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DEVELOPMENT OF FELODIPINE LOADED SMEDDS FOR IMPROVING ORAL BIOAVAILABILITY

A. Anusha and J. Krishnaveni *

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal - 506009, Telangana, India.

Keywords:

Felodipine, Liquid SMEDDS, Solid SMEDDS, Ternary phase diagrams, Effective permeability coefficient (p_{eff})

Correspondence to Author:
Dr. J. Krishnaveni

Assistant Professor,
Department of Pharmaceutics,
University College of Pharmaceutical Sciences, Kakatiya University,
Warangal - 506009, Telangana, India.

E-mail: krishnavenij153@gmail.com

ABSTRACT: Felodipine is a poorly water soluble drug having 15% oral bioavailability. In the present study Self micro emulsifying drug delivery system of felodipine was developed to improve its solubility and bioavailability. SMEDDS were prepared by phase titration method and ternary phase diagram was constructed using Chemix software. Based on solubility of drug in the excipients, capmul MCM, oleic acid, Tween 80 and PEG 400 were selected as oil, surfactant and co-surfactant respectively. Liquid SMEDDS were characterized for self-micro emulsification time, droplet size, poly dispersity index, zeta potential, drug release, *ex-vivo* permeation. The optimized liquid SMEDDS formulation F16 contained capmul MCM (35%), tween 80 (55%), PEG 400 (10%). Formulation F16 has size of 13.66 nm, zeta potential-25.7 mV, drug release 78% in 8 h. The optimized liquid SMEDDS were converted into solid SMEDDS by adsorbing on to neusilin. The drug release was studied in 0.1N HCl and phosphate buffers pH 6.8 using dissolution apparatus II. The dissolution from liquid SMEDDS and solid SMEDDS was significantly high ($P<0.0001$) compared to drug suspension. The drug permeation was studied by normal sac method. SMEDDS formulation showed significantly high permeation ($P<0.007$) compared to drug suspension. Single pass intestinal perfusion study was conducted in rats and the effective permeability coefficient (P_{eff}) of felodipine loaded SMEDDS ($16.3 \pm 0.86 \times 10^{-3}$ ml/min/cm^2) were significantly high ($P<0.05$) compared with drug suspension ($7.5 \pm 0.87 \times 10^{-3}$ ml/min/cm^2). The results of the study confirmed that SMEDDS formulation of felodipine could improve the oral bioavailability significantly.

INTRODUCTION: Felodipine is a calcium agonist used in the treatment of hypertension, heart failure and angina pectoris [1]. It is practically insoluble in water and belongs to a class II drug of BCS classification [2]. The oral bioavailability of felodipine is 15% due to its high lipophilic character [3]. The oral route has been traditionally preferred for prolonged use.

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Approximately 40% of new drug candidates have poor water solubility and the oral delivery of some drugs are frequently associated with low bio-availability, high intra and inter subject variability and a lack of dose proportionality [4, 5].

Several recent techniques have been used for their solubilization including micronization, complexation, solid dispersion, cyclodextrins, nanoparticles and co-precipitation. Recently, much attention has been paid to lipid based formulations to improve the oral bioavailability of lipophilic drugs [6]. Lipid-based formulation approaches, particularly the self- micro emulsifying drug delivery system (SMEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs [7].

SMEDDS formulations are isotropic mixtures of an oil, surfactant and co surfactant (or solubilizer). The basic principle of this system is its ability to form fine oil- in-water (o/w) micro emulsions under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by improving the permeation of drug [8]. Because of small globule size, the drug can be absorbed through lymphatic pathways, thereby bypassing the hepatic first-pass effect. Number of researchers reported that the SMEDDs can improve oral bioavailability of low soluble drugs [7]. Shen HR *et al*., 2006 reported increase in relative bioavailability (1.5 folds) of atorvastatin SMEDDS formulation compared to conventional tablet [9].

Yao J *et al*., 2008 reported increase in intestinal permeation of nobiletin SMEDDS formulation by single pass intestinal perfusion (SPIP) method in rats [10]. Thakkar H *et al*., 2011 developed raloxifene micro emulsions and SMEDDS and reported that the permeation of the drug from the SMEDDS and micro emulsions was significantly high than drug dispersion and marketed formulation [11]. Kim DW *et al*., 2012 reported that the novel flurbiprofen-loaded solid SMEDDS were developed with improved oral bioavailability using colloidal silica, a hydrophobic solid carrier, dextran, a hydrophilic carrier [12]. Yi T *et al*., 2008 reported that the new solid self micro emulsifying formulation prepared by spray-drying was improved the oral bioavailability of poorly water-soluble drugs [13]. The objective of the present study is to develop felodipine loaded self micro emulsifying drug delivery system (SMEDDS) to enhance the oral bioavailability of poorly water soluble felodipine.

MATERIALS AND METHODS: Present investigation was carried out in the year 2016 at University College of Pharmaceutical Sciences, Kakatiya University, Warangal, and Telangana, India.

Materials: Felodipine was obtained as gift sample from Aurobindo pharma Ltd., (Hyderabad, India). Capmul MCM, Captex 200 P obtained from ABITEC corporations, Cleveland, USA. Labrasol, Labrafil M 2125 cs, Capryol PGMC, Lauroglycol 90 obtained from Gattefosse, France (Colorcon, Mumbai). PEG 400, potassium dihydrogen orthophosphate, sodium hydroxide and sodium carboxy methyl cellulose, methanol, obtained from SD chemicals. Tween 80, Dialysis membrane (MWCO 12 to 14 KD) obtained from Himedia, Mumbai.

Animals: Male Wistar rats weighing between 200-250 g were used for *ex-vivo* studies. The animals were maintained at temperature (25 ± 2 °C), humidity (60 ± 5%) and were supplied with food and water. All experiments conducted on animals were approved by the institutional animal ethics committee, and the number obtained was IAEC/30/UCPSc/KU/2016.

UV Method: Felodipine was dissolved in methanol to get a solution of 100 µg/ml. From this stock solution, dilutions were made to obtain the concentrations of 1, 2, 4, 6, 8, 10 and 12 µg/ml. The absorbance of the samples was measured by UV spectrophotometer at 237 nm [14].

Solubility Studies: The solubility of felodipine in various oils, surfactants, and co-surfactants was determined by equilibrium solubility method at 37ºC [8].

Visual Observation Study and Construction of Phase Diagrams: A series of formulations were prepared with varying concentrations of oils (20 - 40%), surfactants (20 - 60%) and co-surfactants (10 - 60%). The oil, surfactant and co-surfactants are mixed by vortexing until a clear solution was obtained.

A visual observation test to assess the self-emulsification properties was carried out by diluting 1000 times with water at 37 °C [15]. The samples which are transparent were considered as nano / micro-emulsions [19]. Phase diagram was constructed using Chemix software (version 3.51).

Preparation of Liquid SMEDDS: Liquid SMEDDS were prepared by dissolving drug in oil followed by the addition of surfactant and co-surfactant, vortexing the mixture after each addition [8].

Characterization of Liquid SMEDDS:

Self-Micro Emulsification Time: The time taken for the emulsion formation was noticed upon drop wise addition of the pre-concentrate (SMEDDS) (100 µl) into 100 ml of distilled water in a glass beaker at 37 °C, on a magnetic stirrer at ~100 rpm.

The tendency to form an emulsion was assessed as "good" when emulsification occurs rapidly in less than 1 min with clear (or) transparent appearance. The tendency to form an emulsion was assessed as "bad" when there is white emulsion formation.

Phase Separation and Stability Study of Micro Emulsion: 100 ml of liquid SMEDDS formulation (100 µl) was added to a test tube containing 5 ml double distilled water at 37 °C. After vortex mixing for 1 min, the sample was kept aside and observed for phase separation and precipitation of the drug, if any. The observations were made at intervals of 2, 4, 6, 8, 12, 24 and 48 h.

Droplet Size, Zeta Potential and PDI: The formulation was diluted 1000 times with double distilled water and subjected to droplet size, zeta potential and poly dispersity index using zetasizer (Nano ZS 90, Malvern instruments, UK).

Effect of Dilution and pH on Droplet Size: The micro emulsion was subjected to dilutions (1:100, 1:500, 1:1000) and size of globule was measured. The formulations were diluted 1000 times with 0.1N HCl and phosphate buffer of pH 6.8 and the size was measured using zeta sizer.

Physical Stability (Freeze - Thawing): Formulations were subjected to 4 to 5 freeze - thaw cycles. Each cycle include freezing at - 20 °C for 24 h followed by thawing at 40 °C for 24 h. After completion of 5 freeze-thaw cycles, the samples were centrifuged at 3000 rpm for 5 min and observed for phase separation and precipitation of drug, if any [16].

Characterization by DSC: Pure drug and solid SMEDDS were evaluated by DSC (822e/200) perkin elmer, India. About 10 mg of sample was taken in aluminium pan, crimped and thermogram was recorded by heating at a rate of 10 ºC/min between temperature ranges of 50 - 200 ºC.

Nitrogen was used as purge gas and the system was cooled by liquid nitrogen.

Estimation of Drug Content: 1 ml of SMEDDS formulations equivalent to 5 mg of felodipine was diluted with 10 ml of methanol, centrifuged at 3000 rpm for 15 min to separate the undissolved excipients. The supernatant was suitably diluted and analyzed spectrophotometrically at 237 nm using UV spectrophotometer [17].

***In-vitro* Drug Release from Liquid SMEDDS:** Drug release from liquid SMEDDS was determined by dialysis bag method using 0.1 N HCl, (pH 1.2) for 2 h followed by phosphate buffer of pH 6.8 for 14 h as medium. Initially, the dialysis tubing was soaked in the medium for 1 h at 40 °C. About 1 ml of SMEDDS formulation / drug suspension containing 5 mg of felodipine was placed in dialysis bag made up of membrane of molecular weight cut off 12000 - 14000 daltons. The dialysis bag was suspended in 100 ml of the medium and the contents were mixed on a magnetic stirrer at 100 rpm at room 37 ºC. Samples (2 ml) were collected at regular time intervals and replaced with equal volume of fresh medium. The Samples were analyzed by UV Spectrophotometer at 237 nm after appropriate dilution of the sample [18].

Preparation of Solid SMEDDS: The optimized formulation was adsorbed onto carriers (Neusilin) to produce solid SMEDDS (S-SMEDDS). The formulation was placed in a china dish, a pre-weighed quantity of inert carrier was added in small increments with continuous mixing to form homogenous powder [19].

***In-vitro* Drug Release from Liquid / Solid SMEDDS:** Drug release from solid / liquid SMEDDS and drug suspension were carried out in USP apparatus using 0.1N HCl and phosphate buffer pH 6.8 as dissolution media. Solid - SMEDDS capsules and liquid SMEDDS, drug suspension equivalent to 5 mg of felodipine were placed in 900 ml of media, rotated at 50 rpm at 37°C. Aliquots of samples were withdrawn at time intervals of 0.25, 0.5, 1, 1.5, 2 h and replaced with fresh medium. The samples were immediately filtered and analyzed for felodipine content by UV method [20].

***Ex-vivo* Studies:**

Normal Sac Method: The study was carried out to assess the permeation of drug from optimized

formulation (5 mg) and drug suspension across the small intestine. The rats were sacrificed by cervical dislocation technique and jejunum of 4 cm segments were isolated, flushed with saline solution and transferred into oxygenated Kreb's ringer solution. The one end of the sac was tied with thread and filled with the sample or control (1 ml) and the other end was tied. The segment was immersed in 100 ml of Kreb's ringer solution and the medium was oxygenated using aerator. At regular time intervals (15, 30, 45, 60, 75, 90, 105, 120 min) samples were withdrawn and analyzed for drug content [21].

Single Pass Intestinal Perfusion Study: The *in-situ* single pass perfusion studies were performed using male Wistar rats weighing between 180 and 250 g using perfusion pump (NE-1600, NEW Era syringe pumps, Wantagh, NY). The rats fasted over night with free access to water were anesthetized by an intra peritoneal injection of thiopentone sodium (60 mg/kg body weight) and placed on a thermostatic surface to maintain body temperature. Under anaesthesia, an incision was made through a midline to expose the abdomen. The lower part of the small intestine segment was exposed and semi circular incisions were made at 10 cm apart and cannulated with poly ethylene tubing by ligation with silk suture. After cannulation the surgical area was covered with cotton soaked in physiological saline. The intestine segment was flushed with phosphate buffered saline pH 6.8 at 37 ºC for 30 min. The perfusates prepared by dispersing SMEDDS formulation equivalent to 5 mg of felodipine containing phenol red (20 µg/ml) in phosphate saline buffer pH 6.8 was passed at a steady state flow rate of 0.2 ml /min for 120 min.

The perfusate samples were collected in test tubes for every 15 min intervals up to 120 min. At the end of the perfusion the circumference and the length of the perfused intestine was measured. Pure drug dispersed in 1% w/v PEG 400 containing the same amount of felodipine was also studied for comparison. Each experiment was performed in triplicate. The perfusate samples were allowed to thaw, deprotenised using methanol, centrifuged and the drug content in the supernatant was quantified by UV method. Effective permeability coefficient in rats and humans and enhancement ratio was calculated by following equations [22].

Effective Permeability Coefficient:

$$P_{eff\ (rat)} = -Q \ln (C_{in}/C_{out})/A$$

Q = rate of perfusion (0.2 ml/min), A= surface area of segment ($2\pi rl$), C_{in} = Drug concentration infused, C_{out} = Drug concentration outflow.

$$P_{eff\ (human)} = 11.30 \times P_{eff\ (rat)} - 0.0003$$

Enhancement Ratio (ER):

$$ER = P_{eff\ (rat)} \text{ of SMEDDS fomulation} / P_{eff\ (rat)\ Control}$$

RESULTS AND DISCUSSIONS:

Solubility Studies: Solubility of felodipine in different oils, surfactants, co-surfactants were shown in **Fig. 1**. Solubility of felodipine in tween 80 (98.25mg/ml) and PEG 400 (96.25 mg/ml) was significantly high compared to other oils and surfactants. Based on solubility of drug, capmul MCM or oleic acid, tween 80 and PEG 400 were selected as oil, surfactant, and co-surfactant, respectively for formulation optimization.

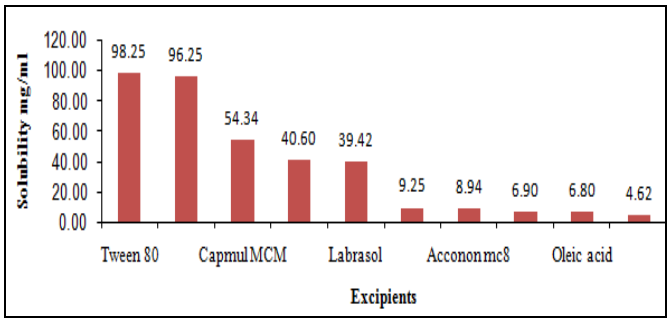

FIG. 1: SOLUBILITY OF FELODIPINE IN DIFFERENT OILS, SURFACTANTS, CO-SURFACTANTS

Ternary Phase Diagram: Formulations (series 1) containing oleic acid, tween 80 and PEG 400 yielded turbidity upon dilution. No transparent system was noticed. The size of globules varied between 525µ to 1731µ. The series I could not provide any region of micro emulsion. Series II formulations prepared by using capmul MCM, tween 80 and PEG 400 were shown in **Table 1**.

Formulations yielded 15 transparent micro-emulsions (F5-F11, F13-F20) and 5 formulations are turbid (F1, F2, F3, F4 and F12). Ternary phase diagram of series II containing capmul MCM, tween 80 and PEG 400 was shown in **Fig. 2**. Chemix software was used to draw the ternary phase diagram. Within micro emulsion forming region four formulations are selected for evaluation studies.

TABLE 1: COMPOSITION OF FORMULATIONS (SERIES II) AND EVALUATION

Formulation code	Capmul MCM (% w/w)	Tween 80 (% w/w)	PEG 400 (% w/w)	Visual observation (1:1000)	Droplet size (nm) (1:50)
F1	20	60	20	Turbid	280.1
F2	20	50	30	Turbid	1320.08
F3	20	40	40	Turbid	229.02
F4	20	30	50	Turbid	1085
F5	20	20	60	Transparent	201.6
F6	25	60	15	Transparent	182.7
F7	25	50	25	Transparent	78.47
F8	25	40	35	Transparent	20.37
F9	25	30	45	Transparent	191.01
F10	25	20	55	Transparent	139.1
F11	30	60	10	Transparent	70.87
F12	30	50	20	Turbid	1547
F13	30	40	30	Transparent	52.31
F14	30	30	40	Transparent	168
F15	30	20	50	Transparent	99.06
F16	35	55	10	Transparent	13.66
F17	35	45	20	Transparent	112.6
F18	35	35	30	Transparent	36.17
F19	35	25	40	Transparent	57.6
F20	35	15	50	Transparent	166.8

Drug 5 mg common in all formulations

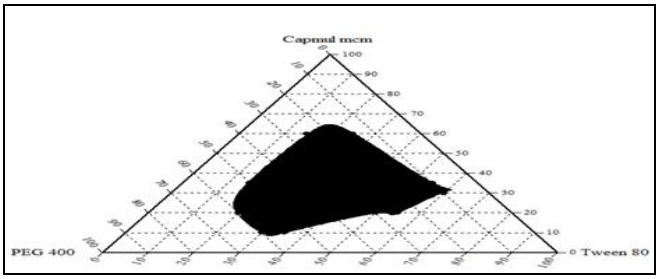

FIG. 2: TERNARY PHASE DIAGRAM OF SERIES II

Assessment of Self-Micro Emulsification Time: Self micro emulsification time of the selected formulations was less than one minute **Table 2** which indicate grade I micro emulsion.

Phase Separation: No precipitation of the drug in selected micro emulsion formulations was observed after 2, 4, 6, 8, 12, 24 and 48 h.

TABLE 2: CHARACTERIZATION OF SELECTED FORMULATIONS

Formulation code	Self emulsification time (sec)	Phase separation	Droplet size (nm)	PDI	Zeta potential (mV)	Drug content (%)	Drug release 12 h (%)
F7	48	X	78.47	0.284	-19.8	98.54	82.6
F11	46	X	70.81	0.210	-21.1	97.5	78.3
F16	36	X	13.66	0.171	-25.7	98.78	85.4
F18	52	X	36.17	0.267	-18.53	97.34	79.2

X: No Phase Separation, PDI: Poly Dispersity Index

Droplet Size, Poly Dispersity Index and Zeta Potential: The droplet size, poly dispersity index and zeta potential of selected formulations were shown in **Table 2**. The formulations yielded very small droplet sizes varying between 13.66 to 78.47 nm, PDI values between 0.171 to 0.284 and zeta potential between -18.53 to -25.7mV. Increasing PEG concentration increased the size of droplets.

TABLE 3: EFFECT OF DILUTION WITH DISTILLED WATER AND MEDIA ON DROPLET SIZE OF THE SMEDDS FORMULATIONS

Degree of dilution	Formulation code and Droplet size (nm)			
	F7	F11	F16	F18
1:50	78.47	70.81	13.6	36.17
1:100	76.21	62.07	15.21	20.41
1:500	75.44	65.29	16.89	44.97
1:1000	73.8	67.47	19.29	50.92
pH 1.2, 1:1000	86.12	68.26	14.61	54.21
pH 6.8, 1:1000	94.92	78.27	18.41	54.21

Effect of Dilution and pH on Droplet Size of Selected Formulations: The effect of dilution and pH was studied for selected formulations and the results were shown in **Table 3**.

There was no significant difference found in droplet size of the formulation. Variable effect of pH was noticed. Whereas, formulations F7, F11, F16 and F18 resulted in increased droplet size due to dilution.

Physical Stability of Pre-concentrate during Freeze - Thawing and Storage: The selected formulations after subjecting of 5 Freeze- Thaw cycles were stable showing no phase separation or precipitation of the drug.

DSC Thermogram:

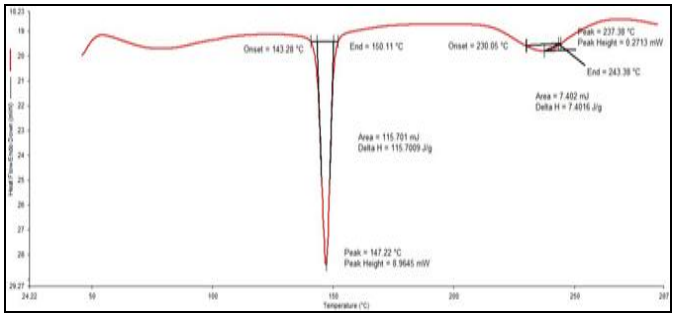

FIG. 3: DSC THERMOGRAM OF SOLID SMEDDS

The DSC thermogram of Solid SMEDDs **Fig. 3** showed sharp endothermic peak at 147 ºC, Which corresponds to the reported melting point 145 ºC of felodipine [29]. As there is no remarkable change in melting point of felodipine and also no peaks corresponds to degradation of drug, drug is compatible with the excipients used.

Cumulative Percent Drug Release from Different Formulations and Drug Suspension by using Dialysis Bag Method (n = 3): The drug release profiles of selected formulations were shown in **Fig. 4.** The drug release from SMEDDS formulation was significantly (85.42% in 12 h) high at P<0.001 when compared to drug suspension (34.6% in 12 h).

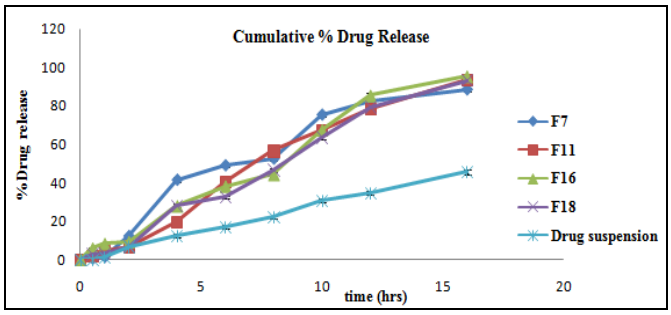

FIG. 4: DRUG RELEASE FROM LIQUID SMEDDS AND DRUG SUSPENSION IN 0.1 N HCl FOR 2 h, AND 14 h IN pH 6.8 PHOSPHATE BUFFER

***In vitro* Drug Release:** A comparison of drug release profiles of solid SMEDDS, liquid SMEDDS and drug suspension in 0.1N HCl were shown in **Fig. 5**. Drug release from liquid SMEDDS (99.1%) and solid SMEDDS (95.2%) was significantly high when compared to drug suspension (54.1%) at P<0.0001. Drug release from liquid SMEDDS, solid SMEDDS and drug suspension in pH 6.8 phosphate buffer were shown in **Fig. 6.** Drug release from liquid SMEDDS (98.54%), solid SMEDDS (93.53%) was significantly high when compared to drug suspension (57.67%) at P<0.0001. There is no significant difference between liquid and solid SMEDDS.

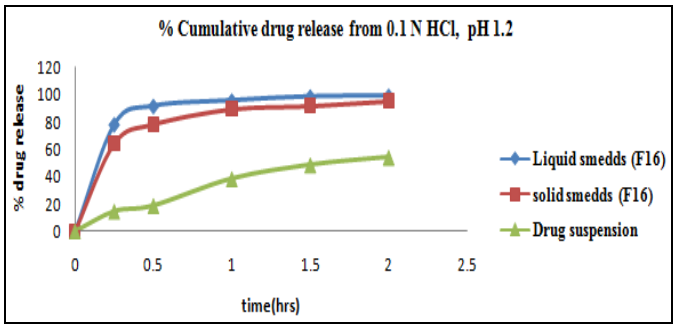

FIG. 5: DRUG RELEASE FROM LIQUID SMEDDS, SOLID SMEDDS AND DRUG SUSPENSION IN 0.1N HCl, pH 1.2

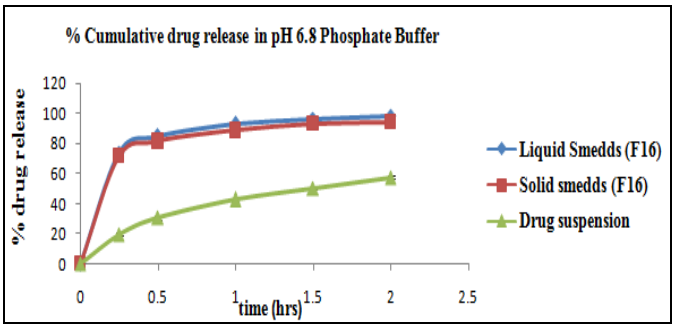

FIG. 6: DRUG RELEASES FROM LIQUID SMEDDS, SOLID SMEDDS AND DRUG SUSPENSION IN pH 6.8 PHOSPHATE BUFFER

***Ex-vivo* Permeation Studies by Normal Sac Method:** The *ex-vivo* drug permeation profile was shown in **Fig. 7.** The release of drug from formulation F16 was significantly higher (P<0.007) (93%) than the drug suspension (62%).

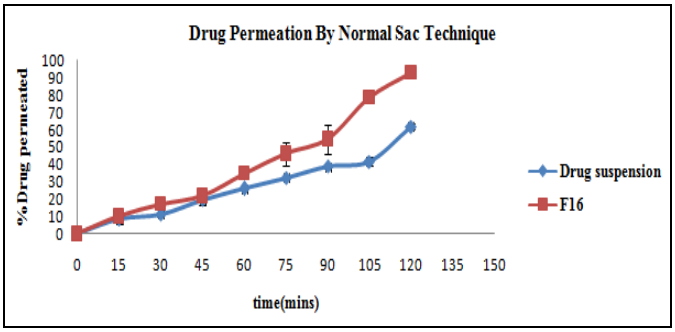

FIG. 7: % DRUG PERMEATION BY NORMAL SAC TECHNIQUE

Single Pass Intestinal Perfusion Study: *In-situ* perfusion study facilitates to ascertain the potential absorption of self micro emulsifying drug delivery system across GI tract. The effective permeability coefficient in rat (P_{eff} rat), predicted effective permeability coefficient in human (P_{eff} human), were showed in **Fig. 8.** The obtained P_{eff} rat values for SMEDDS formulation (F16) and drug suspension were 16.29 ± 0.86 × 10^{-3} (ml/min/cm^2), 7.54 ± 0.87 × 10^{-3} (ml/min/cm^2) respectively. The effective permeability coefficient P_{eff} (rat) of liquid SMEDDS was significantly high when compared to control (drug suspension).

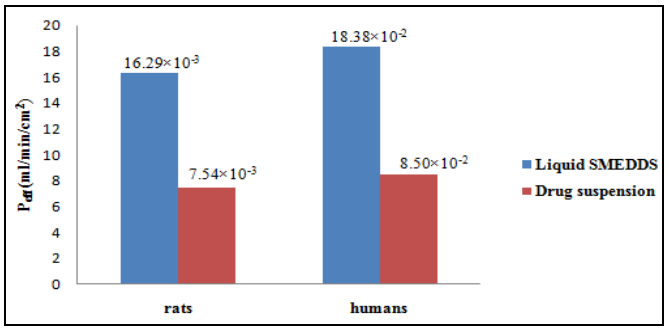

FIG. 8: *IN-SITU* PARAMETERS OF FELODIPINE IN RATS AND HUMANS FOLLOWING ORAL ADMINISTRATION OF SMEDDS FORMULATION (F16) AND DRUG SUSPENSION (CONTROL) (Mean ± SD, n = 3 at p<0.005)

The P_{eff} (human) values were predicted by correlating with the obtained rat P_{eff} values. The significant improvement in P_{eff} (human) of felodipine loaded liquid SMEDDS formulation (F16) compared to control can be attributed to increase in effective surface area for absorption owing to dispersion of drug in micro emulsion droplets. Enhancement ratio was found to be 2.15 ± 07. The enhancement ratio above 1 indicates an enhanced permeation with SMEDDS formulation, conferes their potential as a carrier for improving absorption of felodipine.

Capmul MCM and PEG 400 is mucosal permeation enhancer known to modulate the membrane fluidity and thus enhance the drug formulation contained tween 80 and PEG 400 as S_{mix}.

Statistical Analysis: All studies were done in triplicate and data represent the mean ± standard deviation. The statistical analysis was performed using t-test and ANOVA using graph pad prism software. A difference below the probability level ($P < 0.05$) was considered significant.

CONCLUSION: SMEDDS of felodipine for oral administration were successfully developed using oil (capmul MCM), surfactant (tween 80), and co-surfactant (PEG 400). The drug release from liquid SMEDDS and solid SMEDDS was significantly high ($P<0.0001$) compared to drug suspension. The drug permeation and effective permeability coefficient (P_{eff}) of felodipine loaded liquid SMEDDS was significantly high compared with drug suspension. Present investigation suggests that SMEDDS of felodipine could significantly improve oral bioavailability compared to conventional tablets.

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CONFLICT OF INTEREST: The authors have no conflicts of interest relevant to the content of the manuscript.

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