is used to demonstrate interactions between chemicals, polymers, and copolymers. DTA and TGA are performed using cold liquid nitrogen. The analysis was carried out under dry nitrogen removal. Put 2-5 mg of the sample into an aluminum crucible and crimp the cap tightly to ensure an adequate seal. Heat the sample from low temperature to 300°C with a heating rate of 10C/min.

***In Vitro* Release Studies:**

Drug dissolution was determined in a USP type II dissolution apparatus equipped with eight rotating paddles and tubes. Six formulations were used for release studies and experiments were performed in triplicate. Use 900 ml of pH 6.8 phosphate buffer at 100 rpm. The temperature of the dissolution medium was maintained at 37°C and at the scheduled times 5 ml of sample was removed and filtered. Finally, analyze the filtered sample using a UV spectrophotometer at 364 nm.

***In Vitro* Drug Release Kinetics:**

The drug release kinetics of felodipine nanosponges were determined by plotting the following kinetic model using data collected from in vitro studies (zero order, first order and

Higuchi equations). Determination of drug release mechanism using the Korsemeyar-Peppas equation.

Zero Order Kinetics:

The cumulative amount of drug release was plotted against time.

$$C = K_0 t$$

Where k_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to k_0 and intercept the origin of the axis. This kinetics describes concentration-independent drug release from the formulations.

First Order kinetics:

The first-order graph is plotted by logging the cumulative percentage of drug release remaining vs. time. This kinetics describes concentration-dependent drug release from the formulations.

$$\text{Log } C = \text{Log } C_0 + k_t \backslash 2.303$$

Where C_0 is the initial concentration of the drug, k is the first-order constant, and t is the time.

Higuchi's Model:

Higuchi's model as cumulative percentage release of drug released vs. square root of time.

$$Q = Kt_{1\backslash 2}$$

Where k is the constant reflecting the design variables of the system and t is the time in hours. This model describes the release of drug on the basis of Fickian diffusion as a square root of the time-dependent process of the swelling matrix.

Korsmeyer-Peppas Equations:

The mechanism of drug release, the first 60% of drug release were plotted in korsmeyer et al's equation log cumulative percentage drug release vs. log time and the exponent n was calculated through the slope of the straight line.

$$M_t \backslash M_\square = Kt_n$$

Where $M_t \backslash M_\square$ is the fractional solute release, t is the release time, and K is a kinetic constant characteristic of the mechanism of release tracers. This type of drug release is controlled by a combination of polymer swelling, erosion and diffusion through a hydrated matrix.

Results and Discussion

Preformulation studies:

Physical characteristics:

Physical observation of the drug disclosed that felodipine is an odourless, white-coloured crystalline powder.

Solubility:

Felodipine is soluble in ethanol, dichloromethane, sparingly soluble in DMSO, DMF and insoluble in water.

Melting point:

The melting point of the felodipine was found to be 142°C.

Selection of Wavelength:

The felodipine was examined by using spectrophotometrically between 200-400nm. The maximum absorbance (λ_{max}) was foraged at 364nm which was used for quantitative analysis.

Calibration Curve of Felodipine:

In the calibration curve, linearity was obtained between 10-100µg\ml concentration of felodipine and the regression value for the formulation was obtained to be 0.996. So, we can compute that felodipine obeys Beer Lambert's law at a concentration between 10-100µg\ml. The results are shown in Table 2.

Table 2: Calibration curve of felodipine

S.NO	Concentration(µg\ml)	Absorbance at 364nm
1	10	0.009
2	20	0.012
3	30	0.018
4	40	0.025
5	50	0.029
6	60	0.036
7	70	0.042
8	80	0.048
9	90	0.054
10	100	0.062

Drug- Excipients compatibility studies:

Fourier Transform Infrared Spectroscopy:

Fourier transform infrared (FT-IR) spectra of the samples were achieved using an FTIR spectrophotometer by the KBr disc method. The spectrums were recorded for the pure drug and nanosponge formulations.

Table 3: FTIR interpretation of Ethyl cellulose, Eudragit and PVA

Transition	IR Range (cm^{-1})	Absorption wave number (cm^{-1})		
		Ethylcellulose	Eudragit	PVA
O-H stretching	3650-3200	3473.56	3629.78	3566.14
C-H stretching	2700-3300	2874.70	3002.00	
CH3 stretching	2850-2970	-	-	2947.03
C=O stretching	1820-1665	1735.07	-	-
C=C stretching	1680-1620	1645.67	-	-
N-H bending	1500-1800	-	1717.49	
C-H bending	1300-1500	-	1457.27	-
COOH	1500-1760	-	-	1507.27
C-O stretching	1300-1000	1109.96	1163.96	1218.93
C-H rocking	600-800	-	-	771.47

Table 4: FTIR interpretation of felodipine and formulations (F1-F6)

Transition	IR range (cm^{-1})	Absorption wave number (cm^{-1})						
		Felodipine	F1	F2	F3	F4	F5	F6
NH group	3500-3300	3371.34	3357.84	3367.48	3312	3487	3523	3495
O-H stretching	3650-3200		3232.47	3232.47	3233	3337	3400	3234
Aromatic CH stretching	3050-3000	3069.50	2975.96	3099.39	3063	2995	2995.2	3339
CH stretching of CH_3 and CH_2	2960-2850	2947.99	2975.96	2874.70	2931.60	2951	2951	2951
C=O stretching	1820-1665	1698.21	1777.28	1702.06	1796.57			
C=C stretching	1680-1620		1647.10	1635.52	1700.13			
N-H bending	1500-1800	1622.02	1700.13		1647.10	1564	1715	1569
C=C ring stretching	1600-1480	1496.66	1497.62	1488.94	1488.94	1487	1556	1488
C-H bending	1300-1500			1307.65		1386	1371	1387
COOH	1500-1760		1563.20		1580.56	1715	1556	1716
C-O-C stretching	1320-1210	1277.75	1214.11	1211.21	1213.14	1271	1271	1271
C-O stretching	1300-1000		1054.99	1056.92	1055.95	1161	1056	1162
C-H rocking,	600-800	770.51	649.97	668.29	675.04	669	677	751
Cl stretching	500-600	566.07	555.46	533.28	507.24	524	525	508

Formulation of nanosponges:

Six formulations of felodipine nanosponges (F1-F6) were developed with two different polymers i.e. Ethyl cellulose and Eudragit by using the emulsion solvent diffusion method.

Table 5: Formulation of felodipine nanosponges by emulsion solvent diffusion technique

s.no	Formulation code	Weight of drug(mg)	Weight of polymer(mg)		Weight of PVA(mg)
1	F1	5	Ethylcellulose	10	10
2	F2	5		20	10
3	F3	5		30	10
4	F4	5	Eudragit	10	10
5	F5	5		20	10
6	F6	5		30	10

CHARACTERIZATION OF FELODIPINE NANOSPONGES:

Particle size Measurement:

Size is one of the most important factors for the properties of nanosponges. The particle size of the prepared felodipine nanosponge (F2) was measured using a Malvern zetasizer. Particle size analysis showed that the average size of the felodipine nanosponge using ethyl cellulose was 5112 nm, with a polydispersity index (PDI) value. 1,000 and effect 1.22. The particle size of Nanosponges must be less than 5µm. The average particle size analysis of Ethyl cellulose- Felodipine was less than 5µm.

Determination of zeta potential:

Zeta potential was determined using a Malvern zetasizer meter. The -13.2-zeta potential was found with the highest usage area at 42.4%. These results show the stability of the model (F2).

Percentage Yield Analysis:

From the results, we can conclude that as the concentration of polymer increases the percentage yield also increases. It can also be noted that the yield obtained while using ethyl cellulose as the polymer is much higher when compared to Eudragit.

Table 6: percentage yield of nanosponge formulations (F1-F6)

Formulation code	Percentage yield
F1	73.02%
F2	75.07%
F3	76.42%
F4	70.36%
F5	75.08%
F6	78.56%

Entrapment Efficiency:

Formulation (F2) has the highest encapsulation efficiency at 87.97% and formulation (F4) has the lowest encapsulation efficiency at 68.77%. The change in encapsulation efficiency is due to the change in polymer concentration and the difference in the degree of cross-linking. The prepared nanosponge has a high drug encapsulation of 87.97%.

Table 7: Entrapment efficiency of formulations (F1-F6)

s.no	Formulation code	Entrapment efficiency (%)
1	F1	74.57%
2	F2	87.97%
3	F3	84.49%
4	F4	68.77%
5	F5	77.61%
6	F6	76.80%

Drug content:

The drug content was discovered to be highest for formulation (F2) which is 81.05% and the lowest drug content was found to be 68.01%.

Table 8: Drug content of felodipine nanosponges (F1-F6)

Formulation code	% Drug content
F1	70.90±0.06
F2	81.05±0.53
F3	78.17±0.48
F4	68.01±0.67
F5	74.70±0.27
F6	73.08±0.01

Scanning Electron Microscopy:

SEM analysis of the pure drug of felodipine and formulation (F2) was carried out to evaluate the surface morphology of nanosponges. SEM images show that nanosponges are porous with smooth surface morphology and spherical shape. Due to the evaporation of the solvent, it was found that the nanosponge shell is smooth and porous, the outer surface is shiny and smooth, and the inner surface is porous. The presence of pores is due to the consideration of diffusion of the solvent dichloromethane.

X-ray powder diffraction:

X-ray diffraction is used to predict the crystal properties of the prepared nanosponges and their ability to act as catalysts. The XRPD pattern of the felodipine nanosponge shows that the material is less crystalline. The maximum value in the diffractogram is approximately 10.1 °C, 11.4°C and 23.9°C were observed. However, the felodipine nanosponge showed a broad spectrum and not a crystalline form. May help increase the rate of degradation of nanosponge formulations.

Thermal analysis:

The DTA curve of pure felodipine shows a melting exotherm of 143.3 °C. For this reason, thermograms of the drug were compared and a correlation was found with other formulations and drug polymers. Curves obtained in TGA are shown as a weight loss of 0.87% corresponding to a melting point of 142-145°C for felodipine. No weight loss was observed before the melting temperature, indicating poor water quality. The melting peak was followed by the degradation peak indicating that the heavy drug started at 299.8 °C. Thermal analysis

of drug-loaded nanosponges showed that the crystallinity of the drug decreased, its thermodynamic energy increased and it was amorphous.

In vitro drug release studies:

An in vitro drug release study of the prepared formulations (F1-F6) was performed using type II dissolution apparatus. The amount of drug released in different time intervals was observed. From the in vitro release data, it was found that in all six felodipine nanosponge formulations, the F2 formulation showed an initial immediate release followed by a sustained drug release after 12 hours. After 4 hours the drug was continuously released, showing that felodipine was encapsulated in the nanostructures.

Table 9: Percentage of cumulative drug release of felodipine nanosponges (F1-F6)

s.no	time	Cumulative percentage drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	18.57±0.53	12.02±0.50	14.15±0.49	6.03±0.03	7.85±0.14	7.06±0.81
3	2	23.28±0.83	15.83±0.17	14.63±0.61	17.74±0.19	11.05±0.17	11.76±0.96
4	3	26.93±0.51	24.47±0.27	21.66±0.45	19.18±0.44	20.66±0.34	19.86±0.70
5	4	31.08±0.78	25.26±0.63	24.84±0.68	24.78±0.68	24.78±0.99	23.75±0.80
6	5	33.43±0.80	26.38±0.46	29.68±0.06	28.29±0.26	31.42±0.45	32.80±0.60
7	6	35.63±0.19	27.70±0.14	32.66±0.22	29.13±0.24	34.89±0.05	36.62±0.26
8	7	37.85±0.91	29.86±0.22	38.20±0.57	33.43±0.51	39.27±0.09	41.08±0.04
9	8	39.98±0.43	31.73±0.01	41.36±0.55	39.61±0.07	43.02±0.15	45.44±0.19
10	9	43.48±0.04	34.64±0.53	43.53±0.43	42.36±0.12	46.96±0.28	49.88±0.63
11	10	46.01±0.27	36.35±0.82	53.37±0.06	47.36±0.46	49.09±0.01	52.28±0.06
12	11	48.80±0.04	38.30±0.57	56.23±0.74	50.99±0.26	53.53±0.63	55.07±0.75
13	12	51.31±0.37	40.87±0.23	61.85±0.16	53.04±0.14	58.07±0.12	59.62±0.81

In-vitro drug release kinetics:

Data from in vitro release studies were used to fit the kinetic model. This led to an understanding of the mechanism of drug release from felodipine nanosponges. To determine the release pattern, in vitro release data were analyzed according to zero order, first order, Higuchi and Peppas models. The choice of certain methods depends on the coefficient of

determination of the unlearned (r2) and the r2 value is higher in the Peppas model chosen as the best model. This is confirmed by the range of r2 values for Peppas model 0.994. Formula (F2) has been shown to follow non-Fickian diffusion.

CONCLUSION

Felodipine nanosponges were successfully prepared by emulsion solvent diffusion method with two different polymers, namely hydrophobic polymers (ethylcellulose, Eudragit). This production method has been shown to be simple, requires no special equipment, and can be done efficiently. Preliminary studies have been conducted to investigate the solubility of Felodipine. Solubility testing shows that felodipine is insoluble in water, but soluble in ethanol, methanol, dichloromethane and other solvents. FTIR and UV spectroscopic studies confirmed the spectra obtained by comparing the chemical to a pure chemical standard. The UV spectrum provides maximum absorption at 364 nm. Comparison of the FTIR spectra of felodipine and nanosponge formulations confirmed the absence of new peaks and the disappearance of existing peaks of the drug peak. This shows that there is no interaction between the drug and the polymer used in this study. Scanning electron microscopy analysis of the prepared nanosponges at different magnifications showed that the nanosponges were porous with smooth surface topography and spherical shape. The sponginess and porosity of the nanosponges are clearly visible in the SEM images. Size and zeta potential were determined with a Malvern zetasizer. Dimensional analysis confirmed that the prepared samples were in the nanometer range. Formulation F2 had an average particle size of 5112 nm. The zeta potential values of the nanosponges indicate that the formulated nanosponges are stable. Based on in vitro release data from the diffusion method, the F2 formulation was found to deliver a 40.87% concentration after 12 hours. An increase in drug release was observed as a function of drug: polymer ratio. It was observed that the release rate decreased with the increase of polymer for all formulations. This is because the new nanosponges are believed to offer a structural shell with a hydrophobic core made of ethylcellulose (F1-F3) and Eudragit (F4-F6) and a hydrophilic shell made of PVA macromolecules. The effect of polymer and drug: polymer ratio on the drug release profile of felodipine nanosponges was investigated. It was found that the polymer type did not have a significant effect on the drug release profile, while the drug: polymer ratio had a significant effect on the drug release. As the drug: polymer ratio increased, the drug release from the nanosponges decreased. Data from in vitro release studies were fitted to a model used to find the drug release mechanism from felodipine nanosponges. The best in vitro release model for the Korsemeyar-Peppas

model. The r2 value range for this example is 0.994. Formulation (F2) has been shown to follow the negative behavior of non-Fick diffusion. Felodipine nanosponges can be produced by a cost-effective and simple emulsion solvent diffusion method using hydrophobic polymers such as ethylcellulose and Eudragit. Formulated felodipine nanosponges can be used to treat hypertension and generate drug release, thereby reducing the amount, frequency and side effects.

REFERENCES

1. Food and Drug Administration. (2000). Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Food and Drug Administration, Rockville, MD.
2. Broccatelli, F., Cruciani, G., Benet, L. Z., &Oprea, T. I. BDDCS class prediction for new molecular entities. Molecular pharmaceutics, 2012; 9(3):570- 580.
3. Dudhipala N. Influence of Solid Lipid Nanoparticles on Pharmaco-dynamic Activity of Poorly Oral Bioavailable Drugs. International Journal of Pharmaceutical Sciences and Nanotechnology. 2020 Jul 11; 13(4):4979-83.
4. Yum SI, Schoenhard G, Tipton AJ, Gibson JW, Middleton JC, inventors; Durect Corp, assignee. Oral drug delivery system. United States patent US 8,133,507. 2012 Mar 13.
5. Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K., & He, J. (2005). Global burden of hypertension: analysis of worldwide data. The Lancet, 365(9455), 217-223.
6. Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Himmelfarb, C. D., ... & MacLaughlin, E. J. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology, 71(19), e127-e248.
7. Palem, C. R., Gannu, R., Doodipala, N., Yamsani, V. V., &Yamsani, M. R. (2011). Transmucosal delivery of domperidone from bilayered buccal patches: in vitro, ex vivo and in vivo characterization. Archives of pharmacal research, 34(10), 1701-1710.
8. Narendar, D., Arjun, N., Someshwar, K., & Rao, Y. M. (2016). Quality by design approach for development and optimization of Quetiapine Fumarate effervescent floating matrix tablets for improved oral bioavailability. Journal of Pharmaceutical Investigation, 46(3), 253-263.
9. Dudhipala, N. (2015). Enhancement of Solubility and Dissolution Rate of Trandolapril Sustained Release Matrix Tablets by Liquisolid Compact Approach. Asian Journal of Pharmaceutics (AJP): Free full-text articles from Asian J Pharm, 9(4).