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Research Article

Formulation and evaluation of phenylephrine and Ketrolac loaded ophthalmic self-nanoemulsifying drug delivery system

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Abstract

Aim: The current work aims to develop and evaluate Phenylepherine and Ketorolac loaded Self Nanoemulsifying Drug Delivery System to improve their solubility.

Preparation design: Castor oil was used as the oil, Span 80 as the surfactant, and poloxamer as the co-surfactant in a series of SNEDDS using Phase titration method.

Methodology: As part of the preformulation studies, a solubility test was performed on Phenylephrine and Ketrolac, and calibration curves were developed. To construct pseudo ternary phase diagrams, oil (CAPTEX-200) was mixed with various surfactant and cosurfactant ratios (TWEEN80/PEG-200) in varied concentrations. Span-80 and Poloxomer 188 were used to obtain the desired optimization of co-surfactants. SNEDDS were carried out using the Phase titration technique using castor oil as the carrier oil, Span 80 as the surfactant, and poloxamer as the co-surfactant in a series of SNEDDS. Through the use of SEM, thermal stability tests, and in vitro drug release of phenylephrine and ketorolac, the produced SNEDDS were assessed for phase separation, percent transmittance, drug loading, surface shape and size, and drug release.

Results: Phenylepherine and Ketrolac have been discovered to have maximum wavelengths (max) of 236nm and 241nm, respectively. Calibration curves for phenylepherine and ketorolac were drawn using pH 7.4 phosphate buffer and 1.2 pH 0.1N hydrochloric acid, respectively, as the pH 7.4 phosphate buffer and 1.2 pH 0.1N hydrochloric acid, respectively. They demonstrate high correlation and linearity in the concentration range of 5 to 30 g/ml, with R2 values of 0.998 and 0.997, respectively, within the concentration range. A total of nine formulations with Phenylepherine were tested for thermodynamic stability and were selected for further characterization. The formulations P4, P5, P6, P7, P8, and P9 with Phenylepherine and three formulations with ketrolac (K4, K5, and K6) were tested for thermodynamic stability and were selected for further characterization. P4 and P5 were found to be less clear and turbid based on percent transmittance. The formulations P6, P7, P8, and P9 are clear and transparent, whereas P10 is opaque. K2, K3, K4, K5, K6, and K8 were less translucent and clear than the other colours. In the SEM, it was discovered that the majority of the SNEDDS particles had a reasonably spherical shape, that the surface of the particle exhibited a typical smoothness, and that the particle size was in the micrometre range. It was established that the maximal drug release from the formulations Phenylepherine SNEDDS (P9) and Ketorolac SNEDDS (K9) occurred at 30 minutes (102.20 2.76 percent and 100.74 2.80 percent, respectively) based on in vitro drug release studies.

Conclusion: All of the aforementioned studies, taken together, revealed a significant increase in the bioavailability and solubility of Phenylepherine and ketorolac when administered in the form of SNEDDS. Finally, it can be stated that SNEDDS is a potentially useful approach for increasing the solubility, dissolving rate, and bioavailability of drugs and other pharmaceutical products.

Keywords: *Phenylephrine, Ketrolac, Phase titration, SNEDDS, nano emulsions, poloxomer 188*

1. INTRODUCTION

The oral route is the most acceptable method for medication administration but distribution of hydrophobic drugs through this route is almost 50% hindered. This is due to inadequate solubility, bioavailability, dosage proportionality, and unacceptable patient variability. As a result, developing suitable dosage forms for novel chemical moieties that are poorly soluble in water is one of the most critical issues confronting the pharmaceutical research and development business today. Among the numerous drug delivery methods that have been created and investigated, colloidal drug delivery systems show tremendous promise for resolving issues faced throughout the typical drug development process. Self Nanoemulsions have been found to improve absorption and bioavailability of hydrophobic drugs. Self-nanoemulsions are made up of oils (natural or synthetic), surfactants (solid or liquid at room temperature), and perhaps co-surfactants with some hydrophilicity and water. The resulting mixes are transparent and isotropic microemulsions in the form of tiny droplets or globules with particle sizes less than 100 nm. When these Self Nanoemulsions are employed in drug delivery systems, medicines are integrated into the oil or surfactant, and then water is added to create the Self nanoemulsion spontaneously [1].

SEDDS are isotropic mixes of lipid/oil, surfactant, co-surfactant, and drug ingredient that rapidly form fine oil-in-water micro (SNEDDS) and nano (SNEDDS)-emulsions when exposed to aqueous fluids under circumstances of moderate agitation or digestive motility that would be counteract in the GIT [2]. SEDDS formulations have in vitro lipid droplet diameters ranging from 200nm to 5 mm with a turbid appearance. SNEDDS, on the other hand, have smaller lipid droplet sizes (100 nm) and an optically clear-to-translucent look. Both systems are linked to the formation of high surface area dispersions, which provide ideal circumstances for the enhanced absorption of poorly soluble medicines [1]. These systems can then be immediately integrated into capsules or converted into granules, pellets, and powders for dry filled capsules and tablet formulations. The second alternative is made feasible by novel adaptations of standard equipment that are relatively easy and simple to use, such as melt granulation, adsorption on a solid substrate, spray drying, spray chilling, meltextrusion/spheronization, and supercritical fluid-based techniques [3].

Phenylephrine is a drug that is generally used as a decongestant, pupil dilation, blood pressure rise, and hemorrhoid relief. Ketorolac, also known as Toradol, is a nonsteroidal anti-inflammatory medication (NSAID) used to relieve pain. It is especially suggested for moderate to severe pain. Pre-dissolve the chemical in a suitable solvent and put the formulation into capsules for oral administration of these weakly water-soluble substances. However, as the formulation disperses in the GI tract, the medication may precipitate out of solution, especially if a hydrophilic solvent is employed (e.g. polyethylene glycol). If the medication can be dissolved in a lipid vehicle, there is reduced chance of precipitation during GI dilution because partitioning dynamics favour the drug remaining in the lipid droplets [4]. Another method for poorly soluble medicines is to formulate in a solid solution with a water-soluble polymer to enhance drug component solubility. As a result, such

formulations' physical stability must be evaluated using techniques such as differential scanning calorimetry or X-ray crystallography. In this instance, the SEDD system is an excellent choice. As a result, the current work aims to develop and test a Phenylepherine and Ketorolac loaded Self Nanoemulsifying Drug Delivery System to improve their solubility.

2. MATERIALS AND METHODS

All the drugs that are used in the experiment were of analytical grade and were obtained from SD Fine chem and Spectrum Reagents and Chemicals, India.

2.1 Preformulation studies

2.1.1 Solubility study

The solubility of Phenylepherine and Ketorolac was evaluated in various oils such as Arachis Oil, Castor Oil, Palm Oil, Sunflower Oil, Olive Oil, and Corn Oil. Increasing amount of drugs was allowed to dissolve in 10 mL of oil until it reaches an equilibrium level of saturation. The drug's solubility in oil was estimated in mg per millilitre [4].

2.1.2 Preparation of standard calibration curves of Phenylephrine and Ketrolac

100 mg of Phenylepherine and ketorolac were accurately weighed and dissolved in 10 ml of ethanol and methanol respectively and further volume was made upto 100ml with 7.4 pH phosphate buffer solution and 1.2pH 0.1N hydrochloric acid respectively to attain a 1mg/ml or 1000 µg/ml of stock solution. The λmax was measured between the range of 200 – 400 nm and it was shown as 236nm and 241nm. UV absorbance for each diluted sample were measured at this λmax and calibration curves were drawn for 3, 6, 9, 12, 15 µg/ml concentration samples [5,6].

2.1.3 Optimization of Co-surfactants and Construction of pseudo-ternary phase diagrams

Surfactant and co-surfactant (Smix) were combined in different volume ratios as in table 1 (1:1, 1:2, 1:3, 1:4, 2:1, 3:1, 4:1) in each group, and a 10mL stock of each group was produced. These Smix ratios were chosen in increasing concentrations of co-surfactant relative to surfactant and increasing concentrations of surfactant relative to co-surfactant for a comprehensive investigation of the phase diagrams for the production of microemulsions [7,8,9]. For each phase diagram, oil and specified Smix ratios were completely mixed in varied volume ratios ranging from 1:9 to 9:1 in tiny glass test tubes. Eleven distinct combinations of oil and each Smix; 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, 10:0 (Table 2) were produced to ensure that the maximum ratios were covered for the research to accurately outline the borders of phases generated in the phase diagrams. Pseudoternary phase diagrams were created using the water titration method to determine the presence zone of a nano or microemulsion. To create pseudoternary phase diagrams, the oil phase (CAPTEX- 200) was combined with various surfactant and cosurfactant ratios (TWEEN80/ PEG-200), and the mixture was titrated with distilled water until it became turbid. Using data from the aqueous titration technique, pseudo ternary phase diagrams were created (figure 1). The amount of water added to provide a water concentration of 5-95 % of total volume at 5% intervals. Visual observations were performed after each 5% addition of water to the oil and Smix combination, as indicated in Table.

Table 1. Concentration of polymers for construction of psesudoternary phase diagrams

S.No	Ratio of Smix	Volume of Surfactant (Span 80) (mL)	Volume of Co surfactant Poloxamer 188 (mL)
1.	**1:1**	30	30
2.	**1:2**	20	40
3.	**1:3**	15	45
4.	**1:4**	12	48
5.	**2:1**	40	20
6.	**3:1**	45	15
7.	**4:1**	48	12

Table 2. Selected combination of oil, Smix (4:1) and water for construction of Pseudo-ternary phase diagram

Mixture code	CAPTEX-200 (%)	TWEEN80/ PEG-200 (%)	WATER (%)	Visual Observation
D1	0.9434	0	0.056	separation
D2	0.860	0.0047	0.1219	Turbid
D3	0.7231	0.1121	0.1658	Turbid
D4	0.572	0.1923	0.2342	Turbid
D5	0.4263	0.2588	0.3117	Viscous gel
D6	0.3062	0.3579	0.3363	Milk like
D7	0.2584	0.3736	0.3679	Clear but turbid
D8	0.2042	0.4243	0.3705	Transparent and clear
D9	0.1427	0.4921	0.365	Transparent and clear
D10	0.0911	0.5925	0.3132	Transparent and clear
D11	0	0.8984	0.1115	Turbid lightly

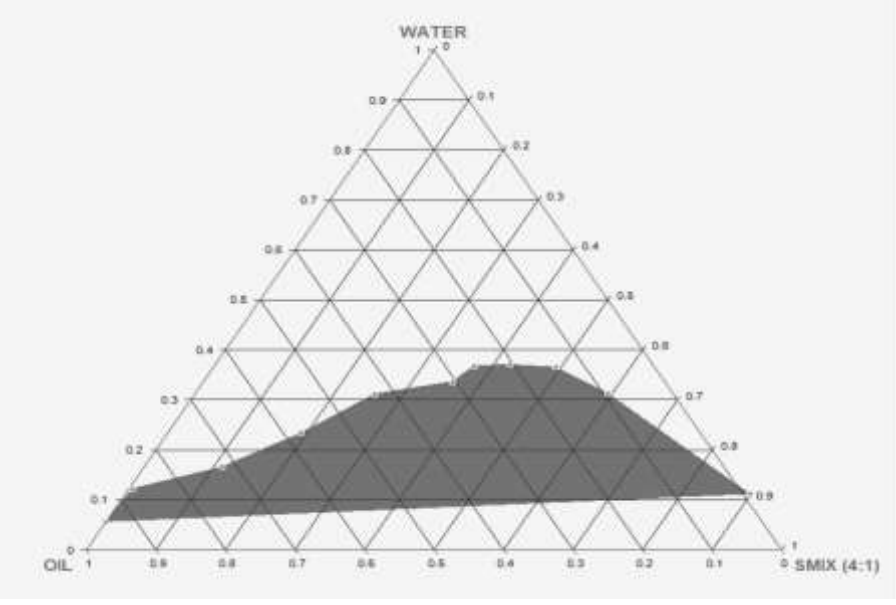

Fig. 1. Surfactant /co-surfactant ratio 4:1 (D1-D11)

2.2 Preparation of SNEDDS using Phase titration method

Castor oil was used as the oil, Span 80 as the surfactant, and poloxamer as the co-surfactant in a series of SNEDDS. The amount of drug in each formulation was kept constant. Precisely measured Oil, surfactant, and co-surfactant were added to the drugs in a beaker as per table 3. The components were gently combined using a magnetic stirrer, and the resultant mixture was placed in ultrasonication for 10-15 minutes to reduce size. The mixture was then heated at 40^0 C until the drug was completely dissolved. The homogeneous mixture was kept at room temperature until it was needed [10].

Table 3. Composition of Phenylepherine SNEDDS formulations

Formulation code	*Drug* (Ketorolac) (mg)	Formulation code	*Drug* (Phenylepherine) (mg)	Ingredients %w/w	
				Olive Oil (ml)	Span 80:Poloxamer (S_{mix}) 4:1 (ml)
K1	20	**P1**	20	10	90
K2	20	**P2**	20	20	80
K3	20	**P3**	20	30	70
K4	20	**P4**	20	40	60
K5	20	**P5**	20	50	50
K6	20	**P6**	20	60	40
K7	20	**P7**	20	70	30
K8	20	**P8**	20	80	20
K9	20	**P9**	20	90	10

2.3 Characterization of SNEDDS

2.3.1 Thermodynamic stability studies

After preparation of all formulations, thermodynamic stability studies were performed, Studies like, heating cooling cycle, freeze thaw cycle and centrifugation were performed as per standard procedures [11].

2.3.2 Phase separation study

A precise 1 ml of drug-loaded SNEDDS was added to 100 ml of distilled water in a glass beaker at 37^0 C and vortexed for 2 minutes before being used in the experiment. During a 2-hour storage period at 37^0C, the mixture was visually inspected for the presence of any phase separation. [12].

2.3.3 Visual assessment

Approximately 100 mL of drug-loaded SNEDDS was diluted with filtered water (100 mL) and gently vortexed with a magnetic stirrer to achieve the desired concentration at 37^0C. Formulations P1, P2, and P9 were somewhat white milk-like emulsions, whereas K1 was a less clear emulsion with a white blue look that was less clear than the others. It was found that the formulations P3-P8 and K2-K9 were clear, with a faint bluish tint, and had acceptable stability. [12,13].

2.3.4 Scanning electron microscopy

In order to analyse the surface morphology of the selected optimal Microemulsion, scanning electron microscopy (SEM) was utilised. The formulations were mounted on alumina stubs with double adhesive tape and gold coated in a HUS-5GB vacuum evaporator. The sample was then examined in a Hitachi S-3000N SEM with a 10KV acceleration voltage and a magnification of 5000X. [14].

2.3.5 Particle size determination

The average particle size of prepared SNEDDS was measured by dynamic light scattering (DLS) at a scattering angle of 173^{o} at 25^{o}C utilising a Nanopartica SZ-100 HORIBA Scientific, Japan. The sample of formulation was diluted to 1:2500v/v with double distilled water to ensure that light scattering was within range of detection. [10]. Zeta potential was estimated by using a Zetasizer (Nanopartica SZ-100 HORIBA Scientific, Japan).

2.3.6 Determination of drug content %

After appropriate dilution of the formulations and using dichloromethane as a blank, the drug content of the oil-based dispersion system of Drug was determined spectrophotometrically at wave length 236nm for phenylephrine and 241nm for ketorolac. [15].

2.3.7 In-vitro drug release study

The consistency of the emulsifying property was determined by calculating the percentage of in-vitro drug release from preapred formulations. The dissolution of the oil in aqueous medium was determined using the Dialysis membrane model, which was then utilised to examine the drug release from the oil. The SNEDDS-filled dialysis bag was attached to the paddle in order to prevent the bag from drifting about in the dissolving medium. As a dissolving medium, 900 mL of phosphate buffer pH (7.4) was employed. It was possible to maintain the bath temperature and bowl temperature at around 37.5^{0} Celsius by using a paddle that could rotate at 50 revolutions per minute. 5ml of the sample was taken out at intervals of 5, 10, 15, 20, 25, and 30 minutes and diluted to a final volume of 10ml. The dissolving jar was replenished with 5ml of new medium. In order to determine the % drug release from the diluted samples, spectrophotometric analysis at 236nm for Phenylepherine and 241nm for Ketorolac was performed on the samples. [10].

3. RESULTS AND DISCUSSION

The maximum wavelength (λ_{max}) of Phenylepherine and Ketrolac were found to be 236nm and 241nm. Calibration curves for Phenylepherine and ketorolac was plotted by using the pH 7.4 phosphate buffer and 1.2pH 0.1N hydrochloric acid respectively. They show a good correlation and linearity within the concentration ranging from 5 to 30µg/ml and shows R^2 value as 0.998 and 0.997.

3.1 Thermodynamic stability studies

On the basis of heating, cooling and centrifugation six formulations were selected out of nine formulations. On the basis of thermodynamic stability studies in table 4, it was found that six formulations, P4, P5, P6, P7, P8, and P9 with Phenylepherine and three formulations, K4, K5 and K6 with ketrolac passed the tests and selected for further characterization.

Table 4. Thermodynamic stability study and visual assessment of SNEDDS of phenylephrine and ketrolac

Formulation code	Phase Separation (Yes/No)	Heating Cooling Cycles (4^0C to 45^0C 72 hrs)	Freeze Thaw Cycle between -21^0C to -25^0C	Centrifugation (3500 rpm 48 hrs)
P1	Yes	Stable	Phase separation	Phase separation
P2	Yes	Stable	Phase separation	Phase separation
P3	Yes	Stable	Phase separation	Phase separation
P4	No	Stable	Stable	Stable
P5	No	Stable	Stable	Stable
P6	No	Stable	Stable	Stable
P7	No	Stable	Stable	Stable
P8	No	Stable	Stable	Stable
P9	No	Stable	Stable	Stable
K1	Yes	Phase separation	Phase separation	Phase separation
K2	No	Stable	Phase separation	Phase separation
K3	No	Stable	Stable	Phase separation
K4	No	Stable	Stable	Stable
K5	No	Stable	Stable	Stable
K6	No	Stable	Stable	Stable
K7	No	Stable	Stable	Phase separation
K8	No	Phase separation	Stable	Phase separation
K9	No	Phase separation	Phase separation	Phase separation

3.2 Visual assessment

Formulations P4 and P5 were somewhat white milky emulsions, whilst P6 was a less clear emulsion with a white bluish look, with a slight white milky appearance. Formulae P7, P8, and P9 had a clear, somewhat blue colour, and showed good stability when tested. When comparing the K2 to K9 formulation to the K1 microemulsion, there is no evidence of phase separation between the two. Based on the findings of the research, it can be concluded that the majority of the formulations are extremely stable under vortex conditions.

3.3 Transmission test

Transmittance of light from selected SNEDDS formulations as well as 50 times, 100 times and 200 times dilution with water was checked by UV-Spectrophotometer at 665 nm by using water as a blank. The results shows the Phenylepherine SNEDDS formulations P4 and P5 were less clear and turbid. Formulations P6, P7, P8, and P9 are clear and transparent. K2, K3, K4, K5, K6 and K8 were less clear and transparent from the data observed in Table 5

Table 5. Transmission test results of Phenylepherine and Ketrolac SNEDDS

Formulation code	% Transmittance			% drug content
	50 times dilution	100 times dilution	200 times dilution	
P4	14.05	35.14	69.45	97.69±0.13

P5	26.25	49.46	88.14	97.31±0.23
P6	60.78	83.12	98.34	98.65±0.23
P7	94.39	98.57	99.17	98.27±0.65
P8	98.56	99.67	99.89	99.04±0.52
P9	99.85	99.96	100.12	99.23±0.16
K2	24.91	39.24	74.42	96.20±0.24
K3	16.34	40.06	82.42	96.22±0.12
K4	20.56	36.48	84.24	96.42±0.12
K5	22.42	48.42	86.76	97.22±0.10
K6	28.66	56.40	89.88	96.06±0.12
K8	26.30	42.60	84.42	99.34±0.16

3.4 Scanning Electron Microscopy (SEM) Evaluation

Surface morphology and shape of SNEDDS formulated with optimized parameters was observed for SEM studies. The study revealed that the most of the SNEDDS was fairly spherical in shape, the surface of the particle showed a characteristic smoothness, and the particle size was in the micrometric range, as depicted by SEM in fig. 2.

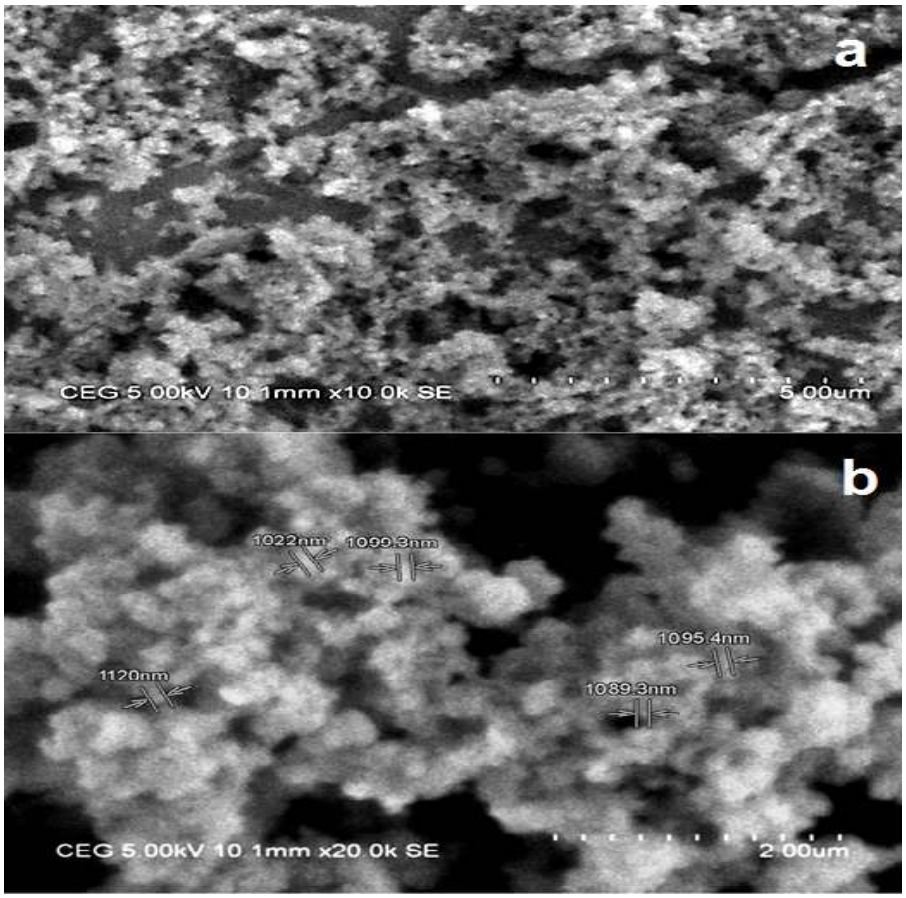

Fig. 2. SEM image of formulations

a. phenylephrine (P9) at 502nm; **b. Ketorolac SNEDDS (K9) at 1022 nm**.

3.5 In vitro drug release study

A dialysis membrane was used to study the drug release profiles of Phenylepherine and Ketorolac SNEDDS particles in phosphate buffer (pH 7.4) after they were packed in the solution. There was a reduction in droplet size, but the surface area increased, allowing for greater breakdown of the medication from SNEDDS. The ratio of Smix to oil has a significant role in the release of the medication from the formulation. Because smaller micro droplets were produced as a consequence of increasing the concentration of Smix in the formulation, the solubility profile of the medication was elevated as a result of this. As a result, the maximum drug release from the formulations Phenylepherine SNEDDS (P9) and Ketorolac SNEDDS (K9) was determined to be at 30 minutes (102.20±2.76 % and 100.74±2.80 %, respectively). Increasing the Smix ratio in P9 and K9 causes a rise in drug release, and the effectiveness of drug delivery is largely determined by the size of microparticles in suspension and the polarity of oil droplets formed, which enables a higher rate of drug release into the aqueous phase. Drug that has been solubilized may not precipitate in the lumen and may undergo fast absorption that is not dependent on the lipid digestion process, if at all.

Formulation code	**% Cumulative Drug Release**					
	5 min	10 min	15 min	20 min	25 min	30 min
P1	22.14±2.42	32.42±2.76	46.42±2.38	54.58±2.32	60.72±2.42	84.42±2.76
P2	41.87±2.32	54.26±1.45	62.30±2.44	73.68±2.62	85.84±2.82	91.66±2.42
P3	36.40±2.82	46.81±1.72	52.02±2.72	61.58±2.34	75.11±2.24	88.29±2.24
P4	47.82±0.25	55.64±2.76	68.89±1.90	73.91±1.98	85.25±0.43	95.30±0.71
P5	43.93±0.21	57.47±1.16	67.53±1.65	79.35±1.34	85.79±1.33	89.59±1.23
P6	42.82±2.21	52.22±2.16	62.12±2.65	70.12±2.24	78.24±2.28	84.42±2.42
P7	56.81±2.76	68.02±2.24	75.11±2.42	81.29±2.34	92.42±2.44	101.42±2.42
P8	46.42±2.42	53.26±1.16	64.62±1.64	70.42±1.46	81.24±2.44	86.72±2.42
P9	63.57±2.76	71.14±2.76	83.08±2.76	89.92±2.76	97.72±2.76	102.20±2.76
Phenylepherine	4.22±2.12	10.66±2.14	14.46±2.18	22.48±2.38	34.38±2.22	46.38±2.26
K1	30.68±2.42	40.96±2.36	44.96±2.82	53.12±2.56	79.26±2.68	82.96±2.74
K2	30.41±2.68	52.8±2.78	60.84±2.38	72.14±2.36	84.38±2.24	90.20±2.12
K3	34.94±2.78	45.35±2.66	50.56±2.74	60.12±2.84	73.65±2.60	86.83±2.88
K4	46.32±2.48	54.18±2.42	67.43±2.44	72.45±2.36	83.79±2.34	93.84±2.68
K 5	42.47±2.30	56.01±2.50	66.07±2.40	77.89±2.44	84.33±2.34	88.13±2.38
K 6	41.36±2.80	50.76±2.12	68.66±2.36	76.78±2.46	88.24±2.78	90.96±2.54
K 7	55.35±2.88	66.56±2.60	73.65±2.72	79.83±2.52	90.96±2.42	99.96±2.38
K8	34.96±2.22	51.8±2.34	63.16±2.46	68.96±2.66	79.78±2.76	85.26±2.86
K9	62.11±2.44	72.68±2.34	81.62±2.94	88.44±2.84	96.26±2.74	100.7 ±2.64
Ketorolac	5.42±2.42	14.70±2.58	18.60±2.56	28.80±2.76	42.28±2.66	54.66±2.88

Table 6. Cumulative Invitro drug release profile of Phenylepherine and Ketrolac SNEDDS
All the values are measured in triplicate n-3 ±SD

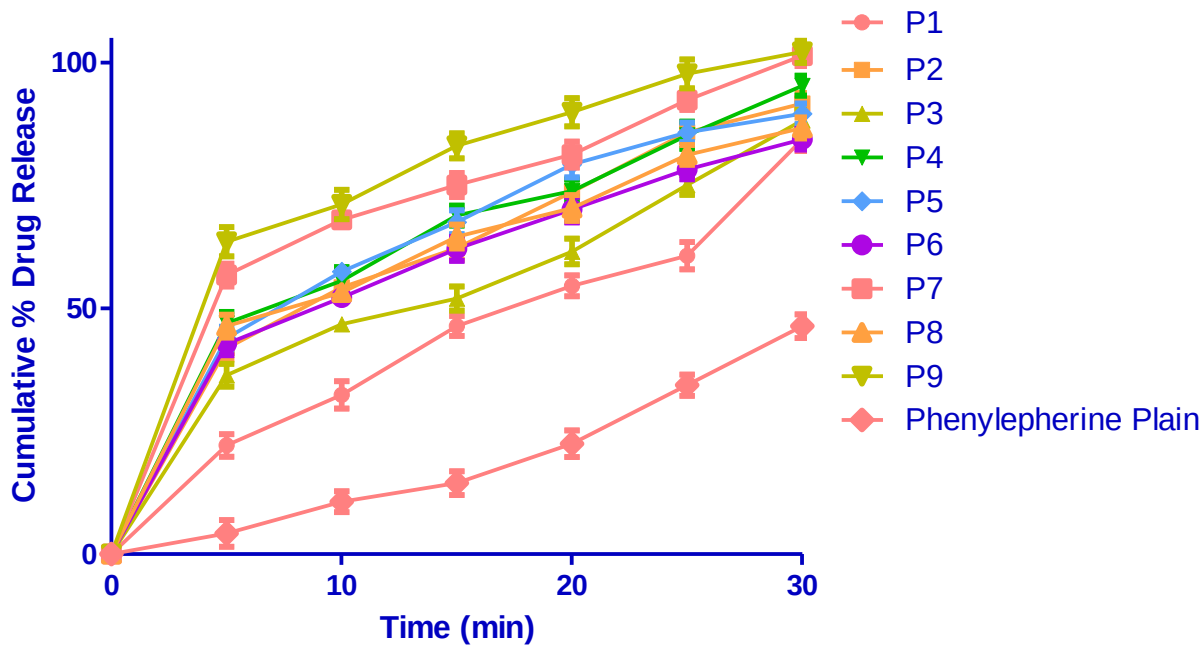

Fig. 3. Cumulative Invitro drug release profile of Phenylepherine SNEDDS P1-P9
All the values are measured in triplicate n-3 ±SD

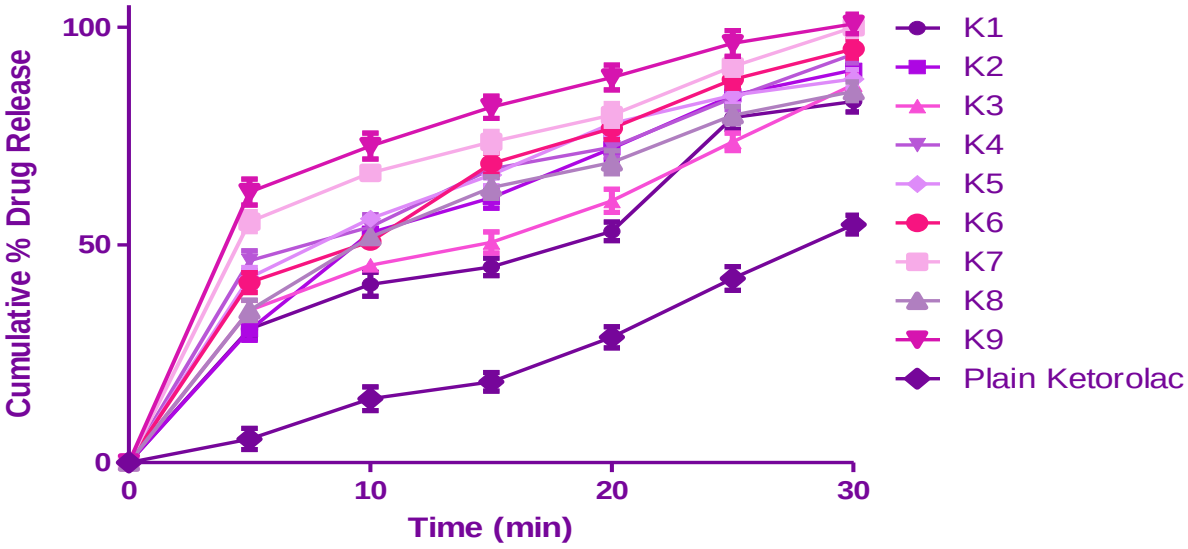

Fig. 4. Cumulative Invitro drug release profile of Ketorolac SNEDDS K1-K9
All the values are measured in triplicate n-3 ±SD

4. CONCLUSION

To enhance the bioavailability of hydrophobic/lipophilic medicines SNEDDS is one of most promising technique to overcome formulation problems towards dissolution/solubility. In this work SNEDDS of Phenylepherine and ketorolac nanoemulsion are successfully produced and evaluated for its in vitro performance. P9 and K9 formulation exhibited promising outcome. All the aforesaid studies in turn demonstrated excellent improvement of bioavailability and solubility of Phenylepherine and ketorolac in form of SNEDDS. Finally it can be concluded that SNEDDS is a potential technique to enhance the solubility, dissolution rate and bioavailability of medicines.

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COMPETING INTERESTS

Authors have declared that no competing interests exist

AUTHORS' CONTRIBUTIONS

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