Preparation and characterization of oxcarbazepine microemulsion

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Background
Oxcarbazepine (OXZ) is an antiepileptic drug used to treat partial seizures. OXZ is available in dosage forms of tablet (150, 300, and 600 mg) and suspension (300 mg in 5 ml) in India. Children and adults complain that the suspension form has a downside in its stability (8 weeks).
Aims
The aim of the present investigation was to develop a microemulsion (ME) of OXZ for enhanced solubility and stability of drug in product.
Materials and methods
An ME comprises isopropyl myristate (oil phase), aerosol OT (a bipolar surfactant), and an aqueous phase comprising ethanol and distilled water in a ratio of 2: 8. Various ratios of oil: surfactant (1: 9 to 9: 1) were taken and the amount of aqueous phase titrated was determined using the water titration method. The data were plotted in a pseudoternary phase diagram and an optimized batch was selected. The batch was characterized by droplet size determination, zeta potential, drug content, and in-vitro dissolution studies.
Results
Size of the globules was found to be 53.65 and 59.15 nm in both ME 1 and ME 2, respectively; thus, it can also be termed as nanoemulsion. Zeta potential shows that the formulation is stable as it has positive zeta, giving 6.13 and 5.21 mV as zeta for ME 1 and ME 2, respectively. pH and conductance were also close to neutral, and hence the system was biocompatible.
Conclusion
Finally, on the basis of physicochemical characterization and stability studies, it can be concluded that water-in-oil ME for OXZ will serve as a novel drug delivery system with increased solubilization capacity and increased stability.

Keywords:
microemulsion, oxcarbazepine, solubility, stability

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Introduction

The oral route for drug administration is the most mainstream for drug administration. Numerous patients experience issues in gulping solid oral dosage form and do not take their drug as prescribed. It is estimated that half of the populace have trouble in gulping, which brings about a high occurrence of patient rebelliousness and ineffectual treatment. Liquid formulations are satisfactory and have appreciative patient compliance, although having an issue of poor stability of drugs [1,2].

Epilepsy is a disorder of the cerebrum that is described by a persisting inclination to create seizures and by its neurobiological, subjective, mental, and social outcomes. Epilepsy is operationally characterized as a gathering of neurologic issue portrayed by intermittent scenes of convulsive seizures, tactile unsettling influences, irregular conduct, and loss of cognizance. 'Epilepsy' originates from the Greek word epilambanein, signifying 'to be seized' or 'to be overpowered unsuspecting' [3–5].

Oxcarbazepine (OXZ) (or 10, 11-dihydro-10-oxo-carbzepine) is a more up-to-date sweet-smelling antiepileptic drug, affirmed in the USA on 14 January 2000 (as characterized by late American Academy of Neurology-American Epilepsy Society rules, a more up-to-date antiepileptic medication is one endorsed by the US Nourishment and Drug Administration since 1990), which was created as a second era and as a subsequent compound to carbamazepine [6,7]. OXZ has a comparable restorative profile to carbamazepine, yet has fewer

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symptoms on patients. Clinically, it has been utilized to treat a few types of epilepsy. It is a planned first-line treatment for the treatment of incomplete and auxiliary summed up tonic–clonic seizures. Augmented discharge antiepileptic drug definitions can accomplish the essential treatment objectives for some patients with epilepsy. OXZ is administered in different dosage forms such as tablets and suspension [8]. Its bioavailability is 40% in tablets or capsules. Being a water-insoluble medication, it needs a novel drug delivery intensifying its dissolvability and bio-availability. Tablets have high-dosage regimen. Furthermore, tablets have issues with the coating and oxidation of same on storage, whereas suspension has a downside of stability – that is, just 2 weeks stability in marketed formulation after the seal is opened. It is evaluated that half of the populace has trouble in gulping, which brings about a high rate of patient rebelliousness and insufficient treatment. Liquid formulation is effective and has higher patient compliance, yet it has issue of poor stability.

Microemulsion (ME) is clear, thermodynamically stable, isotropic mixtures of oil, water, and surfactant, frequently in combination with a cosurfactant [9,10]. It is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10–100 nm. ME is used as potential drug delivery vehicles, largely due to simple manufacturing, scale-up feasibility, and do not require specialized equipments. Oil-in-water (o/w) ME is the most suitable formulation, which is expected to increase the solubility by dissolving compounds with low water solubility into an oil phase [11].

ME is used to overcome poor compliance of patient, to decrease dosage regimen, and to increase stability. The present work aimed to design, characterize, and evaluate ME for OXZ to increase water solubility and to give patient consistence by defining a novel stable drug delivery system.

Materials and methods

Materials

An ME-based drug delivery system has been designed for OXZ obtained as a gift sample from Astron Research Laboratory, Ahmedabad, India, comprising isopropyl myristate (IPM) (the oily phase), aerosol OT (AOT) (a bipolar surfactant), dioctyl sodium sulfosuccinate, and distilled water (the aqueous phase). All excipients, oils, surfactants, and solvents used in the preparation were purchased from Sigma-Aldrich (Banglore, India) and were of analytical grade.

Methods

Screening of oils and surfactants

In the initial screening of oils for the preparation of ME, IPM, ethyl oleate, and oleic acids were used for solubility of OXZ and were screened for maximum drug entrapment, and the best was used for further studies. The solubility of OXZ in various oils (IPM, ethyl oleate, and oleic acid) and surfactants (AOT, Span 20, and Tween 80) as determined by dissolving an excess amount of OXZ in 2 ml of each of the selected oils and surfactants in 5 ml capacity stoppered vials separately for the determination of solubility. An excess amount of OXZ was added to each 5 ml capacity stoppered vial and mixed using a magnetic stirrer. The vials were kept in a shaker for 72 h at 30°C to attain equilibrium. The equilibrated samples were then centrifuged at 3000 rpm for 30 min. The supernatant was taken and filtered through a 0.45 μm membrane filter. The concentration of OXZ was determined in each oil, surfactant, and cosurfactants using UV spectrophotometer at their respective wavelength 306 nm [12]. Only those oil and surfactant were chosen for further study in which the λ_{max} was preserved at 305 nm. Absorbance of each solution was measured. Solubility of OXZ in various oils and surfactants was measured in terms of mg/ml [13–16].

Drug excipient compatibility study

FT-IR spectroscopy study: FT-IR spectral analysis was carried out to evaluate drug– excipient compatibility. An FTIR-8400S spectrophotometer (Shimadzu Corporation, Kyoto, Japan) was used to find the spectra of drug in mixtures of excipients, pure drug, and drug-adsorbed solid ME in aerosol and pure aerosol. All samples were dried under vacuum before obtaining any spectra to remove the influence of residual moisture. For each spectrum, 32 scans were obtained at a resolution of 4 cm^{-1} from a frequency range of 4000–400 cm^{-1}.

Differential scanning calorimetry (DSC) study: DSC of pure drug, drug-adsorbed solid ME in aerosil, and surfactant AOT was carried out using DSC-50 (Mettler, Germany). Samples were placed in aluminum crucible cell with lids firmly crimped to provide adequate seal. The samples were heated from ambient temperature to 300°C at a preprogramed heating rate of 10°C/min.

X-ray diffraction study: The diffraction pattern was recorded in the interval $0°<2\theta<90°$ in a step scan mode of 0.02° per step at every 35.7 s. Powder diffraction study of OXZ and solid-adsorbed ME of OXZ was carried out at room temperature. The powder samples were grinded in an agate mortar

and side loaded. The instrument generator (TTK 450; Anton Paar, Gurgaon, India) was powered at a voltage of 40 kV and a current of 30 mA. The diffractograms were analyzed using the DIFFRAC.SUITE program (Bruker India Scientific Ltd., Banglore, India).

Preparation of ternary phase diagram: The ME comprised oil, water, surfactant, and cosurfactant. The concentration of surfactant: cosurfactant and the aqueous phase varies in the preparation of ME. Hence, it is advised to prepare a pseudoternary diagram. The surfactant concentration is kept constant and the concentrations of aqueous phase and cosurfactant are varied. The increased concentration of oil and surfactant forms reverse micelles capable of solubilizing water molecules in their hydrophilic interior. Further addition of water in this system results in the formation of ME in which water and solvent system exists as droplets surrounded and stabilized by the interfacial layer of the surfactant [13,14]. Upon additional dilution with water, a liquid crystalline region may be formed in which the water is sandwiched between surfactant double layers. Finally, at higher aqueous part, the lamellar structure is broken down and water will form a continuous phase containing droplets of oil stabilized by a surfactant. Phase diagram was prepared using the water titration method. These mixtures of oil and surfactant were mixed to give the weight ratios of 90: 10, 80: 20, 70: 30, 60: 40, 50: 50, 40: 60, 30: 70, 20: 80, and 10: 90. Water was added drop by drop and stirred using a magnetic stirrer until a homogeneous dispersion or solution was obtained. At the end of titration, the system becomes cloudy or turbid. The amount of water required to make the mixture turbid was measured. The procedure was repeated with water alone, ethanol: water (3: 7), and ethanol: water (2: 8). Thus, the different phase diagrams were prepared using, PROSIM software (PROSIM Inc., Philadelphia, USA) [13–15].

Preparation of ME of OXZ: For the preparation of ME, oil (IPM) and surfactant (AOT) were taken in a beaker in appropriate w/w amount. The mixture was kept in probe sonication with heat until AOT solubilized and a clear solution was formed. The drug was then incorporated (amount decided from solubility data) (400–450 mg of drug is incorporated in 5 ml of above system) in the above system and dissolved under stirring condition on a magnetic stirrer. After the drug completely dissolved, the aqueous phase (type I water/solvent mixture) was added dropwise. The aqueous phase was added until the system remained transparent (amount decided using phase diagram). Thus, ME is formed. The formed ME can be administered orally or through nasal route. The formed ME was stored for stability studies and was analyzed for other mentioned evaluation parameters.

Selection of the optimized batch: In total, four phase diagrams were constructed using two types of aqueous phase, type I water and mixture of ethanol and type I water in the ratio of 2: 8 with and without drug. From the 18 batches (only with drug), only two were examined further for various evaluation parameters. The criteria for selection of the optimized batch were droplet size, zeta potential, and % of aqueous phase. The one having lowest size and highest zeta potential and the one incorporating highest amount of aqueous phase was considered to be optimized for each aqueous system. Two batches were then given code ME 1, an optimized batch of water system, and ME 2, an optimized batch of ethanol: water (2: 8) system. Furthermore, both batches were assessed for various evaluation parameters.

Evaluation of microemulsion of oxcarbazepine

Droplet size analysis

Each formulation (ME 1 and ME 2 batches from F1 to F9) was analyzed for droplet size. The prepared ME was inverted twice to ensure complete dispersion of the formulation. After ensuring complete dispersion of the formulation, the droplet size of resultant nanoemulsion was determined using photon correlation spectroscopy, which analyzes the fluctuation in light scattering due to the Brownian motion of the droplets as a function of time using a dynamic light scattering (DLS) spectrophotometer (Model DLS700; Malvern Electronics Company Ltd.; Malvern Instruments Ltd., United Kingdom) using a neon laser of wavelength 632 nm. Light scattering was monitored at 25°C at 90° angle [16–18].

Zeta potential measurement

Each formulation (ME 1 and ME 2 batches from F1 to F9) was analyzed for zeta potential using a DLS spectrophotometer (Model DLS700; Malvern Electronics Company Ltd.) equipped with a 4.0 mW He-Ne red laser (633 nm). Zetasizer measures the potential ranging from –120 to 120 V. For measurement of zeta potential, 2 g of each formulation was diluted with milliQ water (100 ml).

Rheological studies (η)

Viscosity (η) measurements were carried out using a Brookfield viscometer (LVT Model; Brookfield LVT, Massachusetts, USA). A volume of 20 ml of ME was filled in the cylindrical tube and the dial reading was noted at 10, 20, 50, 100, and 150 rpm. Spindle no 90 T was used for η measurement.

Refractive index

Constant transparency is one of the stability indicator of the ME system. An Abbe refractometer was used to determine the refractive index of the ME samples measured at ambient temperature. Measurements were taken in the presence of visible light as the light source. Here, for reference, pure IPM was used as standard [19–21].

Drug content estimation

For determination of drug content, about 10 mg equivalent of the ME was weighed in a 100 ml volumetric flask and dissolved in 100 ml methanol. It was diluted appropriately and drug content was determined spectrophotometrically (306 nm) [12]. As a blank, the ME system (in same amount as used for making test sample) without drug was extracted in 100 ml of methanol and the same was used after proper dilution [22,23].

In-vitro dissolution studies

In-vitro drug release from MEs was observed using the reverse dialysis method. The study was conducted by arranging the assembly on a magnetic stirrer at a speed of 200 rpm and the temperature was maintained at 37°C manually. Dissolution medium comprising 0.1 N HCl was used. Dialysis bags (molecular weight cutoff 3500) that contained 10 ml dissolution medium were equilibrated with the dissolution medium (500 ml) for about 30 min before experimentation. An aliquot of each ME (6 ml) was directly dispersed into the dissolution medium. At predetermined time intervals (10 min to 12 h), the samples (3 ml) were taken from the assembly, and were refilled with the same volume of fresh dissolution medium. The concentration of OXZ was determined using a UV spectrophotometer at λ_{max} 306 nm after appropriate dilution with distilled water [12]. The percent of cumulative amount of OXZ released from the MEs was calculated as a function of time [1,16,24,25].

Results and discussions

Screening of oils and surfactants

Oils, surfactants, and cosurfactants used for the screening are presented in Table 1. The solubility of each in mg/ml is presented in Table 1. Finally, the oil and surfactant having maximum capacity to incorporate drug were selected to form the final system and were used for further study. The final system included IPM as oil and AOT as surfactant. From the results of solubility and screening data of all oils, surfactants, and cosurfactants, IPM was found to have maximum drug incorporation as oil, and AOT was found to have maximum solubility of OXZ as surfactant. Thus, finally, IPM as oil and AOT as surfactant were used for further ME formulation and for phase diagram construction. Thus, this combination was used to form ME.

Drug–excipients compatibility study

FT-IR spectroscopy study

The drug was checked for compatibility studies using FT-IR by scanning at a resolution of 4 cm^{-1} from a frequency range of 4000–400 cm^{-1}Fig. 1 shows the overlaid spectra of FT-IR and the curves of pure drug, adsorbent, and adsorbed ME. The characteristic peaks of primary and secondary amide groups at 1600 and 1700 cm^{-1}, respectively, and of N-H stretching at 3200 cm^{-1} of drug in pure and formulation form remains same, which shows that the drug remained in stable form and no amorphous or polymorphs were observed in final product.

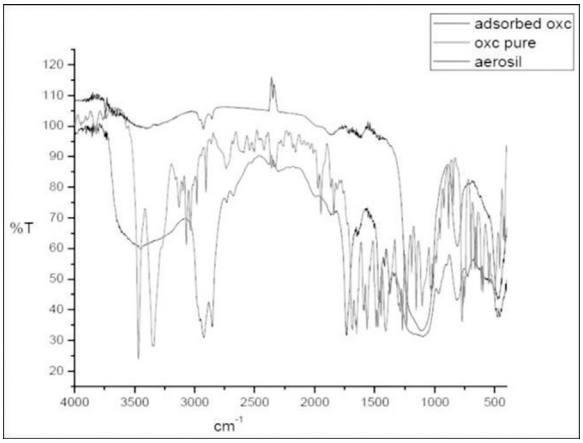
Differential scanning calorimetric study

Thermal analysis of pure drug, adsorbed solid ME in aerosil, and surfactant AOT was carried out using

Table 1 Solubility study of drug

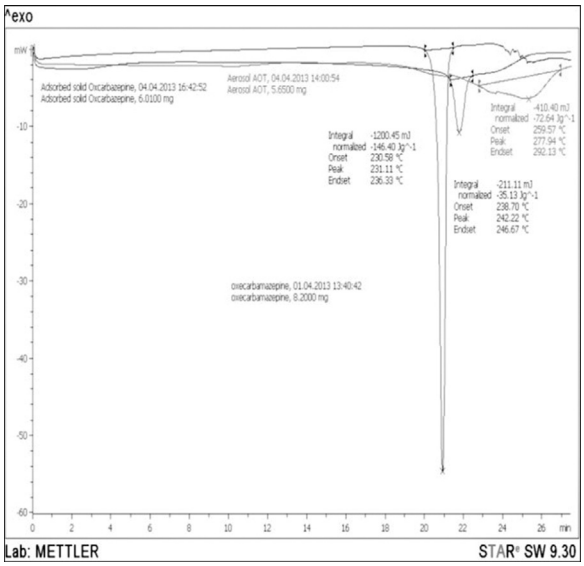
Type of Excipient	Name of Excipient	Solubility(mg/ml)
	IPM	35.89
Oil	Ethyl oleate	5.89
	Oleic acid	3.98
	AOT	25.68
Surfactants	Span-20	8.65
	Tween-80	3.65
	PEG-400	2.65
	Butanol	3.62
Co-surfactant	Hexane	2.58
	Octanol	1.36
	Polaxomer 188	0.85
	Type I water	0.0008
Vehicles	Methanol	12.36
	Ethanol	15.23

Figure 1



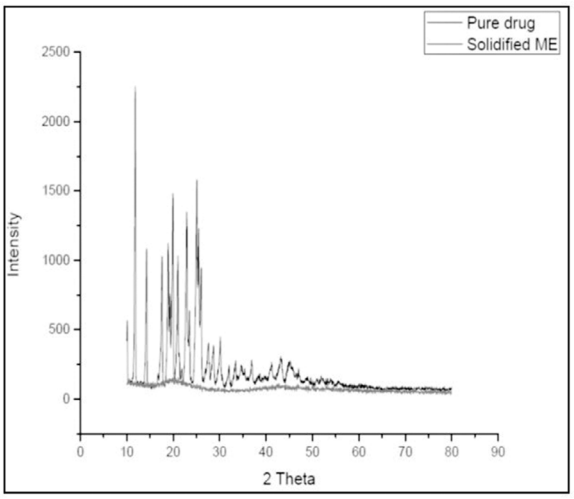
FT-IR spectra of oxcarbazepine, microemulsion, and aerosol OT.

Figure 2



Differential scanning calorimetry (DSC) of oxcarbazepine, microemulsion, and aerosol OT.

Figure 3



Powder X-Ray Diffraction (PXRD) spectra of oxcarbazepine and microemulsion.

DSC-50, Shimadzu, with liquid nitrogen cooling accessory. The samples were heated from ambient temperature to 300°C at a preprogramed heating rate of 10°C/min. The overlaid spectra – that is, DSC overlaid curves of pure drug, AOT, and formulation – are presented in Fig. 2. The sharp peak of drug is seen at 219°C, which is the melting point of drug, and change in enthalpy is –1200 mJ, whereas the same peak is seen in formulation at 219°C, which corresponds with the melting point of the drug and also the change in enthalpy decreases to –211 mJ, which shows narrow and low-intensity peak. Thus, no more drug is in pure form and all are converted into globule form in ME formulation.

X-ray diffraction study

The diffraction pattern was recorded in the interval $0°<2\theta<90°$ in a step scan mode of 0.02° per step at every 35.7 s. Powder diffraction study of OXZ, adsorbent, and solid-adsorbed ME of OXZ was carried out at room temperature. Fig. 3 shows the X-Ray Diffraction (XRD) overlaid curves of pure drug and formulation. Characteristic sharp peaks of drug were seen in pure drug at 2θ value of 10, 11.8, 14.3, 17.6, 20, 23, 25, and 25.5, and the same was seen in formulation but of very low intensity, which gives the recrystallization average as 0.10065; this shows the amorphous conversion of crystalline drug in formulation form and shows that the drug has been converted to globule form and is no longer present in pure form. Thus, the system does not have any incompatibility and is biocompatible.

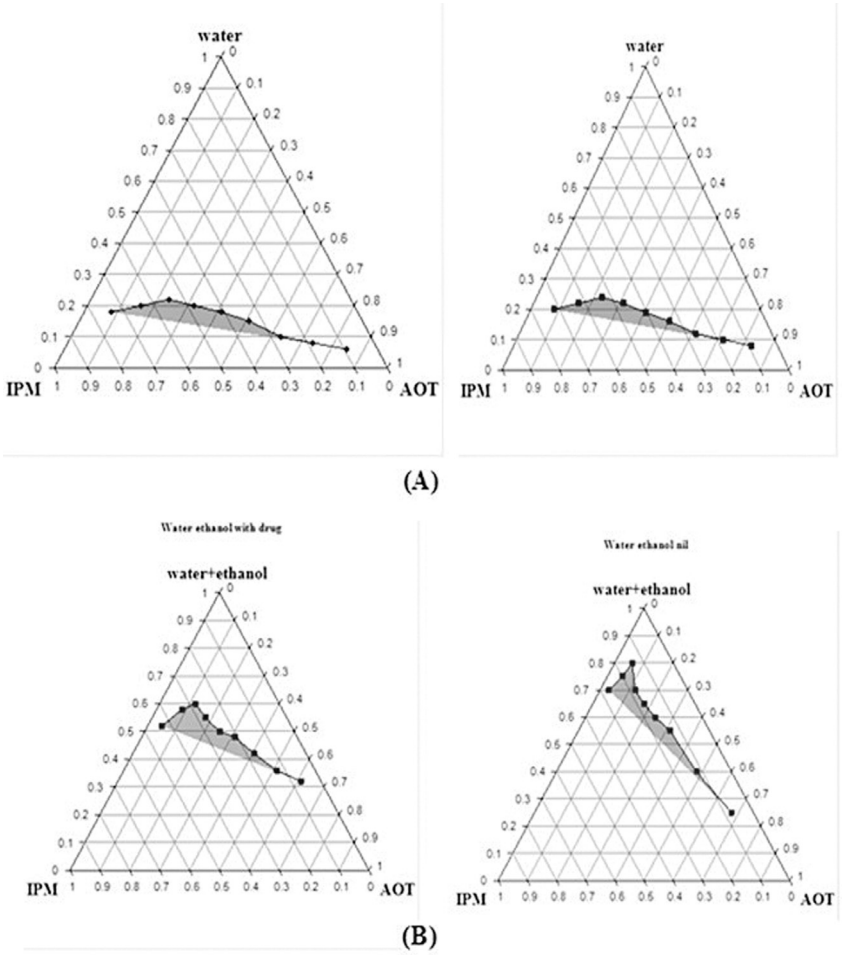
Ternary phase diagram preparation

Four different phase diagrams were constructed using PROSIM software. The phase diagrams below show the concentration of each formulation at specific temperature and pressure. As indicated in Fig. 4a, the water system without drug covers the colored part of triangle giving a stable ME system. The proportion of Oil, Surfactant and Water was in range from 9.2–72%, 82.8–8% and 8–20% respectively without adding drug. The proportion of Oil, Surfactant and Water was in range from 9.4–73%, 84.6–8.2% and 6–18% respectively with drug. Similarly in Fig. 4b , the dark part resembles the area covered in phase diagram under specific temperature and pressure at different concentrations of IPM, AOT, water, and ethanol. The change in area covered and the concentration of each do not change significantly with and without drug. The proportion of Oil, Surfactant and Water was in range from 7.5–27%, 67.5–3% and 25–70% respectively with drug. The proportion of Oil, Surfactant and Water was in range from 6.8–43.2%, 61.2–4.8% and 32–52% respectively without adding drug. Thus, both systems are biocompatible and incorporation of the drug does not show notable significant change in the area of the phase diagram. Thus, optimized batch was further selected from above formulated batches. Selection criteria for optimized batch were maximum incorporation of aqueous phase, minimum size, and maximum zeta potential [26,27].

Preparation of microemulsion

The phase diagrams were prepared using the water titration method and the optimized batch was selected from each system and series of formulations in both phase diagrams, and the one having minimum size, maximum zeta potential, and maximum aqueous phase incorporated was selected for further evaluation. From

Figure 4



(a) Phase diagram of isopropyl myristate (IPM), aerosol OT (AOT), and water with and without drug. (b) Phase diagram of IPM, AOT, and ethanol: water with and without drug.

the phase diagrams, two from each the water system and the ethanol: water system (only with drug), the one having lower size, maximum zeta potential, and maximum aqueous phase was taken for further evaluation and was given code as ME 1 of water system (70: 30 IPM: AOT) and ME 2 of ethanol: water system (2: 8) (70: 30 IPM: AOT).

Evaluation of microemulsion

Droplet size analysis

Droplet size of ME 1 was found to be 53.65 nm (mean) and that of ME 2 was found to be 59.15 nm (mean) and globules were spherical in shape and had smooth surface. The size is in nm, and hence the formulation may also be termed as nanoemulsion [28,29]. Size distribution of both ME 1 and ME 2 is presented in Fig. 5a and b, respectively.

Zeta potential measurement

Zeta potential gives measure of stability. The higher the zeta, the higher is the stability. The range in which it is found stable is from –30 to +30 [23]. The measured zeta potential of ME 1 was 5.13 mV and that of ME 2 was 5.21 mV, which is positive; hence, being positive charge and in the permissible range, it is stable. Zeta potential distribution is shown in Fig. 6a and b for ME 1 and ME 2, respectively.

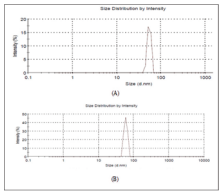
Rheological studies

Rheological studies give information about the viscosity of the formulation. As we need our formulation for oral or nasal application, the viscosity should be less so that applicability becomes easy and the formulation flows easily in the body lumen with less friction *in vivo*. The viscosity was measured at different Rotations Per Minute (RPM), as presented in Table 2, for ME 1 and ME 2. Thus, the viscosity found was in the permissible range. The lower the viscosity, the more beneficial is our formulation.

Refractive index

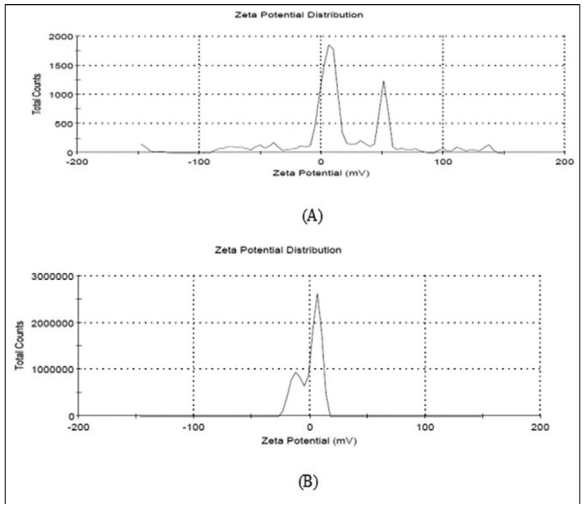
The refractive index of IPM was 1.34–1.43. This shows that formulating the ME with incorporation of surfactant, aqueous phase, and drug did not change

Figure 5



Size distribution of microemulsion using Zetasizer: (a) ME 1 (b) ME 2.

Figure 6



Zeta potential measurement: (a) ME 1 (b) ME 2.

Table 2 Viscosity measurement of microemulsion

RPM	VISCOSITY(Cps) (ME 1)	VISCOSITY(Cps) (ME 2)
10	24	20
20	18	15
50	16	13
100	15	14
150	14.4	13

Table 3 Results of thermal stability of microemulsion

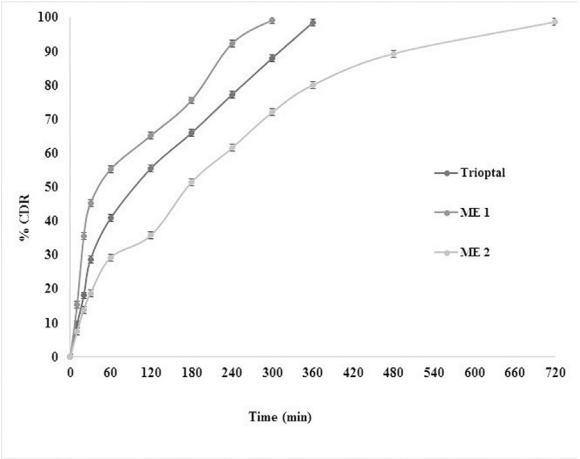
Duration (Days)	Droplet Size (μm)		Zeta Potential		% Drug Content	
	ME1	ME2	ME1	ME2	ME1	ME2
7	53	59	6.13	5.21	81.60	92.5
14	51	57	6.2	5.2	81.23	92.21
21	50	55	5.8	5.1	80.78	92.14
30	48	52	5.6	5.0	80.34	92.04
60	50	51	5.8	5.0	79.56	91.3
90	52	52	5.9	5.2	78	91.12

the physical properties of the oil, and hence the refractive index of the formulation was found to be 1.34–1.43 for both ME 1 and ME 2.

Drug content estimation

Drug content of the formulation was determined by extracting the blank system and the formulation with methanol and then the blank extract was kept as reference. Extract of drug was used as test. The measured drug content was found to be 81.63% in ME 1 and 92% in ME 2. The increase in drug content in ME 2 is due to ethanol content in it and that increases the drug solubility so more drug is incorporated. Thus, drug content was more in ME 2 as compared with ME 1.

Figure 7



In-vitro dissolution profile of ME 1, ME 2, and trioptal.

Thermal stability

Thermal stability is described in Table 3. It indicated that there was no significant change in size from day 0 to day 90. Change in zeta potential was also of 0.2 mV. Hence, the formulations were stable for 3 months. Results of analysis of drug content indicated no significant change. It concludes that prepared ME of OXZ was stable for 3 months.

In-vitro dissolution study

Results of in-vitro drug dissolution study are presented in Fig. 7. It indicated improved drug dissolution compared with the marketed formulation TRIOPTAL (Novartis Pharma, Hydrabad, India). It showed almost 100% drug release within 120 min for ME 1. In-vitro drug dissolution of ME 2 indicated extended release of drug – that is, almost 100% was released after 12 h. This might be due to the composition difference of ME 1 and ME 2. The higher dissolution rate for ME 1 might be due to its type because it is o/w type of ME, and hence oil is in dispersed phase and water as a continuous phase and the drug dissolution rate is higher. Uptake of the droplets of ME 1 by the dissolution medium is higher because oil droplet is surrounded by the water and S/Co-S phase. The dissolution rate is lower in ME 2 because it is w/o type of ME. Hence, the wetting of droplets of ME by the dissolution medium is lower, and hence it required

more time for the dissolution of the drug. This difference in type of ME is due to transition of phase during the preparation of the ME and it might lead to the difference in drug release.

Conclusion

The present study demonstrates that physicochemical characteristics and stability studies of ME for OXZ will serve as novel drug delivery system with increased solubilizing capacity and increased stability. This formulation holds great potential for treating diseases that require fast onset of action (ME 1), which also may reduce dosing frequency, leading to fewer systemic side effects and improved patient compliance. Thus, on the basis of all studies, we can conclude that ME formulation may be considered promising for anticonvulsant long-term therapy in single or combined therapy. Thus, formulated ME proves to be a novel drug delivery system, patient compliant, ideal, and biocompatible novel pharmaceutical formulation for OXZ, an anti-epileptic drug.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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