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Formulation and evaluation of self-nanoemulsifying drug delivery system for improved oral delivery of exemestane hydrochloride

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ABSTRACT

Exemestane HCl (EXM) is a new irreversible steroidal aromatase inhibitor for adjuvant therapy of hormonally sensitive breast cancer in post-menopausal women. EXM's low water solubility hinders solid oral dosage form development. The current work aims to increase EXM solubility by formulating the self nanoemulsifying drug delivery (SNEDDs) system. The water titration approach was employed in the development of SNEDDs. Based on solubility tests, SNEDDs components Caprol Microexpress and Labrafac were selected as oil phase, Tween 80 as surfactant, and Triacetin as co-surfactant. Phase investigations were carried out with various surfactant:co-surfactant ratios (1:1, 1:2, 1:3, 2:1, 3:1). Tween 80: triacetin (1:2) and (1:3) with Caprol Microexpress and Labrafac alone had the greatest nanoemulsion area. Visual evaluation, optical clarity, particle size, medication concentration, and viscosity were used to optimise 10 formulations. F3, F7, and F8 batches had the lowest size at 7.313 ± 1.44 nm, 6.379 ± 0.45 nm, and 14.67 ± 0.37 nm, respectively, with self-emulsification times under 1 min.But optical clarity data was suggested that F7 was not showing any precipitation up to 24 H. Overall, the developed SNEDDS formulation could be a promising approach for the improved oral delivery of EXE with enhanced dissolution and bioavailability.

1. Introduction

Combinatorial chemistry and high-throughput screening (HTS) have revolutionised drug development during the past 20 years. It is now possible to rapidly synthesise and test a large number of molecules using these methods. Dimethylsulfoxide (DMSO), an organic solvent with excellent drug solubility, is commonly used in HTS to dissolve prospective therapeutic candidates.[1] It's because of this that developing chemicals that are water-soluble hasn't been a priority. Moreover, the creation of lipophilic, weakly water-soluble compounds has been preferred due to the demand for increased selectivity and target affinity in novel therapeutic candidates. Most pharmaceutical sector new chemical entities (NCE) are hence very insoluble in water. Before the late 1980s, NCEs with aqueous solubility less than 10 mg/mL were rare, now at least one-third of compounds from the discovery pipeline had solubility less than 1 mg/mL.[2,3]

Almost half of all potential new drugs have problems with issues such as water solubility, oral bioavailability, intra- and inter-subject variability, and dose proportionality. Several formulation strategies are employed to deal with these problems. Surfactants, lipids, permeation enhancers, micronisation, salt production, cyclodextrins, nanoparticles, and solid dispersions are all examples of such modifications.[4,5] In recent years, lipid-based drug delivery systems have received a lot of attention as a potential

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solution to the challenges of developing medications that aren't extremely water-soluble.[6] The medications are solubilized in a solvent or carrier, which can be anything from simple dietary triglycerides (oil) to complicated mixes of triglycerides, partial glycerides (mono- and di-glycerides), surfactants, co surfactants, amphiphilic copolymers, and cosolvents.[7] The resulting products were frequently liquids that needed to be encapsulated in soft gelatin and were distributed by bulk bottle dispensing. In order to increase the oral bioavailability of lipophilic pharmaceuticals, lipid based formulations, with a focus on the self emulsifying drug delivery system (SEDDS), have recently received a lot of attention.[8]

SNEDDS, is an exciting new technology that has the potential to increase both the rate and the extent of the absorption of medications that are poorly water-soluble.[9,10] The commercially available formulation of cyclosporine A, ritonavir, and saquinavir demonstrates the SNEDDS's clinical utility.[11] When diluted with water or the bodily fluids present in the aqueous lumen of the gut, SNEDDS produces fine droplets of emulsion that range in size from 5 to 100 nanometers. This occurs because SNEDDS is a preconcentrate combination that contains surfactants, co-surfactants, and a lipophilic phase.[12,13]

The EXM SNEDDS were made utilising the water titration approach, and the ultrasonication technique will be used to further reduce their size. Develop formulation was characterized for dilution study, optical clarity, emulsification time, drug content, viscosity, size, PDI, and stability studies. It also evaluated for the in vitro dissolution study, in vitro cytotoxicity, and in vivo bioavailability studies.

2. Materials and Methods

2.1. Materials

EXM was received as gifted sample from Astron Research Center, Ahmedabad, India. Caprol micro express, Miglyol 812, and Labrafac cc was gifted by ABITEC CORP. (USA), CHIKA PVT LTD(Japan) and GATTEFOSSE (France) respectively. Tween-80 and PEG-400 were procured from S.D. Fine-Chem. Ltd., Mumbai, India.

2.2. Methods

2.2.1. Calibration curve of EXM by HPLC

In order to create a standard stock solution of the medicine, 10 milligram's of the substance was weighed, then transferred to a 100 millilitre volumetric flask, where it was dissolved in the remaining methanol. Methanolic standard solution of 100 μg/ml was made. A series of 0.5 μg - 5 μg concentration solutions were created by transferring aliquots of the standard solution (ranging from 0.5 ml to 5.0 ml) to a series of 10 ml volumetric flasks and adjusting the volume of each flask to 10 ml with methanol. At a wavelength of 249 nm, the area of the solutions was determined, and a calibration curve was generated. The mobile phase utilised was acetonitrile:methanol (40:60) at a flow rate of 1 mL/min. Phenomenex C18 column (250 mm x 4.6 mm id, 5 μm particle size) was injected with a 20 μl sample.

2.2.2. Screening of components SNEDDS

Screening of SNEDDS components i.e. oils, surfactants and co-surfactants were done base solubility studies.[14] Different oils such as Olive Oil, Sunflower oil, Sefsol 228, Sefsol 218, Caprolmicroexpress, Capmul MCM, Labrafac, Miglyol 812, Capmul gmo-50, Capmul pg-8 was taken. For the surfactants screening Tween 80, Tween 20, Labrasol, Acrysol 135, Acrysol 150 and Acrysol 380 were taken.

2.2.3. Pseduo-ternary diagram

To find the right components and concentration ranges, pseudo-ternary phase diagrams were created. The nanoemulsion areas were defined by constructing a ternary pseudo phase diagram after selecting the right components.[15,16] Isotropy and low viscosity serve as first markers of the nanoemulsion zone. To optimize oil phase, surfactant, and co-surfactant concentrations, several batches were made and titrated with distilled water until turbidity emerged. Two-dimensional ternary phase diagrams can be made by keeping one component constant and altering the other three or by employing a constant surfactant-co-surfactant ratio. With a constant surfactant-to-co-surfactant ratio, pseudo-ternary phase diagram was created.[17]

Sigma plot version 10.0 was used to create a pseudo-ternary phase diagram of nanoemulsion to determine its zone of preparation. The surfactant (Tween 80) and Co-surfactant (Triacetin) were selected in the ratios 1:1,1:2,1:3,2:1,3:1 and nanoemulsion were prepared by decreasing the oil phase (Caprol microexpress. Labrafac) concentration from 90% to 10% and increasing the surfactant/Co-surfactant from 10% to 90% to find the maximum water uptake by nanoemulsion that remains transparent. Oil:co:s ratios (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9) were picked.[9]

2.2.4. Formulation of SNEDDS

The SNEDDS formula was developed using a process known as water titration. In the first step, magnetic stirrer was used to continuously dissolve EXM in oil (700 RPM, 30 min). The medicines (250 mg) were dissolved in oil, and the Smix ratio was added drop by drop while the mixture was being stirred with a magnetic stirrer. To accomplish size reduction, this mixture was ultrasonicated for 30 minutes. Produce SNEDDS and have them tested for a variety of characteristics.

2.2.5. Evaluation of SNEDDS

2.2.5.1. Visual Assessment. The SEDDS formulation is very susceptible to phase separation upon infinite dilution, which can result in the precipitation of a weakly soluble medication. Thermodynamically driven by the need for the surfactant to keep the concentration of the aqueous phase equal to its critical micelle concentration (CMC), gastrointestinal fluid dilution causes a slow breakdown of oral nanoemulsions.[10]

2.2.5.2. Optical Clarity. One millilitre of each formulation was diluted in a glass beaker with 0.1 N HCL, a phosphate buffer with a pH of 5.8, and water. Nanoemulsion absorbance was measured at 560 nm using a UV spectrophotometer immediately after development and again at 0, 6, and 24 hours.[18]

2.2.5.3. Assessment of Efficiency of self emulsification. Assessment of self emulsification were evaluated by measuring time need for the emulsification and based on that different grade given. Table 1 was showing the grading system of emulsification. Phase separation in spontaneously emulsifying systems is greatly influenced by the dilution and vehicle pH. Hence, we diluted (100 times) chosen EXM SNEDDS using different diluents (i.e., water, 0.1 N HCl and phosphate buffer). Storage of the diluted self emulsions at room temperature for 8 hours allowed for the detection of phase separation and drug precipitation.[13]

Table 1: Different grade of SNEDDs based on emulsification time

Grade	Dispersibility	Time of self emulsification
I	Rapid forming emulsion which is clear or slightly bluish in appearance	**<1**
II	Rapid forming, slightly less clear emulsion which has a bluish white appearance	**<2**
III	Bright white emulsion (similar to milk in appearance)	**<3**
IV	Dull, grayish white emulsion with a slightly oily appearance that is slow to emulsify	**>3**
V	Poor or minimal emulsification with large oil droplets present on the surface	**>3**

2.2.5.4. Drug content. HPLC analysis was used to assess the dosage uniformity by determining the EXM content as a percentage.

2.2.5.5. Viscosity measurement. Viscosity was measured in the finished products with a Brookfield DV-II+ Pro model viscometer. Viscosity was determined at 25°C by pouring the chosen formulations into the sample adapter of the viscometer. Spindle 1 was rotated through the sample at a speed of 100 RPM, and the sample's viscosity was evaluated 10 minutes later. Each sample was measured three times to ensure accuracy, and the results were averaged.

2.2.5.6. Droplet size & Polydispersity index. Particle size and distribution were measured using a Malvern laser light scattering Zetasizer model. At 25°C and 90° angle, light scattering was measured.[19] The mean droplet size and Polydispersity index were computed using intensity, volume, and bimodal distribution assuming spherical particles. Polydispersity index (PDI) measures particle homogeneity from 0.0 to 1.0. Particles are increasingly homogeneous when Polydispersity approaches zero.

2.2.5.7. Physical Stability of SNEDDS. The temperature stability test was carried out in accordance with the ICH Q1(C) standard. Samples of the formulations were stored at 2-8 degrees Celsius and 25 degrees Celsius for a month, and then visually inspected and analysed for phase separation, flocculation, and precipitation based on the guidelines provided. Formulated EXM SNEDDS was evaluated for flocculation, creaming, and oil separation using centrifuge.

3. Result and Discussion

3.1. Analytical method development

Peak areas and EXM concentrations 0.5–5 μg/mL were linearly correlated with a R^2 of 0.997. Recovery trials used normal addition. EXM recovered 100.3 ± 0.47%. Interday and intraday RSD values for EXM of 1.05-1.15 percent and 0.25-1.28 percent, respectively, demonstrate the accuracy of the proposed method. EXM LOD was 0.08μg/mL and LOQ was 0.24ng/mL. These statistics demonstrate that the suggested EXM determination method is sensitive. EXM has 0.423 % RSD. The approach is reproducible because RSD values were <1%.

3.2. Screening of the SNEDDS components

Solubility of EXM in different SNEDDS components was shown in Figure 1. From the results, it was found that labrafac cc (25.15 mg/ml) and Caprol microexpreess(22.72 mg/ml) shows highest solubility in comparison to Olive oil, Sefsol-218, Sefsol-228,Capmul gmo-50,Miglyol 812. Highest solubility of EXM in surfactant and co-surfactant was found in Tween 80 and Triacetine.

3.3. Pseudo ternary diagram of EXM

While the free energy required to produce an emulsion is little, its production is thermodynamically spontaneous, therefore precautions were taken to avoid seeing metastable structures.[20] A phase diagram can be used to depict the correlation between the phase behaviour of a mixture and its

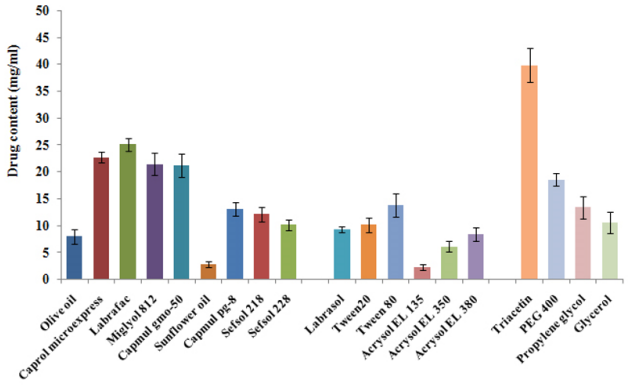

Fig. 1: Drug concentration (mg/mL) in different oils, surfactant and co-surfactant

constituents. In order to locate the o/w nanoemulsion zones and improve the nanoemulsion formulations, individual pseudo ternary Phase diagrams were created for each Smix ratio[21] (Figure 2).

Large nanoemulsion area was observed for Smix with ratios of 1:2 and 1:3. The O/w nanoemulsion zone was located towards the water-rich tip of the phase diagram and at higher concentrations of Smix, suggesting that Tween 80 might be employed without a cosurfactant, however a larger concentration of surfactant would be necessary. In the phase diagram, the highest surfactant concentration that could be solubilized was close to 20% (m/m) of Smix.

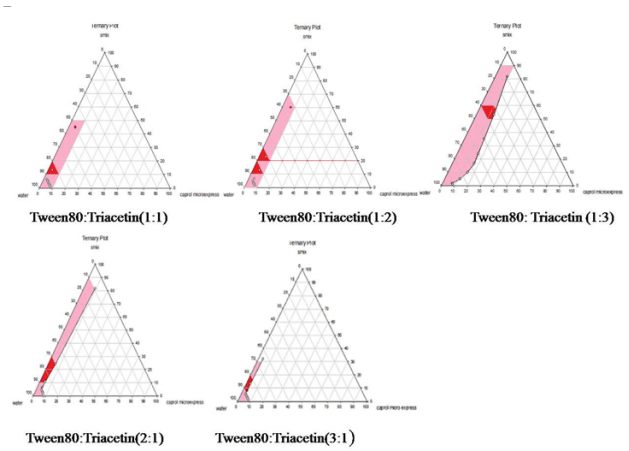

Fig. 2: Ternary phase diagram of Tween 80: triacetine: Caprol microexpress: Water

The addition of cosurfactant to surfactant resulted in a more fluid interfacial coating and no liquid crystalline region in Fig. 2's 1:3 Smix. There was a sizable region of o/w nanoemulsion detected. Up to around 30% (m/m) of Smix was needed to completely dissolve the oil. The nanoemulsion zone expanded when the surfactant concentration in Smix (ratio 1:3) was raised. The entropy of the system may have increased as a result of a decrease in the interfacial tension, making the interface more fluid. Hydrophobic areas of the surfactant monomers may allow for deeper oil phase penetration. When we raised the surfactant concentration in Smix to a ratio of 2:1, the nanoemulsion zone shrank even more than it had when using ratios of 1:2 and 1:3, with the greatest oil concentration that could be solubilized by this ratio being 15% (m/m) using 30% (m/m) of Smix.

With 30% Smix, oil concentrations up to 15% were soluble. The nanoemulsion area grew when the concentration of the cosurfactant was raised from 1:1 to 1:2 relative to the surfactant. The formulation's viscosity dropped as its surfactant content rose. Thus, it is essential to accurately calculate the surfactant concentration and to employ the optimum concentration of surfactant in the formulation; a greater viscosity nanoemulsion may not be suited for the formulation. Pseudo ternary phase diagrams were used to choose formulations for the research in which the medication was totally soluble in the oil phase and the optimal amount of Smix and distilled water could be included. The TPD results demonstrate that the turbidity of the formulation increases as the oil concentration rises and the surfactant mixture falls. Thus, the region of the figure where the Smix concentration is greatest is also known as a nanoemulsion or a monophasic region.[13]

3.4. Formulation of SNEDDS

Ten formulations are selected from the nanoemulsion (clear) area from two phase diagram for further evaluation. The formulation was observed at specific time interval for the precipitation of drug to show the stability of the drug in the formulation, and it is one of the criteria for the selection of the formulation.

Table 2: Composition of different formulation

Batch Number	Composition (mL)		
	Caprol Microexpress	**Tween 80**	**Triacetin**
F1	3.0	3.5	3.5
F2	3.0	2.4	4.8
F3	3.0	1.8	5.4
F4	3.0	4.8	2.4
F5	3.0	5.4	1.8
	Labrafac	**Tween 80**	**Triacetin**
F6	2.0	4.0	4.0
F7	2.0	2.7	5.4
F8	2.0	2.0	6.0
F9	2.0	5.4	2.7
F10	2.0	6.0	2.0

Assuming a total volume of 10 mL, with 250mg of EXM per millilitre, the formulations here all weigh the same. Glass vials with caps were weighed to determine the correct amount of Labrafac, CaprolMicroexpress, Tween 80, and

Triacetin to use. After adding the lipid and surfactant, 250 mg of the medicine was dissolved by vigorously vortexing the liquid until the drug was completely dissolved. During thirty minutes, the solutions were sonicated. These drug-lipid and drug-surfactant combinations were kept at room temperature until usage.

3.5. Evaluation of SNEDDS

3.5.1. Visual assessment

An insoluble medication may precipitate out of a SNEDDS formulation after indefinite dilution. The gastrointestinal (GI) fluids dilute oral nanoemulsions further, and the surfactant's CMC dictates that its aqueous phase concentration must remain constant. Aqueous dilution was tested using purified water since it is well known that non-ionic surfactant nanoemulsions distributed in either SGF or SIF water have no relevance.[18]

All the emulsions prepared following aqueous dilution of the formulations were assessed for stability and it was found that no precipitation of the drug was apparent till 24 hrs. As SNEDDS are either diluted just prior to administration or else in the body, the required droplet stability is more than 6 hrs (i.e., transit time of materials down the small intestine).

Table 3: Visual assessment to check precipitation on aqueous dilution with water

Batch Number	0 hr	6 hr	24 hr
F1	Clear		+
F2	Clear		++
F3	Clear		+
F4	Clear		+
F5	Clear		+
F6	Clear		++
F7	Clear		++
F8	Clear		++
F9	Clear		+
F10	Clear		++

3.5.2. Optical Clarity

Absorbance at 560 nm was taken directly from a diluted SNEDDS sample using a UV Spectrophotometer (SHIMANZU UV-1800) to evaluate its clarity. Nanoemulsion droplet stability is indicated by this term. The results show that formulations with the optimal ratio of Smix ratio and oil, such as F2 (1:2), F4 (2:1), F7 (1:2), F8 (1:3), and F10 (3:1), were stable for up to 24 hours.

At 24 hours, formulas F5 and F9 showed a moderate shift in absorbance values. Absorbance values fluctuated dramatically over time for formulations F3 and F6, suggesting that the droplets were unstable.Table 4

Table 4: Variation in optical clarity with time in water (Values are expressed as mean ± S.D, n=3)

Batch Number	Absorbance at 560 nm		
	0 hrs	6 hrs	24 hrs
F1	0.0105 ± 0.0012	0.0174 ± 0.0026	0.0161 ± 0.0024
F2	0.0167 ± 0.0021	0.0176 ± 0.001	0.0183 ± 0.0001
F3	0.0143 ± 0.0011	0.0157 ± 0.0003	0.0171 ± 0.0022
F4	0.0089 ± 0.0013	0.0139 ± 0.0036	0.0165 ± 0.0026
F5	0.0082 ± 0.0011	0.0125 ± 0.0017	0.0148 ± 0.0017
F6	0.0083 ± 0.0006	0.0112 ± 0.0037	0.0112 ± 0.0012
F7	0.0132 ± 0.0016	0.0126 ± 0.0008	0.0161 ± 0.0009
F8	0.0118 ± 0.0010	0.0227 ± 0.0023	0.0327 ± 0.0011
F9	0.0117 ± 0.0015	0.019 ± 0.003	0.0366 ± 0.0054
F10	0.007 ± 0.0005	0.0132 ± 0.0014	0.0154 ± 0.0018

3.5.3. Viscosity and Drug Content

The formulation was significantly affected by the viscosity. Each formulation's viscosity was measured to fall between the 2.2–3.8 ranges. It turns out that different formulas have different levels of viscosity, as evidenced by the findings. The viscosity of a formulation rises with the number of Tween 80 molecules per unit of volume. Viscosity Table 5 reveals that formulations F3 (2.45±0.37), F7 (2.2±0.21), and F8 (2.3±0.54) had the lowest viscosity of the batch.

Table 5: Viscosity and drug content of formulation (Values are expressed as mean ± S.D, n=3)

Batch number	Viscosity (cps)	%drug content
F1	2.90±0.14	98.33 ± 0.01
F2	2.80±0.46	99.24 ± 0.14
F3	2.45±0.37	96.35 ± 0.07
F4	3.5±0.44	97.79 ± 0.098
F5	3.8±0.32	94.02 ± 0.86
F6	2.45±0.22	97.07 ± 1.06
F7	2.2±0.21	98.96 ± 0.66
F8	2.3±0.54	99.28 ± 0.33
F9	2.9±0.76	95.1 ± 0.24
F10	3.4±0.58	96.98 ± 0.95

HPLC analysis was used to assess drug content and dose form homogeneity. The findings are provided in table 5, which reveals that formulations F1 (98.33 ± 0.01), F2 (99.24 ± 0.14), F7 (98.96 ± 0.66), and F8 (99.28±0.33) had the greatest percentages of drug content. So from we can conclude that above F1, F2, F7, F8 is stable and had a good uniform drug distribution.Table 5

3.5.4. Self Emulsification Time

The phase separation of the spontaneously emulsifying system is highly sensitive to the dilution and pH of the vehicle.[13] Because of this, certain EXM SNEDDS were diluted twice (20 times) and thrice (100 times) using different solvents (i.e. water, 0.1 N HCl and phosphate buffer). Phase separation and drug precipitation were analyzed after letting the diluted nanoemulsions sit out at room temperature for 8 hours.

Table 6: Emulsificationstudy

Batch Number	Grade	Self-Emulsification time (min)
F1	II	<2
F2	II	<2
F3	I	<1
F4	II	<2
F5	III	<3
F6	II	<2
F7	I	<1
F8	I	<1
F9	I	<1
F10	III	<3

Table 7: Particle size of diluted sample ofEXM SNEDDS in water (Values are expressed as mean ± S.D, n=3)

Batch Number	Particle size(nm)
F1	27.70 ± 1.78
F2	22.56 ± 1.43
F3	7.313 ± 1.44
F4	44.33 ± 0.78
F5	15.91 ± 1.04
F6	85.33 ± 3.19
F7	6.379 ± 0.45
F8	14.67 ± 0.37
F9	33.97 ± 1.18
F10	123.1 ± 4.24

From the data shown in Table 6 as the concentration of Tween 80 increases self-emulsification time increases so that it produces unstable formulation. Here F3,F7, F8, and F9 had grade I type emulsion and F1,F2,F4,F6 showed type II emulsion and F5 and F10 showed type III emulsion**.** So F3 (1:3), F7 (1:2), F8 (1:3), F9 (2:1) was best emulsion to be selected for optimized and had no type of separation or droplet stability.

3.5.5. Particle size determination

Droplet size in the nanoscale range is a defining feature of SNEDDS. The rate and degree of drug release and absorption are both affected by the droplet size of the emulsion, making it a critical factor in the self-emulsification performance.[13] Also, it has been suggested that the emulsion's smaller droplet size may facilitate faster absorption and enhance bioavailability. So as to determine whether or not the produced emulsions qualify as nanoemulsions, droplet size analysis was carried out. Keeping an eye on the size distribution as it shifts over time can help with formulation optimization. The data for droplet size in water are tabulated in Table 7.

The result shows that the higher the Tween 80 to triacetine ratio the greater the droplet size. This is evident as smallest particles were observed for formulation F7 and largest droplets were obtained for formulation F6. As the fractions of Tween 80 increases the average droplet size of all formulations increases. Due to small droplet size, all the formulations showed no sign of separation at the end of 24 hrs post dilution, despite high surfactant concentration in some of the formulations. It was seen that droplet size was inversely proportional to optical clarity. The optically transparent dispersions (i.e., low absorbance due to optical clarity) had the lowest droplet size and as the optical clarity decreases, droplet size increases.[8,17]

4. Conclusion

Based on solubility data labrafac cc, Caprol microexpreess, Tween 80 and Triacetine was shows highest solubility in comparison and selected as oil, surfactant and cosurfactant for the formulation of EXM SNEDDS. From the all over result, it was found that F3, F7 and F8 batch has lowest size with the less than 1 min time for self-emulsification. But Optical clarity based stability studies showing that F7 batch is most stable. F7 batch composed of Labrafac, Tween 80 and Triacetin which have 6.379 ± 0.45 nm. In conclusion, the study demonstrated that SNEDDS can be a promising strategy for improving the oral bioavailability of poorly water-soluble drugs like EXE.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Furka A. Forty years of combinatorial technology. *Drug Discov Today*. 2022;27(10):1–12. doi:10.1016/j.drudis.2022.06.008.
2. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. *J Pharm Pharmacol*. 2010;56(7):827–40. doi:10.1211/0022357023691.
3. Tang J, Sun J, He ZG. Self-Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs. *Curr Drug ther*. 2007;2(1):85–93. doi:10.2174/157488507779422400.
4. Nair A, Khunt D, Misra M. Application of quality by design for optimization of spray drying process used in drying of risperidone nanosuspension. *Powder Technol*. 2019;342:156–65. doi:1016/j.powtec.2018.09.096.
5. Kesharwani R, Jaiswal P, Patel DK, Yadav PK. Lipid-Based Drug Delivery System (LBDDS): An Emerging Paradigm to Enhance Oral Bioavailability of Poorly Soluble Drugs. *Biomed Mater Devices*. 2022;doi:10.1007/s44174-022-00041-0.

6. Witika BA, Poka MS, Demana PH, Matafwali SK, Melamane S, Khamanga SMM, et al. *Pharmaceutics*. 2022;14(4):836. doi:10.3390/pharmaceutics14040836.
7. Siepmann J, Faham A, Clas SD, Boyd BJ, Jannin V, Bernkop-Schnürch A, et al. Lipids and polymers in pharmaceutical technology: Lifelong companions. *Int J Pharm* . 2019;558:128–42. doi:10.1016/j.ijpharm.2018.12.080.
8. Ruiz PSL, Serafini MR, Alves IA, Novoa DMA. Recent progress in self-emulsifying drug delivery systems: a systematic patent review (2011-2020). *Crit Rev Ther Drug Carr Syst*. 2022;39(2):1–77. doi:10.1615/CritRevTherDrugCarrierSyst.2021038490..
9. Baloch J, Sohail MF, Sarwar HS, Kiani MH, Khan GM, Jahan S, et al. Self-nanoemulsifying drug delivery system (SNEDDS) for improved oral bioavailability of chlorpromazine: in vitro and in vivo evaluation. *Medicina (B Aires)*. 2019;55(5):210. doi:10.3390/medicina55050210.
10. Prajapati B, Rao S, Barot T. Development of Solid Self Microemulsifying Drug Delivery System (S-SMEDDS) of Aripiprazole by using D-Optimal Mixture Design. *High Technol Lett*. 2020;26:721–31.
11. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery. *Pharmaceutics*. 2020;12(12):1194. doi:10.3390/pharmaceutics12121194.
12. Ashfaq M, Shah S, Rasul A, Hanif M, Khan HU, Khames A, et al. Enhancement of the solubility and bioavailability of pitavastatin through a self-nanoemulsifying drug delivery system (SNEDDS). *Pharmaceutics*. 2022;14(3):482. doi:10.3390/pharmaceutics14030482.
13. Rathore C, Hemrajani C, Sharma AK, Gupta PK, Jha NK, Aljabali A, et al. Self-nanoemulsifying drug delivery system (SNEDDS) mediated improved oral bioavailability of thymoquinone: optimization, characterization, pharmacokinetic, and hepatotoxicity studies. *Drug Deliv Transl Res*. 2023;13(1):292–307. doi:10.1007/s13346-022-01193-8.
14. Katdare A, Khunt D, Thakkar S, Polaka SN, Misra M. Comparative evaluation of fish oil and butter oil in modulating delivery of galantamine hydrobromide to brain via intranasal route: pharmacokinetic and oxidative stress studies. *Drug Deliv Transl Res*. 2020;10(4):1136–46. doi:10.1007/s13346-020-00739-y.
15. Bhattacharya S, Prajapati BG. Formulation and optimization of celecoxib nanoemulgel. *Asian J Pharm Clin Res*. 2017;10(8):353–65. doi:10.22159/ajpcr.2017.v10i8.19510.
16. Prajapati B. Nanoemulgel"Innovative Approach For Topical Gel Based Formulation. *Res Rev Healthc Open Access J*. 2018;doi:10.32474/RRHOAJ.2018.01.000107.
17. Prajapati BG, Patel AG, Paliwal H. Fabrication of nanoemulsion-based in situ gel using moxifloxacin hydrochloride as model drug for the treatment of conjunctivitis. *Food Hydrocoll Heal*. 2021;p. 100045. doi:10.1016/j.fhfh.2021.100045.
18. Vikash B, Pandey NK, Kumar B, Wadhwa S, Goutam U, Alam A, et al. Formulation and evaluation of ocular self-nanoemulsifying drug delivery system of brimonidine tartrate. *J Drug Deliv Sci Technol*. 2023;81:104226. doi:10.1016/j.jddst.2023.104226.
19. Kochar P, Nayak K, Thakkar S, Polaka S, Khunt D, Misra M, et al. Exploring the potential of minoxidil tretinoin liposomal based hydrogel for topical delivery in the treatment of androgenic alopecia. *Cutan Ocul Toxicol*. 2020;39(1):43–53. doi:10.1080/15569527.2019.1694032.
20. Cates ME, Andelmans D, Safran SA, Roux D. Theory of Microemulsions: Comparison with Experimental Behavior+. *Langmuir*. 1988;4:802–6.
21. Prajapati BG, Jivani M, Paliwal H. Formulation and optimization of topical nanoemulsion based gel of mometasone furoate using 32 full factorial design. *Indian Drugs*. 2021;58(5):19–29. doi:10.53879/id.58.06.12796.

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