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Development of nanoemulsion of antiviral drug for brain targeting in the treatment of neuro-AIDS

S. M. Nemade[1], S. P. Kakad[2*], S. J. Kshirsagar[3] and T. R. Padole[3]

Abstract

Background: Delivery of drugs via the nasal route directly to the brain utilizing the olfactory pathway is purportedly known to be a more efficient method to deliver neuro-therapeutics to the brain by circumventing the BBB, thereby increasing the bioavailability of these drugs in the brain. The main objective of the project work is to improve the bioavailability of the antiretroviral drug and to minimize the side effects of this therapy which are observed at the higher side in the chronic HIV treatment. The advantage of nasal drug delivery is its noninvasiveness and self-administration. Nanoformulation provides fast onset of action and helps to achieve site-specific delivery. In the current work, nanoemulsion formulation was developed with a ternary phase system. In vitro characterization of nanoemulsion was performed.

Result: Optimized batch B2 had a zeta potential of − 18.7 mV showing a stable emulsion system and a particle size of 156.2 nmin desirable size range. Batch B2 has the least variation in globule size with PDI 0.463. Results from ex vivo studies revealed that developed nanoemulsion (B2) possessed a higher rate of drug release compared to other formulations.

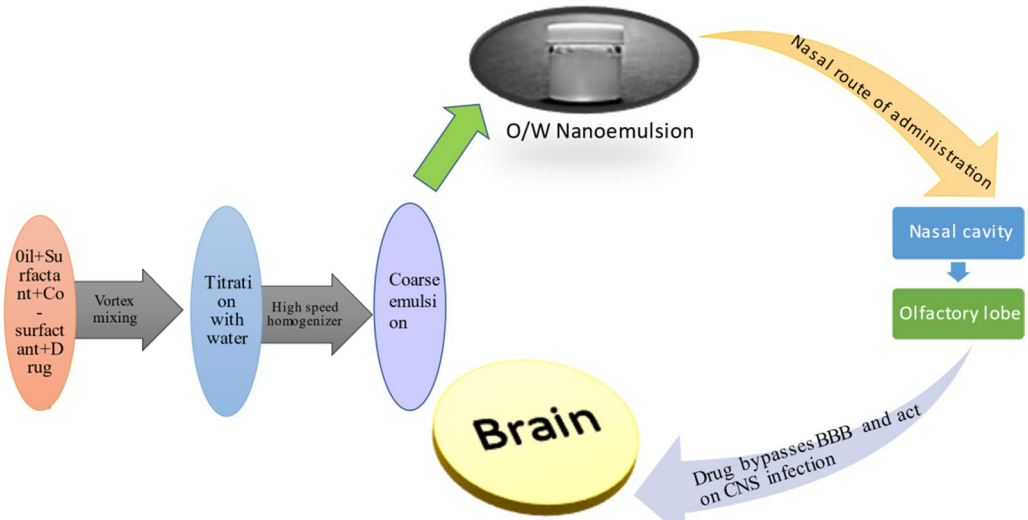
Conclusion: Phase diagrams indicated more width of the nanoemulsion region with an increase in surfactant ratio. Stable nanoemulsion was prepared with a combination of surfactant and co-surfactants. Nanoemulsions could prove one of the best alternatives for brain delivery of potent medications.

Keywords: Antiretroviral therapy, Nanoemulsion, Nose-to-brain delivery, Ex vivo diffusion study, Cytotoxicity study

*Correspondence: smitadarade87@gmail.com

[2] Department of Pharmaceutics, MET's Institute of Pharmacy, BKC, Adgaon, Nashik, Maharashtra 422002, India
Full list of author information is available at the end of the article

Graphical Abstract



1 Background

The delivery of drugs to the brain has been fraught with the low bioavailability of drugs in the brain. This is caused by the "Blood–Brain Barrier" (BBB) and the "Blood–Cerebrospinal Fluid Barrier" (BCSFB) which block therapeutics from gaining access to the (CNS) [1, 2]. Drugs that are administered via oral and intravenous are faced with this challenge of BBB, thereby making the treatment of neurodegenerative diseases difficult to manage [3]. Delivery of drugs via the nasal route directly to the brain utilizing the olfactory pathway is more significant, delivering successively to the brain by passing the BBB, thereby increasing the bioavailability of drugs in the brain [4, 5].

Nervous system alterations occur due to direct or indirect effects of HIV infection, collectively known as neuro-AIDS [6, 7]. The estimated overall prevalence of nervous system disorders among patients receiving highly active antiretroviral therapy but also requiring neurological care is over 25% [8]. According to WHO (Global HIV & AIDS statistics—2020), there are ~ 34 million people in the world infected with HIV [8]. Out of 95 percent of these cases as well as deaths from AIDS that occur in the developing world [9], dementia (HIV-associated dementia) is becoming common in HIV-infected adults having a prevalence of up to 40% in western countries [10, 11].

The evaluation of the nanoemulsions includes (1) appearance testing by visual as well as under radiation observation; (2) stability testing by centrifugation; (3) stability under differential atmospheric conditions includes temperature, humidity, and change in forms such as cracking (flocculation) and creaming; (4) viscosity with respect to (i) change in time and (ii) change in RPM; and (5) pH of the formulation of such parameters indicates whether the formulation remains stable under certain circumstances. Characterization of the formulation includes (i) droplet size analysis, (ii) zeta potential, (iii) percent transmittance, (iv) morphology studies by transmission electron microscopy, (v) pH of the formulation, (vi) refractive index studies, and (vii) drug content and some other tests like polydispersity test, dye test, fluorescence test, dilution test, conductance test, and filter paper test. Furthermore, ex vivo diffusion study with the help of sheep nasal mucosa and cytotoxicity studies using cultured cell beds so that any damaging effects to tissues can be determined [12, 13].

Tenofovir disoproxil fumarate, the oral pro-drug of tenofovir, is a nucleotide reverse transcriptase inhibitor [14]. It inhibits viral polymerases by directly competing with the natural deoxyribonucleotide substrate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination [15, 16]. Tenofovir disoproxil fumarate is used to treat HIV and chronic hepatitis. Tenofovir has poor water solubility and low bioavailability (25%), thus a suitable candidate to formulate nanoemulsion for nasal drug delivery [12, 16].

2 Materials and methods

Tenofovir disoproxil fumarate was gifted by Mylan Pharmaceutical Private Limited, Nashik, India. Oleic acid (oil) was gifted by S.D. Fine-Chem Limited, Mumbai, India. Tween 60 and tween 80 were purchased from Merck Specialties Pvt. Ltd. Mumbai, India. Ethanol and methanol were purchased from Changshu Yangyuan Chemicals, China. The water used was semi-quartz distilled. All other chemicals and reagents used were of analytical grade, procured commercially, and used as received.

2.1 Determination of partition coefficient

The partition coefficient of the drug in oil and water was determined with the shake flask method. The drug was partitioned into the oil and water phase. After shaking for 1.5 h, the mixture was kept aside after appropriate dilution. The concentration in oil was determined on the UV spectrophotometer (UV 1800 Shimadzu) at 260 nm [17].

2.2 Screening of oil for nanoemulsion

The solubility of tenofovir disoproxil fumarate (TDF) in various oils like oleic acid, olive oil, and castor oil was determined by dissolving the excess amount of TDF in 5 ml of each selected oil in stoppered vials separately for the determination of solubility. The mixture vials were then kept in a shaker for 48 h to get equilibrium. The equilibrated samples were then centrifuged at 9000 RPM for 10 min. The supernatant was collected and filtered through a 0.45-µm membrane filter. The concentration of drug was determined in each oil by a UV spectrophotometer (UV 1800 Shimadzu) with suitable dilution with 0.1 N HCl at a wavelength of 260 nm [6].

2.3 Screening of surfactant and co-surfactant

Surfactants and co-surfactants were selected based on their capability to form stable nanoemulsion with relevant surfactants at minimum concentration. Of the several surfactants, tween 80 provided better outputs. Based on trials, ethanol was chosen as a co-surfactant [6].

2.4 Construction of phase diagram

On the basis of drug solubility in various nanoemulsion components, different combinations of oil, water, and surfactant/co-surfactant were selected. The pseudo-ternary phase diagrams of oil, surfactant/co-surfactant, and water were developed using the surfactant titration method [18]. The mixtures of oil and water at different weight ratios varying from 1:9 to 9:1 were titrated with surfactant/co-surfactant mix in a dropwise manner. Pseudo-ternary phase diagram was achieved by titrating with four different ratios of surfactant and co-surfactant (1:1, 1:2, 2:1, and 4:1) until it turns from hazy to transparent. After the identification of nanoemulsion region in the phase diagrams, formulation component ratios were selected in order to form the nanoemulsion [19, 20].

On the basis of the solubility study, oleic acid was selected as the oil phase. Tween 80 and ethanol were selected as surfactant and co-surfactant, respectively. Distilled water is used as an aqueous phase. The drug was dissolved in the required quantity of oil, surfactant, and co-surfactant with varying ratios. Distilled water was added to the above mixture as a fixed ratio. Surfactant and co-surfactant were added gradually with continuous stirring, which resulted in the formulation of a transparent and homogenous nanoemulsion [20, 21].

2.5 Characterization of nanoemulsion

2.5.1 Thermodynamic stability studies

The formulation consists of a couple of immiscible phases, so as to overcome the problems such as instability these thermodynamic stability studies were performed. Prepared formulations were centrifuged at 3000 rpm for 30 min and then examined for phase separation. Those formulations that did not show any phase separation were taken for the heating and cooling cycles at a temperature of 4 °C and 45 °C for 48 h. The formulations were then observed for phase separation. The formulations which were stable at these temperatures passed the thermodynamic stability test and were selected for further evaluation studies [21, 22].

2.5.2 Evaluation of the nanoemulsion

The nanoemulsion prepared with optimized composition was evaluated for the parameters like zeta potential, viscosity, pH, conductivity, and refractive index [23]. The results are given in Tables 3 and 4.

2.5.3 Transmittance test

To assess the transparency and clarity of the nanoemulsion, this test was performed. The transparency of nanoemulsion was checked by measuring transmittance at 650 nm with 0.1 N HCl as blank by using a UV spectrophotometer (UV 1800 Shimadzu). It was determined with the formula in Eq. 1. The results are given in Table 5.

$$\text{Absorbance} = -\log(\%T/100). \tag{1}$$

2.5.4 Drug content estimation

Nanoemulsion containing 100 mg drug was dissolved in 100 ml 0.1 N HCl taken in a volumetric flask. Then, the solvent was filtered; 1 ml was taken in 50 ml volumetric solution and diluted up to the mark with 0.1 N HCl and analyzed spectrometrically at 260 nm (UV 1800 Shimadzu). The concentration of tenofovir in mg/ml was obtained by using a standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch [2, 24].

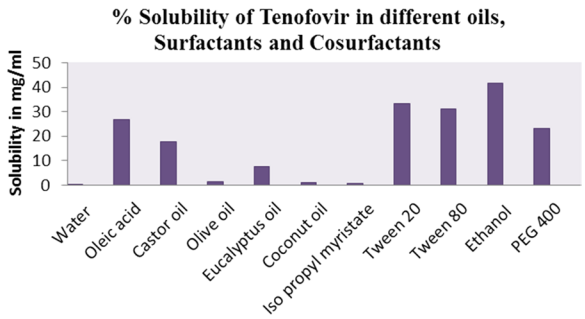


Fig. 1 Solubility of TNF in different oils, surfactants, and co-surfactants

2.5.5 Particle size and zeta potential measurement

The particle size and zeta potential of the optimized nanoemulsion were determined by dynamic light scattering with Zetasizer ver.7.12 (Malvern Instruments Ltd.) [22, 24]. The results are shown in Tables 3 and 4.

2.5.6 Ex vivo diffusion studies

Egg membrane and sheep nasal mucosa were used for preliminary preclinical evaluation of nasal dosage forms. Sheep nasal mucosa is used for an experiment as it mimics human nasal vasculature. A diffusion study was carried out using an isolated egg membrane for the trial batches (B1–B4) in phosphate buffer pH 6.4 (PBS 6.4) for a period of 3 h using a Franz diffusion cell [25, 26]. Diffusion of drug from egg membrane was observed. Later, best batch B2 was forwarded to diffusion study from sheep nasal mucosa. The sheep nose piece was obtained from a local slaughterhouse; the nasal mucosa layer was excised and used for diffusion study. Nasal mucosa was placed in Franz diffusion cells having a diffusion area of 0.785 cm^2. PBS pH 6.4 was added to the receiver chamber maintained at 37 °C temperature. Franz cell was pre-incubated for 20 min, and formulation equivalent to10 ml of B2 sample was placed in the donor chamber. Withdrawn 1 mL samples from the receiver chamber at predetermined time intervals, added 1 mL of PBS 6.4 after each sampling to maintain sink condition. All the samples were filtered and analyzed using a UV spectrophotometer at 224 nm, and cumulative drug release was determined [27, 28].

Observations after diffusion from goat nasal mucosa are mentioned in Table 6.

3 Results

3.1 Formulation and optimization of nanoemulsion

The solubility of tenofovir in various oils was investigated and found to be highest in oleic acid, i.e., 26.69 ± 0.3 mg/ml (Fig. 1). Among surfactants, in tween 80 the drug showed the highest solubility of 30.31 ± 1.5 mg/ml. In ethanol, the drug showed the highest solubility among the co-surfactants of 41.57 ± 0.6 mg/ml, followed by PEG 400. The nanoemulsion existence region was determined by constructing phase diagrams. From the pseudo-ternary phase diagrams, it was concluded that the highest nanoemulsion zone was obtained for the nanoemulsion having tween 80 and ethanol in the ratio of 4:1 as shown in Fig. 2 and (Table 1) [29, 30].

3.2 Dispersion stability studies

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature on formulation stability. In the thermodynamic stability studies, the formulation selected was subjected to stress tests like heating–cooling cycle and centrifugation. It was observed that all formulations were stable, clear liquid, and no phase separation occur under stress condition. This confirms the liquid formulations were stable for the storage [31, 32]. Nanoemulsions are thermodynamically stable formulation composed of a fixed proportion of oil, surfactant, co-surfactant, and water which does not tend to show any phase separation after multiple changes in the temperature and centrifugation. After centrifugation at 3000 RPM for 20 min, all the formulations were still stable, clear liquid, and no phase separation occurred under stress conditions. The conditions are mentioned in Table 2. It proves that the formulations are thermodynamically stable [33, 34].

3.3 Evaluation of the nanoemulsion composition

The nanoemulsion prepared by the selected composition was evaluated for the parameters like droplet size, PDI, zeta potential, viscosity, pH, conductivity, and refractive index. The result is given in Tables 3 and 4.

It was observed that there was no any significant difference between placebo formulation and formulation with drug. It indicates the formulation has isotropic nature. This confirms the drug was in a dissolved state and uniformly distributed in liquid formulation.

3.4 Transmittance test

From the results of the transmittance test in Table 5, it was observed that the transparency of the formulation goes on decreasing as the concentration of S-mixture. So it shows high transparency of the first formulation, and later it gets decreased [18].

The viscosity of four formulations was observed in the range of 400–500 cps, and after the variations in the RPM it is concluded that the system of all the nanoemulsion formulations was observed as a shear thinning system.

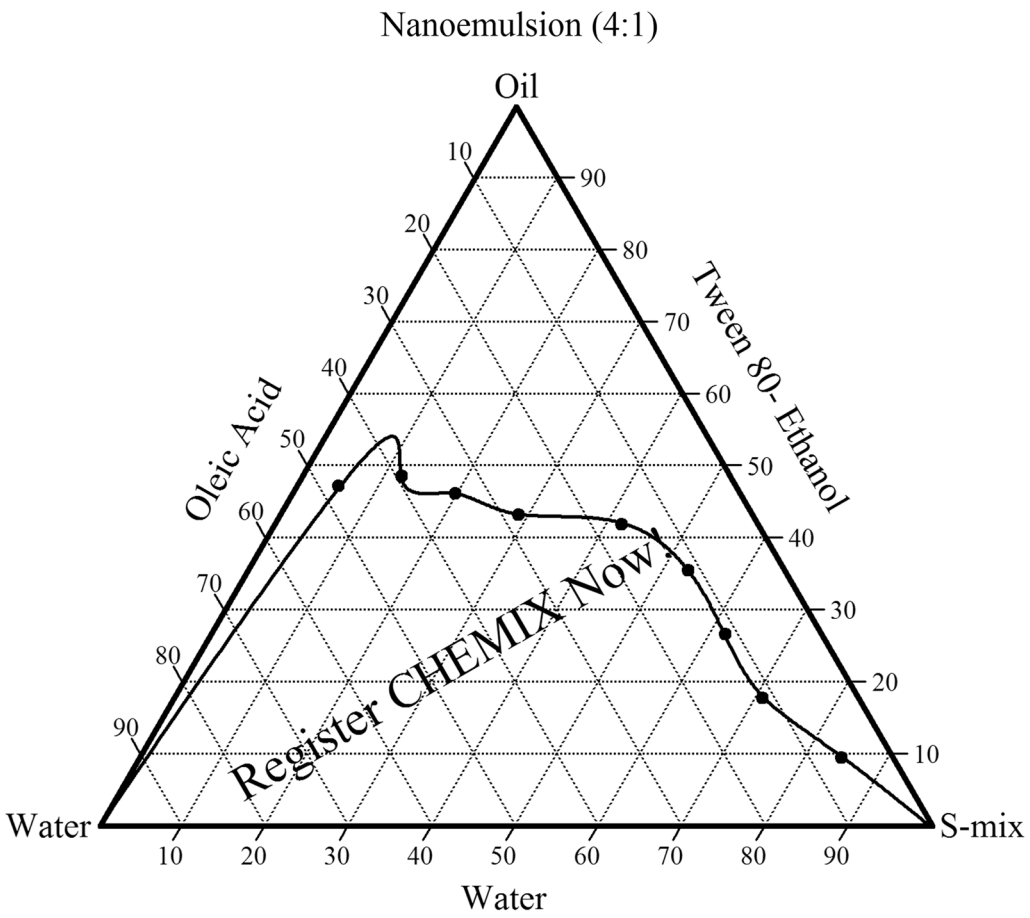


Fig. 2 Ternary phase diagram studies for ratio 4:1

That is viscosity gets decreased by a sudden increase in the resistance. But with respect to time the viscosity of the formulations remained stable and no major fluctuations were observed in it.

Nasal pH has a range which is between 5.6 and 6.5, and the observed values of the pH of all the formulations were in the range so it proves that the developed nanoemulsion formulations are applicable to the nasal drug delivery system.

3.5 Drug content estimation

The concentration of tenofovir in mg/ml was obtained by using a standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch. The results are given in Table 5. Drug content determination helps to find out the amount of drug entrapped in the formulation. From results, more drug content was observed in batch B2 than in other batches [23, 35].

Table 1 Trial batches preparation

Batch no.	Oil %	S-mixture % (4:1)	Water %	Appearance	Stability
B1	10	84	6	Transparent	Stable
B2	18	70	12	Transparent	Stable
B3	26	61	13	Transparent	Stable
B4	36	53	11	Transparent	Stable
B5	42	42	16	Turbid	Unstable
B6	44	28	28	Cloudy	Unstable
B7	46	20	34	Cloudy	Unstable
B8	48	12	40	Cloudy	Unstable
B9	47	5	48	Cloudy	Unstable

3.6 Particle size, polydispersity index, and zeta potential measurement

The particle size and zeta potential of the optimized nanoemulsion were determined by dynamic light

Table 2 Thermal and centrifugation stability of tenofovir nanoemulsion

Nanoemulsion formulation	Thermal stability			Centrifugation stability at 3000 rpm
	Storage at 4 °C	Storage at R.T. (27 °C)	Storage at 45 °C	
B1	√	√	√	√
B2	√	√	√	√
B3	√	√	√	√
B4	√	√	√	√

scattering with Zetasizer ver.7.12 (Malvern Instruments Ltd.). The results are shown in Figs. 3 and 4. The zeta potential is −18.7 and the size (z average) is 156.2 nm with PDI 0.463. The ideal size of globules in nanoemulsion is in between the range of 100 and 500 nm, the polydispersity index should be narrow, and the zeta potential should be within the range of −15 to +20 mV for prediction of stability of nanodroplets in emulsion [35, 36]. The obtained results are appropriate with these values. Batch B2 has a large globule size, but it has the minimum polydispersity index that means the variation in the globule size throughout the formulation is very less in the batch B2 [37, 38].

3.7 Ex vivo diffusion studies

Ex vivo study was performed using egg membrane in nanoemulsion batches B1, B2, B3, and B4. Here, batch B2 shows greater drug diffusion that is 74.98 ± 1.06% after 3 h. For the sheep nasal mucosal membrane, B2 batch showed 75.9841 ± 0.14% of diffusion in the system, which is determined by taking triplicate readings with standard deviation ($n = 3$) [35]. From the above studies, it is concluded that B2 is the optimized batch and has a greater diffusion ratio compared to all other batches. The diffusion of the drug from the formulations is comparable through egg membrane and sheep nasal mucosa (Fig. 5; Table 6) [39, 40].

Table 5 Drug content and percent transmittance

Sr. no.	Batch	% Transmittance	Drug content
1	B1	88.93 ± 0.4%	92.77 ± 0.3%
2	B2	87.82 ± 0.8%	94.19 ± 0.6%
3	B3	87.79 ± 0.6%	93.25 ± 0.6%
4	B4	87.51 ± 0.5%	93.79 ± 0.8%

4 Discussion

HIV treatment is a combination of antiretroviral drugs. Most people who treat their HIV will take two or more drugs each day for the rest of their lives. Sticking to the treatment plan isn't always easy. The main purpose of this study was to improve the bioavailability of the antiretroviral drug and to minimize the dose of the antiretroviral drug and ultimately reduce the side effects of this therapy which is observed at the higher side in the other formulations/administration process [41]. Nasal route delivery to the brain utilizing the olfactory pathway is purportedly known to be more efficient and deliver

Table 3 Evaluation of nanoemulsion

Sr. no.	Batch label	Conc of oil (%)	Conc. of S. mix (%)	Drug amount (mg)	Droplet size (nm)	PDI	Zeta potential
1	B1	4.69	42.26	25	155.8	0.508	−12.1
2	B2	4	45	25	156.2	0.463	−18.7
3	B3	8.85	35.41	25	160.3	0.289	−5.29
4	B4	10	33	25	241.7	0.497	−2.26

Table 4 Physicochemical parameters of developed tenofovir nanoemulsion

Sr. no.	Batch label	Drug amount (mg)	Viscosity (cps)	Refractive index	pH
1	B1	25	428 ± 0.2	1.47 ± 0.5	5.2 ± 0.1
2	B2	25	420 ± 0.7	1.472 ± 0.3	5.5 ± 0.3
3	B3	25	412 ± 0.1	1.45 ± 0.9	5.7 ± 0.2
4	B4	25	491 ± 0.5	1.47 ± 0.4	6.1 ± 0.3

			Size (d.nm)	% Intensity	StDev
Z-Average(d.nm)	156.2	Peak1	221.9	92.2	98.45
PdI:	0.463	Peak2	43.83	4.6	9.197
Intercept:	0.954	Peak3	5008	3.2	604.0

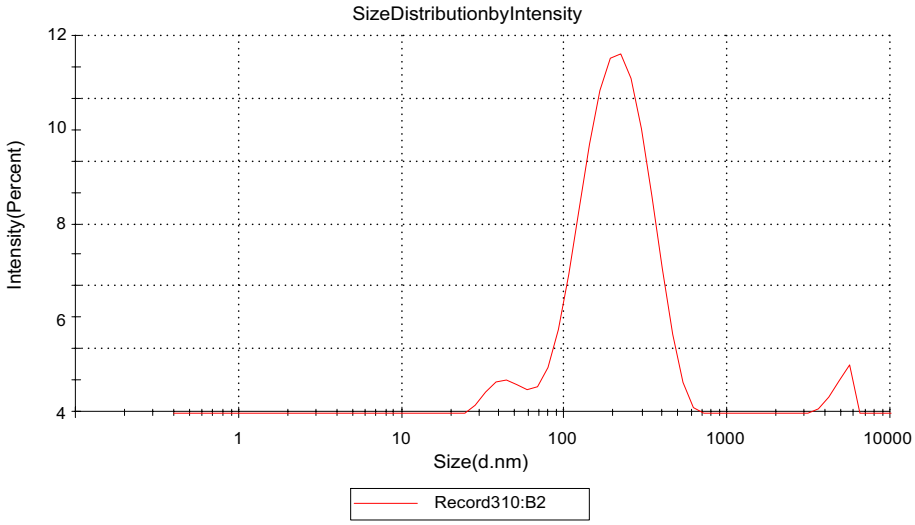


Fig. 3 Particle size and polydispersity index graph of optimized nanoemulsion batch

			Mean (mV)	Area(%)	StDev(mV)
Zeta Potential (mV):	-18.7	Peak1	-18.7	100.0	4.52
Zeta Deviation(mV):	4.52	Peak2	0.00	0.0	0.00
Conductivity (mS/cm):	0.0463	Peak3	0.00	0.0	0.00

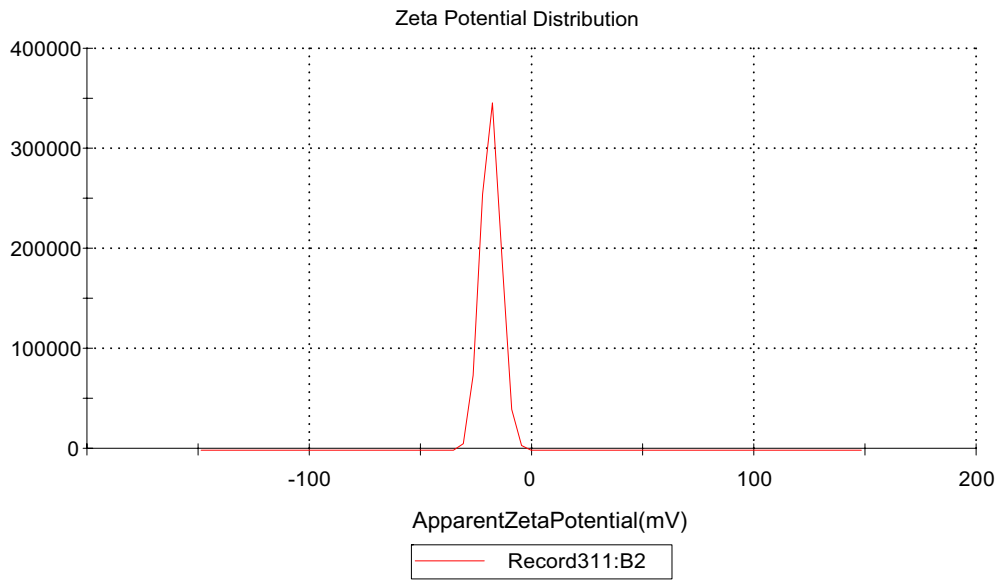


Fig. 4 Zeta potential graph of optimized nanoemulsion batch

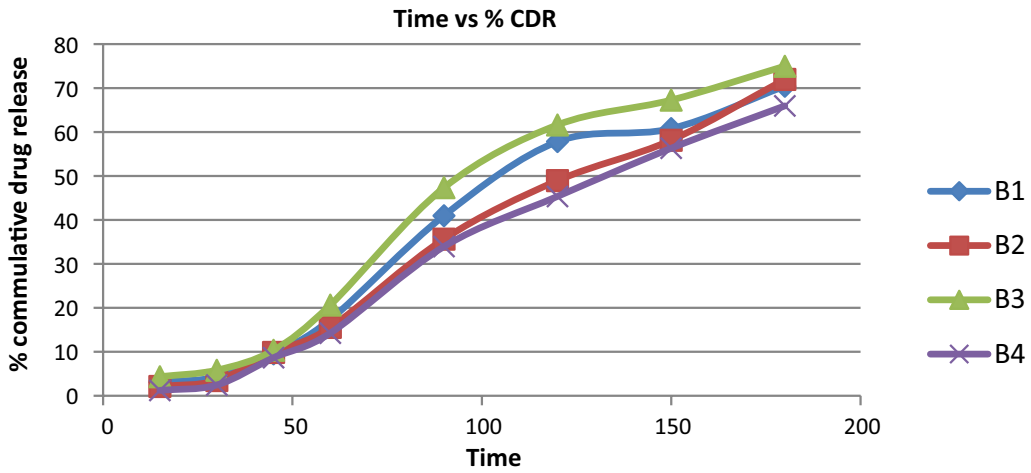


Fig. 5 Comparison of diffusion study profiles of batches B1–B4

neuro-therapeutics to the brain by passing the BBB, thereby increasing the bioavailability of drugs in the brain. The advantage of this method is that nasal drug delivery administration is noninvasiveness in nature, essentially painless, and particularly suited for children [42].

Tenofovir disoproxil fumarate is selected for the study. On the basis of drug solubility in various nanoemulsions components, different combinations of oil, water, and surfactant/co-surfactant were selected. The pseudo-ternary phase diagrams of oil, surfactant/co-surfactant, and water were developed using the surfactant titration method. Phase diagrams indicated more width of the nanoemulsion region with an increase in surfactant ratio. Diffusion study was carried out using egg membrane for the trial batches (B1–B4) and sheep nasal mucosa for the optimized batch (B2) in phosphate buffer (PB) pH 6.4 for a period of 3 h using diffusion cell apparatus. Firstly, in the study using egg membrane in batches B1, B2, B3, and B4 of nanoemulsions, batch B2 shows greater diffusion that is 74.98 ± 1.06, and for the sheep nasal mucosal membrane B2 batch showed 75.9841 ± 0.14 of drug release.

The drug amount was kept fixed in all batches (25 mg). Oil (%) and surfactant mix (%) are variable in all batches. B2 batch has the highest surfactant mix (%), showing comparatively better diffusion. With respect to the dependent variable zeta potential, batch B2 was showing the highest magnitude (− 18.7 mV), showing good stability of emulsion. The polydispersity index of 0.463 is within the acceptable range. Other batches (B1, B3, and B4) have a very small magnitude of zeta potential which may lead to droplet coalescence and aggregation during storage. Surfactant mix concentration of 45% was found

Table 6 % CDR values after diffusion profile studies

Time (min)	B1	B2	B3	B4	B2
	Diffusion study through egg membrane				Diffusion study through sheep nasal mucosa
15	3.11 ± 0.214	2.11 ± 1.13	4.34 ± 0.913	1.22 ± 0.753	4.34532 ± 0.14
30	4.27 ± 1.35	3.47 ± 0.87	5.82 ± 1.03	2.45 ± 0.434	5.78417 ± 0.25
45	9.55 ± 0.587	9.88 ± 0.741	10.34 ± 0.642	8.66 ± 1.23	10.2446 ± 0.15
60	17.34 ± 0.623	15.55 ± 0.61	20.66 ± 1.20	14.26 ± 0.946	20.4604 ± 0.11
90	40.98 ± 0.975	35.65 ± 1.22	47.34 ± 0.946	33.94 ± 0.846	46.9353 ± 0.16
120	57.82 ± 0.813	48.96 ± 1.34	61.62 ± 1.09	45.36 ± 1.115	60.7482 ± 0.11
150	60.77 ± 1.29	58.14 ± 0.974	67.26 ± 0.976	56.31 ± 0.643	65.7842 ± 0.09
180	70.42 ± 0.750	74.98 ± 1.06	71.96 ± 0.853	65.94 ± 1.054	75.9841 ± 0.14

to give good stability to internal phase globules. Considering the results of four batches, B2 is found to be the optimum combination of drug, oil, and surfactant mix.

5 Conclusion

Nanoemulsion was found to be one of the potential drug delivery strategies for nose-to-brain delivery. For poorly soluble and poorly permeable drugs, nanoemulsion approach increases the surface area and gives lipophilic nature to disperse the drug. The development of nanoemulsion formulation was done with ternary phase studies. Surfactant selection is the heart of preparing stable dispersions. TNF could be given via the nasal route after performing clinical studies on such preparations. For CNS HIV infection, nose-to-brain delivery options are emerging strategies. The advantage of this method is that nasal drug delivery administration is noninvasiveness in nature, essentially painless, and particularly acceptable for all age-groups. Nanoformulation provides fast onset of action and helps to achieve site-specific delivery.

Abbreviations

TDF: Tenofovir disoproxil fumarate; BBB: Blood–brain barrier; RPM: Revolutions per minute; BCSFB: Blood–cerebrospinal fluid barrier; HIV: Human immunodeficiency virus; PB: Phosphate buffer; AIDS: Acquired immune deficiency syndrome; CNS: Central nervous system.

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Author contributions

SMN, SPK, SJK, and TRP read and approved the final manuscript.

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Availability of data and materials

All the data are available in the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Quality Assurance Techniques, MET's Institute of Pharmacy, BKC, Adgaon, Nashik, Maharashtra 422003, India. [2]Department of Pharmaceutics, MET's Institute of Pharmacy, BKC, Adgaon, Nashik, Maharashtra 422002, India. [3]Department of Pharmaceutics, MET's Institute of Pharmacy, BKC, Adgaon, Nashik, Maharashtra 422003, India.

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