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Design and development of microemulsion drug delivery system of felodipine for improvement of oral bioavailability

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Abstract

Microemulsion drug delivery system is a novel and versatile approach for overcoming the formulation difficulties of drugs with poor aqueous solubility. The main purpose of this work was to develop an oral microemulsion formulation for enhancing the bioavailability of felodipine. Felodipine is a antihypertensive drug a calcium channel blocker it belongs to BCS class Ⅱ .It shows extensive first pass metabolism. The bioavailability of felodipine is 15% hence it was suitable candidate for design microemulsion. The solubility of drug was determined in various oils, surfactants and cosurfactants for selection of components of formulations. Pseudo ternary phase diagram is a useful and important tool to study the phase behaviour of microemulsions Pseudo-ternary phase diagrams were constructed to obtain the appropriate components and their concentration ranges that result in large existence area of microemulsion. Microemulsion was prepared with 6%Isopropyl Myristate(IPM), 30% Tween 80&10% PEG-400 and54% water respectively. Phase behaviour of the selected components was investigated by construction of ternary phase diagrams. Optimized formulation was evaluated for drug content, zeta potential, droplet size, pH, viscosity, in-vitro drug release profile and stability study. Globule size of optimize batch F3 was found to be 77.57nm. In vitro release study had shown 85.34% drug release from microemulsion which was more compared to pure drug suspension (55.1%).

Key words: Microemulsion, non-ionic surfactant, conductivity, interfacial tension, particle size.

Introduction

Felodipine (FD), an antihypertensive agent, a second-generation calcium antagonist of the 1, 4-dihydropyridine (DHP) type, lowers blood pressure by selective dilatation of arterial smooth muscles in peripheral resistance vessels. Natural CDs are cyclic oligosaccharides, containing 6 (α- cyclodextrin), 7 (β-cyclodextrin) or 8(γ- cyclodextrin) α-1, 4-linked glucopyranose units, with hydrophilic outer surface and hydrophobic cavity. Felodipine has significant therapeutic potential in treating hypertension. Unfortunately though it has good therapeutic potential, it is poorly water soluble. It comes under Class II drugs which have lowsolubility and high permeability. In hypertension or angina, initially 5 mg. one daily and adjusted to maximum dose 10 mg one daily dose of Felodipine is given orally.[1]Felodipine has maximum solubility in acidic pH.Felodipine has some adverse effect such as nausea, abdominal pain.The extent of its absorption after ingestion and its ability to be distributed into various body tissues determines its ability to exert action in vivo.

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In this study the use of a microemulsion to improve the extent of absorption and the overall bioavailability was investigated. This novel drug delivery system has been reported to improve the rate and extent of absorption of lipophilic drugs.[2-6]Microemulsions are homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilizedby a surfactant, usually in combination with a cosurfactant (typically a short-chain alcohol). As pharmaceutical drug delivery systems, microemulsions have many advantages, including clarity, high stability, and ease of preparation.

Material and Methods

Felodipine was gifted byIpca lab Ltd Mumbai, Iso-propyl Myristate (IPM) –, Tween 80 –, Polyethylene Glycol 400(PEG 400) –,Merck
Loba Chemical.

Selection of oil, surfactants & cosurfactants for microemulsion

The solubility of felodipine in various oils such as Oleic acid, Isopropyl myristate, castor oil, surfactants such as tween 80,tween 20,span 80 and cosurfactants such as polyethylene glycol 400, polyethylene glycol 200. Drug was added in excess to different oils, surfactants and cosurfactants and stirred for 24 hrs on

magnetic stirrer. After stirring, samples was centrifuged at 3000 rpm for 3-5 min and the drug in the supernatant was analyzed at λmax 237 nm after proper dilution with Methanol.

Construction of pseudoternary phase diagram

Pseudo ternary phase diagram is a useful and important tool to study the phase behaviour of microemulsions. Pseudo ternary phase diagram is constructed to obtain the appropriate components and their concentration ranges that can result in large existence area of microemulsion. Once the appropriate microemulsion components are selected, ternary pseudo phase diagram is constructed to definethe extent and nature of the microemulsion regions. To produce such diagrams, a large number of samples of different composition are prepared. The microemulsion region is initially delineated by its isotropic nature and low viscosity. In this study, the Pseudo ternary phase diagrams of oil (Iso-propyl myristate), surfactant/co surfactant (Tween 80/ PEG 400) and water were developed by using water titration method to obtain the components concentration ranges of that can result in large existence area of microemulsion. Surfactant was blended with cosurfactant in fixed weight ratios (1:1, 2:1, 3:1, 4:1). For each phase diagram, the ratio of oil to the Smix was varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 (v/v). Aliquots of each surfactant and cosurfactant mixture (Smix) were mixed with oil at room temperature with continuous stirring. Water was added drop wise to each oil-Smix mixture under vigorous stirring. After equilibrium, the samples were visually checked and determined as being clear microemulsions.

Method of preparation[7]

ME formulations were prepared by the water titration method by varying the ratio of oil, surfactant,co-surfactant,andwater,keeping the concentration of Felodipine constant in each case. Preparation of microemulsion on the basis of the solubility studies, isopropyl myristate was selected as the oil phase. Tween 80 and PEG 400 were selected as surfactant and cosurfactant, respectively. Distilled water was used as an aqueous phase. Surfactant and cosurfactant (Smix) were mixed at different mass ratios (1:1,2:1,3:1,4:1). Predetermined quantities of the drug were dissolved in the oil. Sonication was performed in bathsonicated for 5 minutes to dissolve drug. Surfactant and co-surfactant were added and mixed gently for 1hrs with the help of a homogenizer(Lab stirrer REMI) at 1000 rpm at room temperature. The mixture was then finally titrated with distilled water until a stable and transparent ME was obtained.which resulted in the formulation of a transparent and homogenous microemulsion.Different batches of microemulsion with or without drug were prepared and select final preparation based on the transparency and physical observation.The final concentration of nifedipine in the microemulsions was 5%.

Evaluation

pH measurement[8]

pH of the microemulsion was measured using (Digital pH meter MK VI).The electrode was rinsed with deionized water and blot was dried with a soft, clean paper .Then the electrode was dipped into the test solution. Then pH was recorded when the reading was stable after insertion of the electrode into the solution.

Qualitative test[9]

Dilution and Dye solubility tests were performed for determination of type of ME.

Dilution test

The prepared drug loaded microemulsion was diluted with water and it was found to be optically clear.

Dye solubility test

The water soluble dye amaranth was added in microemulsionand.it was found uniformly distributed throughout the microemulsion without any lump formation.

Centrifugation test

This test was used to specify the stability of the microemulsion whether it was monophasic or biphasic. In this, the samples were centrifuged at 3000 rpm for 30 minutes and then were examined for whether the system was monophasic or biphasic.

Conductivity measurement

The electroconductivity of the resultant system was measured by an electroconductometer (chemilineconductometer). For the conductivity measurements, the tested microemulsions were prepared with a 0.01N aqueous solution of sodium chloride instead of distilled water.

Viscosity measurement

The rheological property of the microemulsion was evaluated by a Brookfield LVDV 111 + CP viscometer at 30ºC using a CPE 42 spindle at 5 rpm.

Percent transmittance

Transparency of both optimised ME formulation and its diluted forms (10 and 100 times with distilled water) was determined by measuring percentage transmittance through ultraviolet (UV) spectrophotometer (UV-1800 shimadzu). Percentage transmittance of samples was measured at 650 nm with purified water, taken as blank.

Globule size& zeta potential determination
The globule size & zeta potential were measured with Malvernzetasizer (Malvern Instruments Ltd).

Drug content
ME containing 10 mg of drug was transferred to a 25 ml volumetric flask and the volume was made up with methanol . The drug was allowed to dissolve in the solvent for 30 min. Than the solution was filtered and 1ml was taken in 100ml of volumetric flask and diluted up to mark with methanol. From this,1ml pipetted into a 10 ml volumetric flask and volume was made up to 10 ml with methanol. The resultant solution was analysed spectroscopically at 237nm.The drug loading efficiency was determined by:

$$\text{Drug loading efficiency} = \frac{\text{Amount of drug in known amount of formulation}}{\text{initial drug load}} 100$$

***In vitro* studies[10]**
In-vitro study was carried out using cellophane membrane. The cellophane membrane was activated in distilled water for 4 hours than 2% sodium bicarbonate and 1m molEDTA for 2 hours. Felodipine ME and plain drug suspension (each equivalent to 5 mg of felodipine) were placed in the donor compartment. The receptor compartment was filled with dialysis medium (500ml of0.1 N HCL). Whole assembly was put on magnetic stirrer (500rpm) .At a fixed time interval ,5 ml of the sample was withdrawn from the receiver compartment through a side tube and the cell was replenished to their marked volumes with freshly prepared buffer solution and analysed spectrophotometrically at 237 nm. Addition of solution to the receiver compartment was performed with great care to avoid trapping of air.The samples were filtered from filter paper and percent drug release was calculated.

Stability studies[11]
Optimized microemulsion were subjected to stability study for a period of 1 month at cold temp (4-8^{o}C), room temperature and at elevated temperature (50 ± 2^{o}C). During the period of storage the ME was subjected for percentage transmittance, pH, and phase separation.

Results and Discussion

Pseudoternary Phase diagram: Ratio ofSurfactants &cosurfactants (4:1) show maximum microemulsion area. So this ratio was selected for further formulation. Results are shown in Table 1 Phase diagram was plotted based on readings which are shown in Figure 1.

Characterization of optimized microemulsion (F3)
Qualitative tests
From the dilution test and dye solubility test the prepared microemulsion was found to be o/w type.

Centrifugation test
The microemulsion was found to be optically monophasic even after centrifuging at 3000 rpm for 30 minutes.

Various testsPhmeasurement,Percentagetransmittance,Viscositymeasurement,
Electro conductivity measurement,Droplet size & zeta potential,Centrifugationtest,Drug content were performed.Result of characterization of optimized formulation is shown in Table 4.

Globule size : Globule size of the microemulsions was found to be 77.57 nm.

Zeta potential
Zeta potential was found to be negatively charged (-6.20) to the system (Malvern Instruments Ltd). Hence the formulations will not cause any problem due to electrostatic interaction between the microemulsion.

In vitro release of drug
Drug release from optimized ME,&pure drug suspension, were found to 85.34%,55.1%. ME showed higher drug release as compared to the PDS, which may be due to the solubility-enhancing component of the surfactant and co-surfactant.

Conclusion

The developed ME, containing IPM (6%), Tween 80 (30%), PEG 400 (10%), and distilled water (54%), was found to be a transparent fluid with a globule size of 77.57 nm. ME showed higher in vitro drug release when compared with pure drug suspension . The relative bioavailability of the drug from ME was found to be 85.34% within 6 hrs .Hence, it can be concluded that the ME formulation can be employed to improve the bioavailability of a poorly soluble drug showing first-pass metabolism.

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Table 1: Pseudoternaryphase diagram reading

S/No.	Oil:smix Ratio	Oil:smix In ml	1:1(smix) 50:50	2:1(smix) 100:50	3:1(smix) 150:50	4:1(smix) 200:50
	Dilution with water until microemulsion remains					
1	1:9	1ml:9ml	30	40	65	80
2	2:8	2ml:8ml	20	45	60	85
3	3:7	3ml:7ml	3	3	7	12.4
4	4:6	4ml:6ml	2	2	6	6.2
5	5:5	5ml:5ml	1	1	2	3.2
6	6:4	6ml:4ml	1	1.14	2.85	3.08
7	7:3	7ml:3ml	0.7	1	1.4	2.84
8	8:2	8ml:2ml	0.6	0.10	1.3	1.56
9	9:1	9ml:1ml	0.4	0.8	1.12	1.52

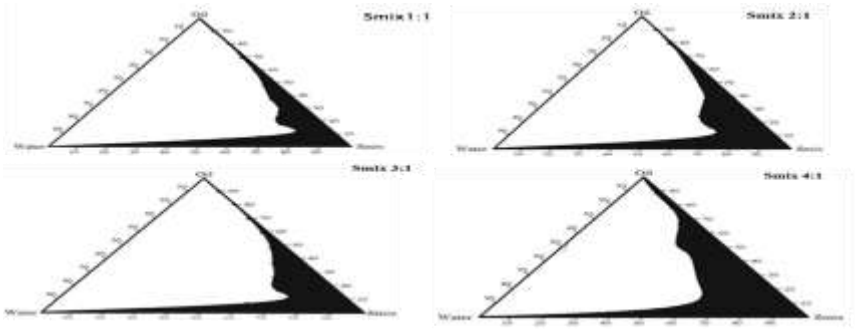

Figure 1 :Pseudoternary phase diagrams of IPM/Tween 80 /PEG 400

Table 2 :Optimization of microemulsion (Blank batches)

Formulation code	Oil %	Surfactant %	Co surfactant %	Water %	Percentage Transmittance (nm)	Viscosity (Physical observation)	pH
F1	2	10	10	78	90.8%	Transparent	7.1
F2	4	20	10	66	94.8%	Transparent	7.4
F3	6	30	10	54	98.5%	Transparent	7.9
F4	8	40	10	42	74.8%	Cloudy	8.4

Table 3: Drug Loaded Microemulsion

Batch no.	IPM (%)	Tween 80 (%)	PEG400 (%)	Water (%)	Felodipine mg	Percentage Transmittance (nm)	Drug content	pH
F1	2	10	10	78	100	88.8%	72%	7.2
F2	4	20	10	66	100	92.8%	85%	7.5
F3	**6**	**30**	**10**	**54**	**100**	**98.2%**	**96%**	**7.8**
F4	8	40	10	42	100	68.8%	88%	8.1

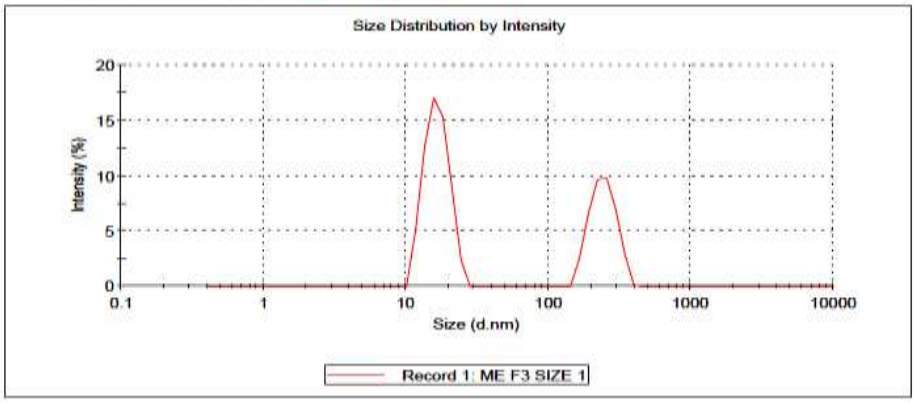

Figure 4 :Globul size of Formulation (F3)

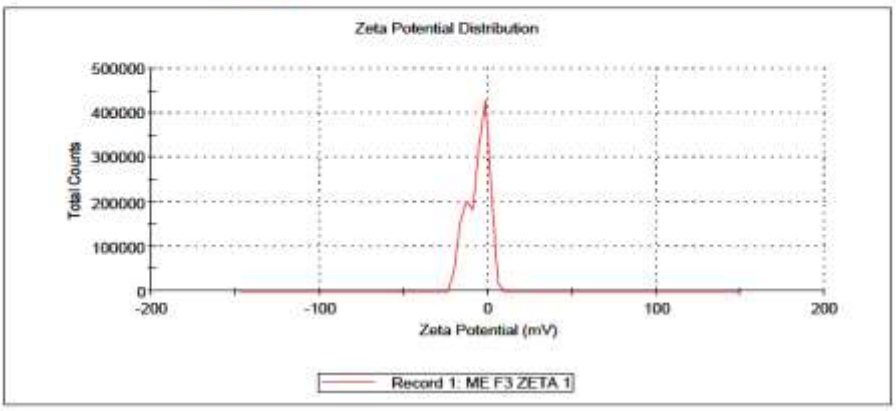

Figure 5: Zeta potential Formulation (F3)

Table 4 :Results of characterization of Optimized microemulsion

S.No	Test Optimized	Result
1	pH	7.8
2	Drug content	96%
3	Conductivity (µS/cm)	8.579
4	% Transmittance(nm)	98.2%
5	Zeta potential (mV)	-6.20
6	Globule size (nm)	77.57

Table 5 :In vitro drug release study

S.No.	Time in min.	Cumulative percent drug release (ME F3)	Cumulative percent drug release (PDS)
1	15	10.12	8.1
2	30	15.22	9
3	60	21.89	10.2
4	90	28.98	14.7
5	120	35.87	18.6
6	150	49.1	22.5
7	180	55.65	26
8	210	61.22	32.2
9	240	68.91	38.2
10	270	71.2	42.8
11	300	78.82	48.5
12	330	84.16	50.23
13	360	85.34	55.1

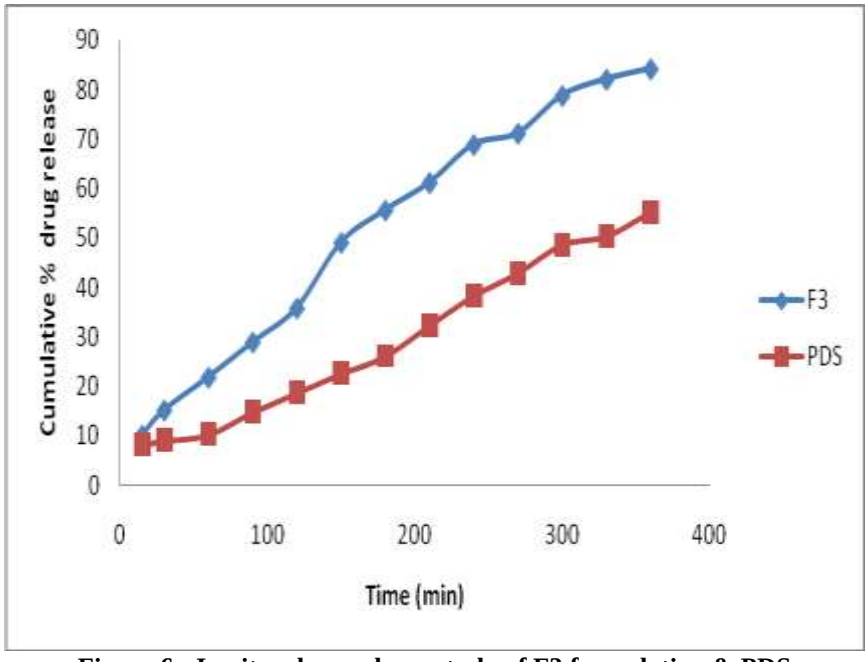

Figure 6 : In vitro drug release study of F3 formulation & PDS

Table 6 : Phase Separation observation

Temperature (ºC)	Phase separation	
	Initial Reading	After 1 month
2ºC-8ºC	Not observed	Not observed
Room Temp	Not observed	Not observed
Elevated Tem. (50± 2ºC)	Not observed	Not observed

Table 7 : Percent transmittance observation

Temperature (ºC)	Percent transmittance	
	Initial Reading	After 1 month
2ºC-8ºC	96.9%	95.8%
Room Temp	97.8%	97.5%
Elevated Tem. (50± 2ºC)	97.8%	97.2%

Table 8 : pH observation

Temperature (ºC)	pH	
	Initial Reading	After 1 month
2ºC-8ºC	6.8	6.2
Room Temp	7.9	7.4
Elevated Tem. (50± 2ºC)	7.5	6.9

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