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A SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM FOR IMPROVEMENT IN ORAL BIOAVAILABILITY OF NIMODIPINE: *IN VIVO* EVALUATION

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Keywords:

SNEDDS, Nimodipine, Hypertension, Solubility, Bioavailability studies

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ABSTRACT: The current research involves the study of a Nimodipine self-nanoemulsifying drug delivery system (SNEDDS) with improved bioavailability and solubility. Fifteen formulations of Nimodipine SNEDDS were prepared prior to evaluation of particle size, emulsification time, percentage drug release, percentage transmittance, thermodynamic stability and *in-vitro* drug release. The formulation F13 was chosen as an optimized formulation with the composition of Peceol, Transcutol P, and PEG 400. The optimized Nimodipine SNEDDS formulation (F13) subjected to drug-excipient compatibility studies by FTIR. The particle size of the optimized Nimodipine SNEDDS formulation was 25.9 nm, PDI is 0.382, and zeta potential -12.7 mV that are optimal for the stability of the emulsion. SEM studies of Nimodipine SNEDDS indicated spherical shape and uniform particle distribution. Furthermore, Pharmacokinetic studies were conducted in rats, and plasma drug concentration-time curves revealed that significant increase in optimized SNEDDS concentration compares to that of a drug. Hence a potential SNEDDS formulation of Nimodipine developed with increased dissolution rate and solubility and bioavailability.

INTRODUCTION: The majority of drugs discovered to date lack complete solubility in water, thus leading to fewer bioavailability, high inter-subjective variability, and lack of dosage proportionality [1]. Hence there is a striving need for the development of suitable drug formulations for these highly hydrophobic drugs. The most viable approach for this problem is SNEDDS which show considerable increase in bioavailability of sparingly water-soluble drugs. SNEDDS are isotopic combination of oil, co-surfactant and surfactant that are specifically formulated for enhancement of oral bioavailability and oral adsorption of class II to class IV drugs of Biopharmaceutical Classification System (BCS) [2, 3].

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SNEDDS can be formulated as capsules that form stable oil-in-water emulsion with gastrointestinal fluids. This *in-situ* emulsification will further lead to solubilization of drug. Formation of dispersions and micellar suspensions of drug leads to increase in bioavailability of the drug [4]. The efficiency of drug absorption from SNEDDS depends on its particle size, charge, polarity of emulsion, surfactant ratio and self-emulsifying ability [5, 6]. Finer oil droplets would pass through stomach easily to facilitate even distribution of drug in GI track. SNEDDS provide higher interfacial area for portioning of drug and also protect the drug from harsh environment in gut. SNEDDS have the advantage of ease of manufacturing when compared to other delivery systems [7].

Nimodipine is chemically 1, 4-dihydropyridine that acts as calcium channel blocker. Nimodipine prevents calcium-dependent muscle contraction and vasoconstriction. In humans, Nimodipine is readily absorbed through oral administration and peak concentrations are generally attained within one

hour. Bioavailability is 100% by intravenous administration and 3-30% through oral administration due to extensive first-pass metabolism [8].

The present study is aimed at Developing and characterization of Nimodipine SNEDDS formulation for enhancement of the bioavailability of drug during oral administration.

MATERIALS AND METHODS:

Materials: Nimodipine is a gift sample from Aurobindo pharma limited, Hyderabad. Coconut oil, Acrysol K-140, Carbitol, Tween 20, PEG 400, Capmul MCM and Brij 35, Cremophor EL and Kolliphor EL Caproyl 90 obtained from Gattefosse India Pvt. Ltd., Mumbai. Peceol, Kolliphor HS 15, Plurololeique, and Glycerol were procured from BASF, Mumbai.

Solubility Data: The solubility of Nimodipine in various oils, surfactants and co-surfactants is determined by added excess drug to 2 ml of each excipient and later determining dissolved drug determined spectrophotometrically at 238 nm [9].

Pseudo Ternary Phase Diagram: Construction of pseudo ternary phase diagram carried by aqueous titration method at temperature 25°C for identifying the nanoemulsion region for the selected oil, Surfactant, and co-surfactant (S_{mix}) of varying volume ratio (1:1, 2:1, 3:1). Chemix software used for the plotting and analysis [10, 11].

Development of Nimodipine SEDDS Formulation: Fifteen Nimodipine SEDDS formulations prepared by using Peceol oil phase, Transcutol P surfactant and PEG 400 Co-surfactant respectively. In brief, Nimodipine (30mg) was taken in glass vials and heated to 40ºC. The excipients added to this oily mixture with continuous stirring. The contents sonicated for 15 min, samples preserved at 25°C for further analysis **Table 1**.

TABLE 1: FORMULATION OF NIMODIPINE SEDDS

S_{mix} (Surfactant: Co-surfactant)	Oil: S_{mix}	Formulation Code	Nimodipine (mg)	Oil (Peceol) (ml)	S_{mix} (Transcutol P: PEG 400) (ml)	Water (ml)
	2:8	F1	30	0.3	1.2	0.3
	3:7	F2	30	0.45	1.05	0.45
1:1	4:6	F3	30	0.6	0.9	0.6
	5:5	F4	30	0.75	0.75	0.75
	6:4	F5	30	0.9	0.6	0.9
	4:6	F6	30	0.6	0.9	1.9
2:1	5:5	F7	30	0.75	0.75	2.05
	6:4	F8	30	0.9	0.6	2.2
	7:3	F9	30	1.05	0.45	2.35
	8:2	F10	30	1.2	0.3	2.5
3:1	3:7	F11	30	0.45	1.05	2.4
	4:6	F12	30	0.6	0.9	2.6
	5:5	F13	30	0.75	0.75	2.8
	6:4	F14	30	0.9	0.6	3
	7:3	F15	30	1.05	0.45	3.2

% Transmittance Measurement, Drug Content and Thermodynamic Stability Studies: All the fifteen Nimodipine SNEDDS were preceded for Percentage transmittance and drug content analysed for drug concentration at λ_{max} 238nm and thermodynamic stability studies conducted in order to access any phase separation and stability of the nanoemulsion [12, 13].

***In-vitro* Drug Dissolution Studies:** The Nimodipine SEDDS formulations whose weight is equivalent to 2mg of the drug were packed into hard gelatin capsules. The phosphate buffer (pH 1.2) is maintained at 35-37°C at 50 rpm. A sample of 4-5 ml each withdrawn at intervals for analysis. Contents filtered and drug concentration analyzed at 238 nm [14, 15].

Characterization of Nimodipine SEDDS:

Determination of Droplet Size: The determination of droplet size of Nimodipine SEDDS formulations determined using Malvern Instrument UK make Photon correlation spectroscopy [16].

Determination of Zeta Potential: The zeta potential of the Nimodipine SEDDS formulation was measured after dilution with water in ratio of 1:2500 (v/v) using zeta meter.

Stability Studies: The Nimodipine SNEDDS formulations sealed in gelatin capsules. The stability of formulations analyzed for six months at 25°C temperature and 60% RH and 40°C temperature and 75% RH using Thermolab stability chambers (Mumbai, India) [17].

Pharmacokinetic Study of Nimodipine: Wistar rats weighing between 150-180 g that were healthy during the period of the experiment were chosen for the experiment at controlled temperature of 25°C, 45% RH and 12 h alternate cycle of light and dark. The animal room is facilitated with 100% fresh air exchange with continuous supply of power and water.

Rats fed with standard diet and water *ad libitum*. The protocol approved by the institutional animal ethics committee with IAEC NO: 1292/ac/09/ CPCSEA/24/A.

Study Design: The Wistar rats were categorized into two groups. The rats offered with food post four hours of dosing. Group 1 was administrated with Nimodipine pure drug suspension in methanol. Group 2 was administrated orally with the optimized Nimodipine SNEDDS formulations diluted in methanol (0.5%) at a dose of 10mg/kg. 500 µL blood samples collected from the femoral artery at varying time intervals of 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24 h post dose. The samples transferred into Eppendorf tubes containing heparin prevent clotting. The plasma separated by centrifuging the blood at 5000 rpm in cooling centrifuge for 5 - 10 min and stored frozen at −20°C prior to analysis [18].

HPLC Determination of Nimodipine in Rat Plasma: The determination of drug in rat sample was chromatographically carried out over a HIQ sil C18 column (250×4.6 mm i.d., 5 µm particle size) at absorption wavelength 289 nm maintaines at flow rate of 1 ml/min. A mixture of ACN and Ammonium acetate (80:20v/v was used as mobile phase. About 0.1% 1-hexanesulfonic acid monohydrate sodium salt chosen an ion-pairing reagent. The retention times about 2.28 min for Nimodipine and 2.58 min for (dibucaine) IS [19].

Pharmacokinetic Analysis: The pharmacokinetic parameters evaluate were C_{max} (maximum plasma concentration), T_{max} (time to attain C_{max}), AUC_{0-t} (area under plasma concentration-time curve from zero to the last sampling time), $AUC_{0-\infty}$ (area under plasma concentration-time curve from zero to infinity).

The AUC_{0-t} was calculated formula

$$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$$

RESULTS AND DISCUSSION:

Solubility Studies: The solubility of Nimodipineis 2.35ug/ml. Based on drug solubility, Peceol, Transcutol P and PEG 400 were chosen as oil, surfactant and co-surfactant respectively and saturation solubility was found to be 80.77, 240.01 and 90.26 mg/ml respectively.

Pseudo Ternary Phase Diagram: The phase diagram constructed reveals that the emulsifying property of formulations increases with concentrations of surfactant and co-surfactant were shown in **Fig. 1, 2** and **3**.

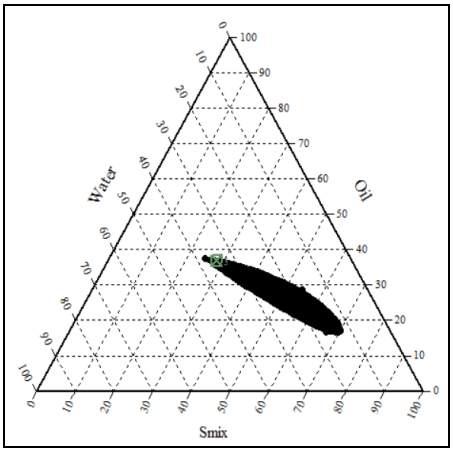

FIG. 1: TERNARY PHASE DIAGRAM OF PECEOL, TRANSCUTOL P AND PEG 400 OF 1:1 RATIO S_{mix}

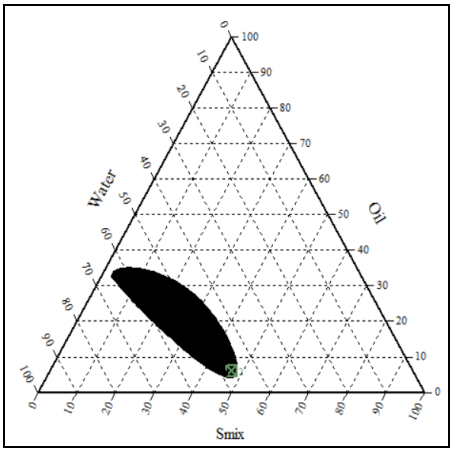

FIG. 2: TERNARY PHASE DIAGRAM OF PECEOL, TRANSCUTOL P AND PEG 400 OF 2:1 RATIO S_{mix}

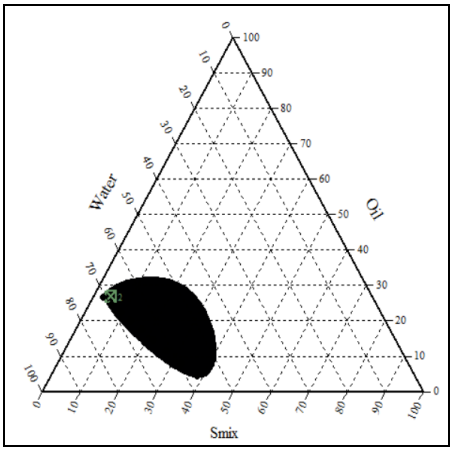

FIG. 3: TERNARY PHASE DIAGRAM OF PECEOL, TRANSCUTOL P AND PEG 400 OF 3:1 RATIO S_{mix}

Preparation of Nimodipine SNEDDS Formulation: Fifteen formulations of Nimodipine SNEDDS prepared as isotopic mixture of Peceol (oil), Transcutol P (surfactant), and PEG 400(co-surfactant). All the fifteen formulations prepared were clear and transparent.

Thermodynamic Stability Studies: The results of thermodynamic stability study indicated no phase separation. No significant change observed in visual description.

% Transmittance Measurement and Drug Content: Nimodipine SNEDDS Formulation F13 exhibited a maximum percentage transmittance value > 98% indicating highest clarity of emulsion and drug content is in the range of 92.49-98.19%. Formulation F13 exhibited maximum drug content of 98.19% when compared with other formulations

***In-vitro* Dissolution Studies Nimodipine SEDDS Formulation:** The dissolution of the drug from SEDDS formulation F13 was faster in comparison to other SNEDDS formulations and pure drug **Fig. 4, 5** and **6**.

Particle Size and Polydispersity Index of Nimodipine SNEDDS: The particle size of the optimized Nimodipine SNEDDS formulation is 25.9 nm & Z-Average of 27.2nm, indicating that nanometer range **Fig. 7**. The polydispersity index is 0.382 indicate the mid-range of polydispersity.

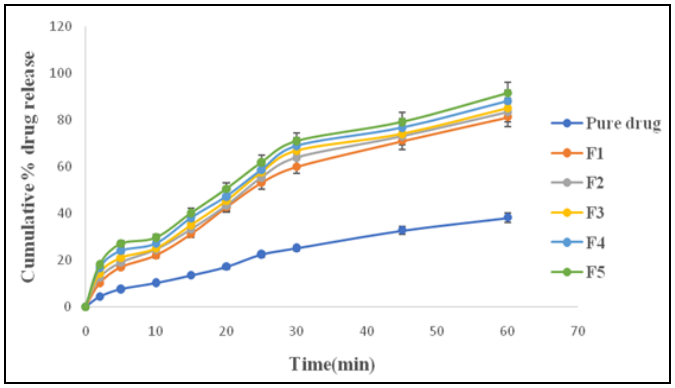

FIG. 4: DISSOLUTION PROFILES OF NIMODIPINE PURE DRUG AND SNEDDS FORMULATIONS (F1 TO F5)

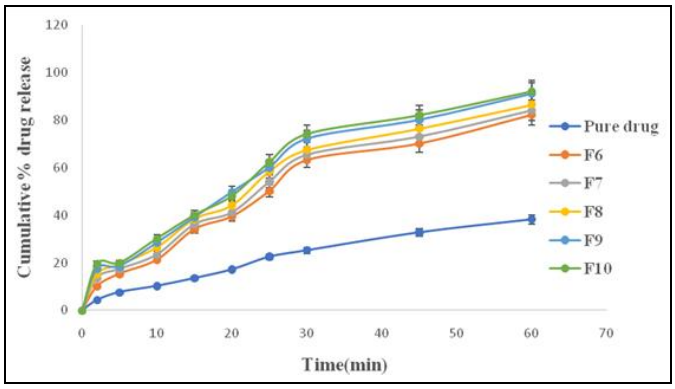

FIG. 5: DISSOLUTION PROFILES OF NIMODIPINE PURE DRUG AND SNEDDS FORMULATIONS (F6 TO F10)

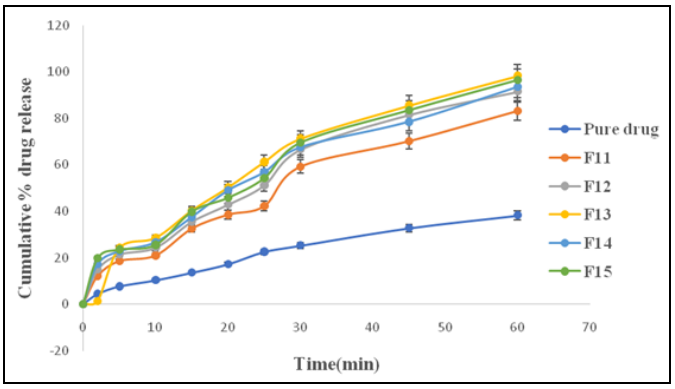

FIG. 6: DISSOLUTION PROFILES OF NIMODIPINE PURE DRUG AND SNEDDS FORMULATIONS (F11 TO F15)

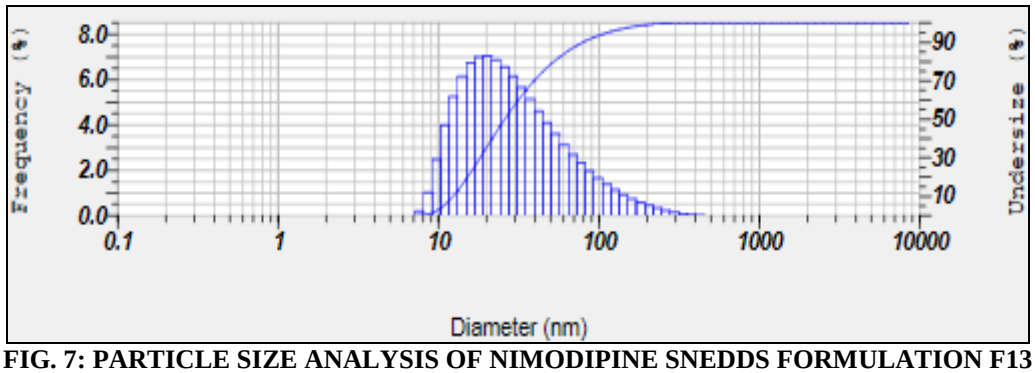

FIG. 7: PARTICLE SIZE ANALYSIS OF NIMODIPINE SNEDDS FORMULATION F13

Zeta Potential (ZP) of Nimodipine SNEDDS: The ZP of the optimized Nimodipine SNEDDS formulation is-12.7 mV which indicates the stability of the formulations in **Fig. 8**.

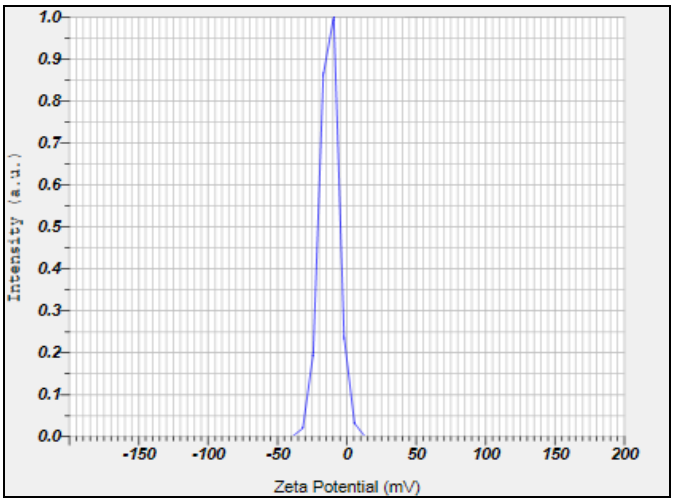

FIG. 8: ZETA POTENTIAL OF THE F13

Stability studies: Stability studies conducted for six months for formulation F13. The results indicated no significant change in parameters like drug release and drug contents.

***In-vivo* Drug Bioavailability Data:**

Pharmacokinetic Parameters of Pure Drug Suspension and SNEDDS of Nimodipine: Fig. 9 indicates plasma concentration vs time curve in animals prior to single oral dose of Nimodipine SNEDDS formulation in comparison with Nimodipine pure suspension. The Nimodipine plasma concentrations of samples treated with SNEDDS formulation were found to be significantly higher **Table 2**.

C_{max} value of of the SNEDDS 4.54±1.06ng/ml was significant ($p<0.05$) in comparison with pure drug suspension formulation 2.65±0.41ng/ml. T_{max} of SNEDDS formulation and pure drug was 1.00±0.05h and 2.00±0.01h, respectively. The $AUC_{0-\infty}$ infinity of SNEDDS formulation was higher (13.05±3.24ng.h/ml) than the pure drug (8.71±2.13ng.h/ml). Statistically, AUC_{0-t} of the SNEDDS formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of Nimodipine from SNEDDS formulation.

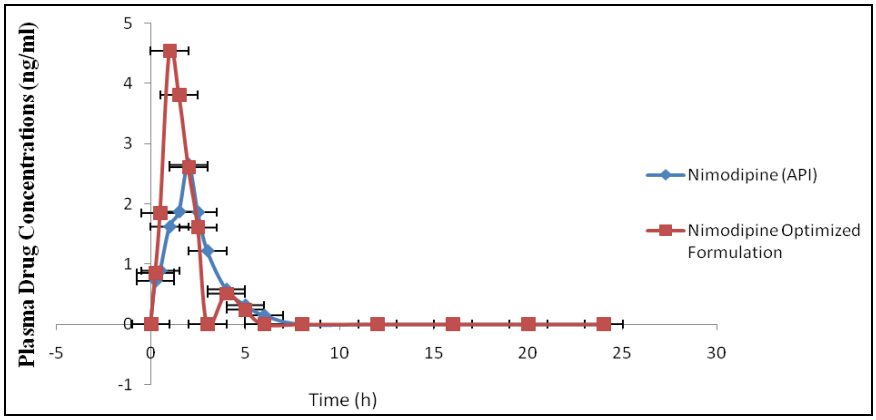

FIG. 9: PLASMA CONCENTRATION PROFILES OF NIMODIPINE SNEDDS AND PURE DRUG

TABLE 2: PHARMACOKINETIC PARAMETERS

Parameters	Nimodipine Pure drug	Nimodipine –SNEDDS Optimized Formulation
C_{max} (ng/ml)	2.65±0.41	4.54±1.06
AUC_{0-t} (ng.h/ml)	5.42±1.34	8.53±2.14
AUC_{0-inf} (ng.h/ml)	8.71±2.13	13.05±3.24
T_{max} (h)	2.00±0.01	1.00±0.05
$t_{1/2}$ (h)	5.12±0.02	3.50±0.04

CONCLUSION: In the current research, SNEDDS of Nimodipine prepared and analyzed for various parameters. Peceol (oil), Transcutol P (surfactant) and PEG 400 (co-surfactant) were optimized for SNEDDS formulation, respectively. From pseudo ternary phase diagram, it is evident that an increase in Transcutol P concentration enhances the emulsification property of the formulations. Fifteen formulations prepared (F1-F15) and F13 exhibited a percentage transmittance value higher than 98% indicating the highest clarity of emulsion. Maximum % drug content of 98.19% exhibited by the formulation F13. The percentage drug release from liquid SNEDDS formulation F13

(98.25±4.77%) was faster than pure drug substance (38.49±3.88%). The FTIR studies indicate no interaction between the drug and excipients. The particle size of formulation F13 was found to be 25.9 nm, PDI is 0.382 and zeta potential of -12.7 mV. The SEM studies indicate spherical shape for the optimized Nimodipine SNEDDS formulation (F13) with uniform and relatively narrow particle distribution. The stability studies indicated no significant change in the drug content and drug release. Nanoemulsion may serve as a promising alternative approach for the oral delivery of Nimodipine with increased bioavailability. The *in-vivo* bioavailability studies indicate that the SNEDDS exhibited a significantly greater C_{max} than the pure drug with the promising strategy of enhanced oral bioavailability.

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REFERENCES:

1. Wu X, Xu J, Huang X and Wen C: Self-micro emulsifying drug delivery system improves curcumin dissolution and bioavailability. Drug Dev Ind Pharm 2011; 37: 15-23.
2. Lipinski C: Poor aqueous solubility-an industry-wide problem in drug discovery. Am Pharm Rev 2002; 5: 82-85.
3. Palmer IS: New horizons in drug metabolism, pharmacokinetics and drug discovery. Drug News Perspect 2003; 16: 57-62.
4. Nazzal S: Optimization of a self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int J Pharm 2002; 240: 103-14.
5. Abdalla A and Mader K: Preparation and characterization of a self-emulsifying pellet formulation. Eur J Pharm Biopharm 2007; 66: 220-26.
6. Saritha D, Penjuri SCB and Nagaraju R: Formulation and evaluation of self-emulsifying drug delivery system (SNEDDS) of Indomethacin. IJPSR 2014; 4(2): 17-23.
7. Tang B, Cheng G, Gu JC and Xu CH: Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discov Today 2008; 13(13-14): 606-12.
8. Kale A, Amit, Patravale and Vandana: Design and Evaluation of Self-Emulsifying Drug Delivery Systems (SNEDDS) of Nimodipine. AAPS Pharm Sci Tech 2008; 9(1): 191-6.
9. Cheer SM and McClellan K: Manidipine a review of its use in hypertension. Drugs 2001; 61(12): 1777-99.
10. Chaudhari P and Bhalerao A: Method validation for spectrophotometric estimation of cilnidipine. Int J Pharm Pharm Sci 2012; 4(5): 96-98.
11. Talegaonkar S, Mustafa G, Akhter S and Iqbal ZI: Design and development of oral oil-in-water nanoemulsion formulation bearing atorvastatin: *in-vitro* assessment. J DisperSci and Tech 2010; 31(5): 690-701.
12. Setthacheewakul S, Mahattanadul S, Phadoongsombut N, Pichayakorn W and Wiwattanaptapee R: Development and characterization of solid self-emulsifying drug delivery system of cilnidipine. Eur J Pharm Biopharma 2010; 76: 475-85.
13. Rajinikanth PS, Keat NW and Garg S: Self-nanoemulsifying drug delivery systems of valsartan: Preparation and in-vitro characterization. International Journal of Drug Delivery 2012; 4(2): 153-63.
14. Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK and Ali M: Development and bioavailability assessment of Ramipril nanoemulsion formulation. Eur J Pharm Biopharm 2012; 66: 227-43.
15. Costa P and Sousa Lobo JM: Modelling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13: 123-33.
16. Dixit P, Jain DK and Dumbwani J: Standardization of an *ex-vivo* method for determination of intestinal permeability of drugs using everted rat intestine apparatus. Pharmacol Toxicol Methods 2012; 65: 13-17.
17. Sonia A, Rishikesh G and Prajapati S: Self-microemulsifying drug delivery system. Asian J Pharm Clin Res 2016; 9(2): 33-38.
18. Zhang J, Peng Q, Shi S, Zhang Q, Sun X and Gong T and Zhang Z: Preparation, characterization, and *in-vivo* evaluation of a self-nanoemulsifying drug delivery system (SNEDDS) loaded with morin-phospholipid complex. Int J Nanomedicine 2011; 6: 3405-16.
19. do Nascimento DF, de Moraes MO, Bezerra FAF, Andréa Vieira Pontes, Uchoa CRA and de Moraes RA: Determination of nimodipine in plasma by HPLC-MS/MS and pharmacokinetic application. Brazilian Journal of Pharmaceutical Sciences 2010; 46(4): 665-77.

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