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Topical delivery of macitentan self-nanoemulsion for ocular anti-inflammation potential and effect of cosurfactant

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Macitentan is an approved orally active endothelin receptor antagonist used for the treatment of pulmonary arterial hypertension (PAH). It is poorly soluble and also exerts slow absorption after oral administration. Endothelins play a major role in vascular hemostasis and ocular inflammatory reactions. Self-nanoemulsifying drug delivery systems (SNEDDS) of macitentan were prepared using an oil-surfactant mix, and PEG 600, Transcutol HP, or ethanol as co-surfactant. The potentiality of ocular anti-inflammation has also been examined after the administration of macitentan delivery systems of self-nanoemulsion in a carrageenan-induced (upper palpebral region: 100 µl, 3 % w/v) rabbit eye model. Nanoemulsion regions were identified of macitentan-loaded SNEDDS formulation after constructing ternary diagrams. Formulation containing Transcutol HP (MT2) exhibited globule size (47.35 ± 0.295 nm), PDI (0.191 ± 0.008), and zeta potential (-12.0 ± 0.81) with highest corneal permeation of about 90 % in 6 h compared to PEG 600 as cosurfactant. Improved corneal permeation has been observed after topical application of self-nanoemulsion containing Transcutol HP. Symptoms of ocular inflammation disappeared within 1 h after MT2 instillation in carrageenan-induced rabbit eye whereas, more than 2 h of acute inflammation continued in the untreated eye. Macitentan self-nanoemulsion containing Transcutol HP could be used for the management of ocular inflammation.

Keywords: Cosurfactant, Corneal permeation, Macitentan, Nanoemulsion, Ocular antiinflammation, Ocular delivery

Introduction

Orally active endothelin receptor antagonist (ERA), macitentan is an approved drug for the treatment of pulmonary arterial hypertension (PAH) to decrease the disease progression and bring down the hospitalization cases[1]. In one study macitentan improved the remedial effect on PAH and also decreased the pro-inflammatory cytokines (tumor necrosis factor-a, interleukin-1, 6) in the lungs of a monocrotaline-induced rat model[2]. Accumulation of inflammatory cells, amplified cytokines, and growth factors in pulmonary vascular remodeling have also been reported by Chami *et al.*[3]. Perivascular inflammatory cells, mast cells, T and B lymphocytes, and dendritic cells are known to accumulate in patients with PAH[3]. Endothelins, the vasoconstricting peptides have a key role in vascular haemostatis and are important mediators in ocular inflammatory reactions[4]. Endothelin-1 (ET1) is an imperative moderator in ocular inflammation through arachidonic acid cascade. Ocular inflammation caused due to different factors may lead to uveitis, iritis, and permanent vision loss[4]. Bosentan reduced inflammation after oral administration in an endotoxin-induced rat model[5]. Macitentan oral administration is reported to be teratogenic in rats and rabbits and is also contraindicated by the FDA during pregnancy[6]. An intermediate metabolite of macitentan causes hepatotoxicity and it may have an adverse effect on spermatogenesis. An attempt has been taken in this study to enhance the pre-ocular solubility and increase the absorption after topical administration of macitentan self-nanoemulsion preconcentrate[7]. Homogenous anhydrous mixtures of oil, surfactant (lipophilic and hydrophilic agent), co-emulsifier or solubilizer, and drug procedure spontaneously oil-in-water nanoemulsion upon dilution with water under mild stirring[7]. Surfactants are rarely used in ophthalmic formulation due to the probability of eye irritation. However, surfactants with oils caused less irritation than in aqueous solutions of dexamethasone and diclofenac[8]. Surfactants and co-surfactants facilitate nanoemulsification and improve drug release and tissue permeation hence self-nanoemulsion in ocular delivery

is important. Ocular delivery of drops faces challenges due to the protective mechanism and anatomic structure of the eye[9]. Low corneal drug absorption of the eye drop may be due to the short precorneal residence time. This warrants frequent instillation of highly concentrated drug solutions for achieving desired therapeutic efficacy. As a result of which it produces a high concentration for a short duration followed by a long period of substantial dose, warning ocular and systemic side effects[10]. The anatomical emblematicity of the eye and its compromised physicochemical factors like tearing and non-productive absorption limit the in vivo drug release profiling. Macitentan shows poor aqueous solubility along with a slow absorption after oral administration[11]. Nanoparticles of Self-nanoemulsifying drug delivery systems (SNEDDS) could surpass the tight junction barriers of epithelial and endothelial retinal cells, and hence possibly an important role in ophthalmic drug delivery. SNEDDS, the anhydrous and isotropic mixture of various components (i.e. oil, surfactants, co-surfactants/cosolvents, and active ingredient) are generally used for the enhancement of drug solubility followed by improved bioavailability. Micro/Nano-emulsions are very much suitable for ocular therapy for their transparency[12]. The specific combination of lipids and surfactants can make an efficient self-emulsifying system. Other than enhancement of solubility and permeability, SNEDDS protects the drug from oxidation and hydrolytic/enzymatic degradation. Polyethylene glycol and Transcutol HP are the co-surfactants reported to increase the permeability through the corneal barrier of gatifloxacin and levofloxacin to many folds[13]. Macitentan self-nanoemulsion has been developed using selected polymeric and non-polymeric cosurfactants for the improvement of drug release and corneal permeation. Macitentan SNEDDS for ocular delivery has also been examined for the control of ocular inflammation using carrageenan induced rabbit eye model.

Experimental Section

Macitentan was a gifted sample by Aurobindo Pharma, India. Super refined olive oil, peanut oil, soybean oil, sunflower oil, sesame oil, Croduret 40 (polyoxyl 40 hydrogenated castor oil), Etocas 35 (polyoxyl 35 castor oil), Crodamol GTCC (caprylic/capric triglycerides) and Synperonic PE/F127 (block copolymers) were obtained as gift samples from Croda Inc, US. Labrafac PG (Propylene glycol dicaprylate), Capryol 90 (propylene glycol caprylate), Peceol (glyceryl monooleate), Labrafil M 2125 CS (linoleoyl polyoxyl-6 glycerides), Labrafil M 1944 CS (oleoyl polyoxyl-6 glycerides), Labrasol ALF (caprylocaproyl polyoxyl-8 glycerides), Gelucire 44/14 (lauroyl polyoxyl-32 glycerides), Gelucire 50/13 (stearoyl polyoxyl-32 glycerides) and Transcutol HP (Diethylene glycol monoethyl ether) were also received gift samples from Gattefosse, France. Capmul MCM (glyceryl caprylate), Captex 355 (Glycerol Caprylate Caprate), Capmul PG-8 (propylene glycol monocaprylate), and Acconon C-44 (PEG-32 lauric glycerides) were kindly gifted by Abitec corp. US. Kolliphor ELP (polyoxyl 35 castor oil), Kolliphor RH 40 (polyoxyl 40 hydrogenated castor oil), Kolliphor HS 15 (polyoxyl 15 hydroxystearate), Kollisolv MCT 70 (medium chain triglycerides) and Kollicream IPM (isopropyl myristate) were received from BASF India. Polyethylene glycol (PEG 600) was purchased from Merck, India. The reagents used in the entire process were of pharmacopoeial grade and GRAS (generally recognized as safe). Whenever required fresh double distilled water was used.

Pseudo-ternary phase diagram

In the range of 1:9 and 9:1 ratios (by weight) of surfactant and co surfactant with oil and water the pseudo ternary phase diagrams were plotted employing water titration method at room temperature[14]. With gentle agitation and drop-wise addition of water, the mixtures were further diluted to examine the existence of a self-emulsification region, which was identified by visual clarity and marked as points over the phase diagram. A natural emulsification process where droplets spontaneously mixed in water forming a milky emulsion was regarded as good emulsification. A poor or no emulsification with instant coalescence of oil globules was noted as bad. The self-emulsification region as the indicative composite of the area under these points was further used for the development of the formulations. Ternary diagrams of oil (Captex 355), surfactant (Croduret 40 SS and Kolliphor HS 15), and co-surfactant (PEG 600/Transcutol HP) were mapped using Origin Pro 8 (Origin Lab Corporation, USA).

SNEDDS formulation

SNEDDS were formulated using Captex 355, Croduret 40 SS, Kolliphor HS 15 (as oil and surfactant mix), and PEG 600, Transcutol HP or ethanol (as co-surfactants, CoS) (Table 1). Macitentan was weighed

Table 1 — Development of macitentan SNEDDS formulation for ocular delivery

Components (mg)	MP1	MT1	ME1	MP2	MT2	ME2	MP3	MT3	ME3
Macitentan	10	10	10	10	10	10	10	10	10
Captex 355	50	50	50	50	50	50	50	50	50
Croduret 40	50	50	50	60	60	60	60	60	60
Kolliphor HS 15	50	50	50	60	60	60	60	60	60
PEG 600	100	-		60			40		
Transcutol HP		100			60			40	
Ethanol			100			60			40

MP, MT, and ME denote SNEDDS formulations containing PEG 600, Transcutol HP, and ethanol as the co-surfactants, respectively

(10 mg) and placed in screw-capped vial containing the mixture of oil, surfactant mix, and co-surfactant[15]. The content was vortexed to obtain a clear and isotropic mixture. Prior to further characterization, the SNEDDS were stored at ambient conditions for 48 h and observed for turbidity and phase separation.

FTIR

The FTIR spectra of the pure drug and its formulations were obtained in the range of 4000-500 cm^{-1} using a FTIR spectrophotometer (Model: JASCO FTIR-4100 Type A, Easton, MD, USA). The spectra were analysed to identify characteristic functional groups and to evaluate any possible drug-excipient interactions within the formulation.

Accelerated physical stability studies

The pre-concentrates obtained from Table 1 in their anhydrous and emulsion form were exposed to accelerated physical stability studies as described below[16].

Centrifugation study

The formulations were centrifuged at 5000 rpm for 30 min in a centrifuge (Remi, Mumbai, India) and meticulous scrutiny was performed visually for any instability like phase separation, creaming, or cracking. The absence of phase separation, creaming, and cracking in the formulations were sorted out for heating and cooling cycles.

Cooling and heating cycle

The formulation robustness was tested by cooling and heating cycles between 4 °C and 40 °C with a minimum storage duration of 48 h at individual conditions. Formulation without any phase separation and absence of creaming or cracking was exposed to freeze-thaw stress studies.

Freezing and thawing

Freezing and thawing stress on the formulation was carried out at temperatures between (-21 and 25 °C) with storage of a minimum of 48 h at each stage of temperature. Instability in the formulation due to the centrifugal stress at 5000 rpm for 5 min was observed. Self-emulsification study was performed on the formulation[17].

Self-emulsification assessment

Self-emulsification efficiency and spontaneity with respect to the time of the SNEDDS concentrates were evaluated by diluting 0.5 ml in 500 ml of distilled water in a USP 31 dissolution apparatus II (TDT06L, Electrolab, India) at 37 ± 1 °C under a continuous and gentle stirring at 50 rpm[17,18]. A visual assessment of the formulations was executed using the grading scheme as described by Shafiq *et al*. and the formulations conceded the crucial parameters of physical stability. Self-emulsification and precipitation studies of grade A and grade B were selected for further studies[18].

Analysis of self-emulsification

Measurement of transmittance

The measurement was carried out by mixing 100 mL of distilled with 0.1 mL of the SNEDDS with gentle agitation. The UV-visible spectrophotometer was used for finding transmittance at 500 nm.

Turbidity analysis

For quantifying turbidity self-nanoemulsion sample (0.3 mL) was diluted to 300 mL of water and analyzed in HACH turbidimeter (Model 2100AN, Loveand CO, USA) after triplicate calibration with formazin standards. A nephelometric turbidity unit (NTU) was used to quantify the turbidity.

Globule size determination

Globule size with polydispersity index (PDI) and zeta potential (ZP) of the SNEDDS were obtained after dispersing 0.1 ml of formulation into 100 ml of water, employing the method of dynamic light scattering (DLS) in Zetasizer Nano ZS (Malvern

Instruments, Malvern, UK).The mean size values of 3 independent replicates were recorded.

TEM analysis

The morphology of the SNEDDS was observed through a transmission electron microscope (TEM) (FEI Tecnai G2 20 TWIN, Czech Republic). The selected concentrates were dispersed and 100 times diluted in Millipore water with a slight shake. A diluted drop was placed on a carbon-coated TEM grid, removing the surplus sample with the help of tissue paper. The grids were dried at 40 °C for 24 h before analysis. The FEI instrument was used with a magnification of 62000′ and 200 kV with a camera distance of 105 mm from the sample.

In vitro dissolution test

An in vitro dissolution test was performed maintaining sink condition at pH 6.8 of 200 mL of phosphate buffer saline as dissolution medium, mimicking the corneal surface temperature (34.0 ± 0.2 °C). At 50 rpm paddle speed for 6 h, the test was performed in a United States Pharmacopoeia dissolution Tester type II (Electrolab, TDT06 L, India). The pure drug and the SNEDDS in vitro release were tested using a dialysis membrane tied on the diffusion tube fixed to the propelling paddles. Aliquots were sampled through a 0.45 mm membrane filter at predetermined time intervals and spectrophotometrically analyzed at 274 nm in triplicate.

Corneal permeation

Intact sheep eyes were obtained within 1 h of its sacrifice from the local slaughter house[15]. The cornea was cut out from the eye keeping a 6-7 mm ring of sclera. The dissected parts were rinsed with distilled water followed by phosphate buffer saline. On the modified Franz diffusion cell the cornea was mounted and tied facing the outer surface towards the donor chamber. A pre-weighed amount of sample was placed on the outer corneal surface and an area of 1.54 cm^2 was exposed towards the acceptor chamber. The receptor compartment was kept at 34 ± 0.2 °C containing pH 6.8 phosphate buffered saline 200 ml with continuous agitation at 50 revolutions per minute for 6 h. At regular time intervals, aliquots were withdrawn and analyzed spectrophotometrically at least three times.

Effect of Macitentan SNEDDS on ocular Inflammation

A day prior to the experimentation, male rabbits (Newzealand variety, weighing about 1.5–2 kg) were transferred to the laboratory and liberated with food and water. The experimental protocol (IAEC/SPS/SOA/13/2018) was thoroughly reviewed and approved by IAEC of Siksha O Anusandhan (Deemed to be University) prior to commencing. The animals without any visible ocular abnormalities were divided into two groups having four in each and placed in restraining boxes.[19]Rabbit eye was anesthetized using Proparacaine Hydrochloride 0.5 % Ophthalmic Solution USP prior to induction of inflammation. Carrageenan (100 µl, 3 % w/v) was injected to the upper palpebral region of the rabbit eye to induce acute conjunctival inflammation[20]. Within an hour of the injection clear sign of inflammation was observed with redness. The SNEDDS (MT2) formulation was sterilized by filtration using cellulose membrane (Whatmann GmbH, Germany; 0.2 mm) followed by administration into the cul-de-sac region of the inflamed eye of the rabbit (50 µL). Visual qualitative examinations were observed and photographed.

Results and Discussion

Visual observations and phase diagram studies

The SNEDDS formulations developed were examined for their dispersion and solubilization performance in small and large volumes of aqueous medium. The emulsions formed were clear to milky white, homogeneous solutions. Emulsions were found relatively transparent with the decrease of oil to surfactant ratio compared to the increased ratio. Opacity increased with the increase of oil content in the emulsions. Since surfactants are poorly tolerated due to their irritant property, a system with a higher part of oil and lower surfactant concentration was preferred for the study. Ternary diagrams were constructed and the self-nanoemulsifying area and concentrations were identified to form a stable SNEDDS formulation. Monophasic zone area of the Ternary diagrams (Fig. 1) was evaluated as: A ≈ 42.6 % (Dark Red), B ≈ 51.3 % (Orange), and C ≈ 46.8 % (Light Blue).It was observed that the combination of Transcutol HP as the co-surfactant exhibited the greatest monophasic zone in the phase diagram, indicating the possibility of forming a homogenous, clear, isotropic, and stable nanoemulsion compared to others. The phase diagrams prepared with a 1:1 ratio of Smix: co-surfactant were studied for the existence of the monophasic zone. Co-surfactants enhanced the formation of nanoemulsions by lowering the

Table 1 — Development of macitentan SNEDDS formulation for ocular delivery

Components (mg)	MP1	MT1	ME1	MP2	MT2	ME2	MP3	MT3	ME3
Macitentan	10	10	10	10	10	10	10	10	10
Captex 355	50	50	50	50	50	50	50	50	50
Croduret 40	50	50	50	60	60	60	60	60	60
Kolliphor HS 15	50	50	50	60	60	60	60	60	60
PEG 600	100	-		60			40		
Transcutol HP		100			60			40	
Ethanol			100			60			40

MP, MT, and ME denote SNEDDS formulations containing PEG 600, Transcutol HP, and ethanol as the co-surfactant

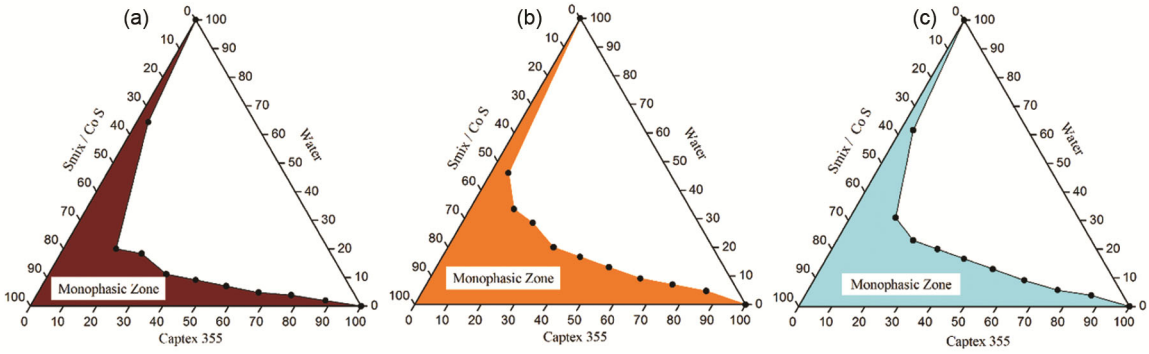

Fig. 1 — Pseudo-ternary phase diagrams of Captex 355, Smix (Croduret 40 SS and Kolliphor HS 15) and water system in presence of co-surfactants (a) PEG 600, (b) Transcutol HP and (c) Ethanol

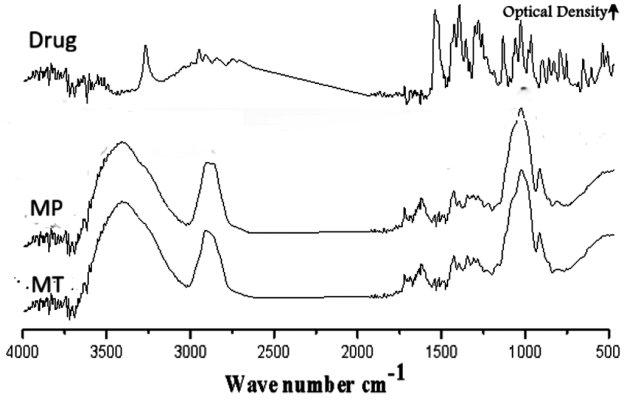

Fig. 2 — FTIR spectra of pure Macitentan and its formulations (MT and MP)

interfacial tension and escalating the fluidity of the interface. Independent formulations were fabricated (Table 1) with the preset quantity of oil and drug as indicated by the phase diagram study[21,22].

FTIR

The FTIR spectra of pure Macitentan and its formulation (MT and MP) are depicted in Fig. 2. In the FTIR spectrum of the pure drug, characteristic absorption bands were observed at 1383 cm^{-1} and 1160 cm^{-1}, corresponding to the asymmetric and symmetric stretching vibrations of the -SO_2 group, confirming the presence of sulfonyl radicals in the drug structure. A peak at 929 cm^{-1} was attributed to S-N stretching, indicating the sulfonamide functional group. The broad band at 3229 cm^{-1} was attributed to N-H stretching. The formulation MT and MP showed the characteristic peaks of the drug without any significant shift.

Stability analysis

Evaluation of physical stability is important as the emulsions tend to phase separation due to thermodynamic instability. In-situ solubilization of SNEDDS probably forms relatively stable nanoe mulsions exhibiting absence of creaming, cracking or precipitation. Drug crystal of nanoemulsion may precipitate out on long-term storage. After visual examination, Macitentan SNEDDS were found to show no creaming, cracking, or precipitation ascertaining their thermodynamic stability (Table 2).

Self-emulsification evaluation

Physically stable formulations were selected for the self-emulsification assessment test. SNEDDS formulation of poorly soluble drugs may lead to phase separation and precipitation with higher dilution. Spontaneous emulsification tendency is regarded as relatively stable in which droplets spread easily in

Table 2 — Accelerated physical stability and physicochemical characteristics of the SNEDDS

Formulations	MP1	MT1	ME1	MP2	MT2	ME2	MP3	MT3	ME3
Centrifugation	√	√	√	√	√	√	√	√	√
Heating / cooling cycle	√	√	√	√	√	√	√	√	√
Freeze thaw cycle	√	√	√	√	√	√	√	√	√
Self –emulsification	Grade C	Grade B	Grade B	Grade A	Grade A	Grade B	Grade B	Grade A	Grade B
Inference	Failed	Passed	Passed	Passed	Passed	Passed	Passed	Passed	Passed
Physicochemical characteristics									
Globule size (nm)				55.3 ±0.285	47.35 ±0.295		96.75 ±0.190	57.36 ±0.173	
PDI				0.319 ±0.006	0.191 ±0.008		0.458 ±0.009	0.148 ±0.017	
Zeta potential (mV)				–13.6 ±2.27	–12.0 ±0.81		–9.18 ±1.49	–9.45 ±1.79	

Grade A: rapidly formed clear or slightly bluish microemulsion; Grade B: rapidly forming slightly bluish white less clear emulsion; Grade C: a bright white emulsion. Data are shown as mean ± SD, (n = 3)

water to form an emulsion. On the contrary, poor emulsion formation due to the tendency of coalescence of droplets, especially upon stop stirring could result in early phase separation. Self-emulsification and precipitation studies were performed with water for examining this possibility. Self-emulsification time of SNEDDS formulations observed as 12-25 s could be regarded as relatively good emulsions (MP2, MT2 and MT3) as per (Table 2). Formulations MP2, MT2, and MT3 were considered comparatively stable for nanoemulsion and taken for further evaluation. According to SNEDDS created by a published study[23], self-emulsification time of SNEDDS formulations observed as 12–25 s might be considered as a pretty excellent emulsion (MP2, MT2, and MT3).

Percentage transmittance studies

The optimized formulations were tested for percentage transmittance after dilution. Enhanced Smix and co-surfactant proportion increased optical clarity and percentage transmittance. Formulations with Smix to co-surfactant ratio of 2:1 gave nearly 100% transmittance without any change even after 24 h of dilution. This indicates that the integrity is sustained throughout its droplet size distribution probably in nanometer range still after 24 h of dilution.

Turbidity analysis

Turbidity decreased from 178 NTU to 8 NTU when Smix and co-surfactant ratio increased from 1:1 to 3:1 respectively, showing good emulsification ability. Extent of turbidity has been utilized to determine efficient self-emulsification as a quick, convenient and reproducible tool for depiction in SNEDDS development. It determines whether the dispersion reaches equilibrium rapidly and measures the scattered light intensity linked to the diversification of globules present in the system[24].

Globule size analysis

Globule size analysis is imperative in this nanoemulsifying system as the extent of drug release and absorption are directly dependent on it (Fig. 3). Average globule size of the formulations having percent transmittance closer to 100 was 47.35 to 96.75 nm (Table 2). Polydispersity index values in the range of 0.191 to 0.458 were the indication of good nanoemulsion formation and found independent of globule size. Zeta potential (ZP) of -9.18 to -13.6 is supposed to be the firm indication for ensuring physical stability of nanoemulsion[25].

SNEDDS formulations MP2 and MT2 (post 24 h dilution) were observed for their internal structure through TEM, and images are shown in Fig. 4. Similar results were observed through TEM as of dynamic light scattering (DLS). The nanoemulsion diluted to a predetermined concentration exhibited spherical shape oil globules without coalescence. Drug precipitation was not observed under the microscope and almost consistent with that of the DLS globule size analysis. Electrophoretic mobility can sufficiently resist aggregation of the oil droplets. The measured extent of the ZP can also predict the stability and shelf-life of the formulation. In a system of larger negative or positive zeta potential particles resist to aggregate, however, they tend to approach

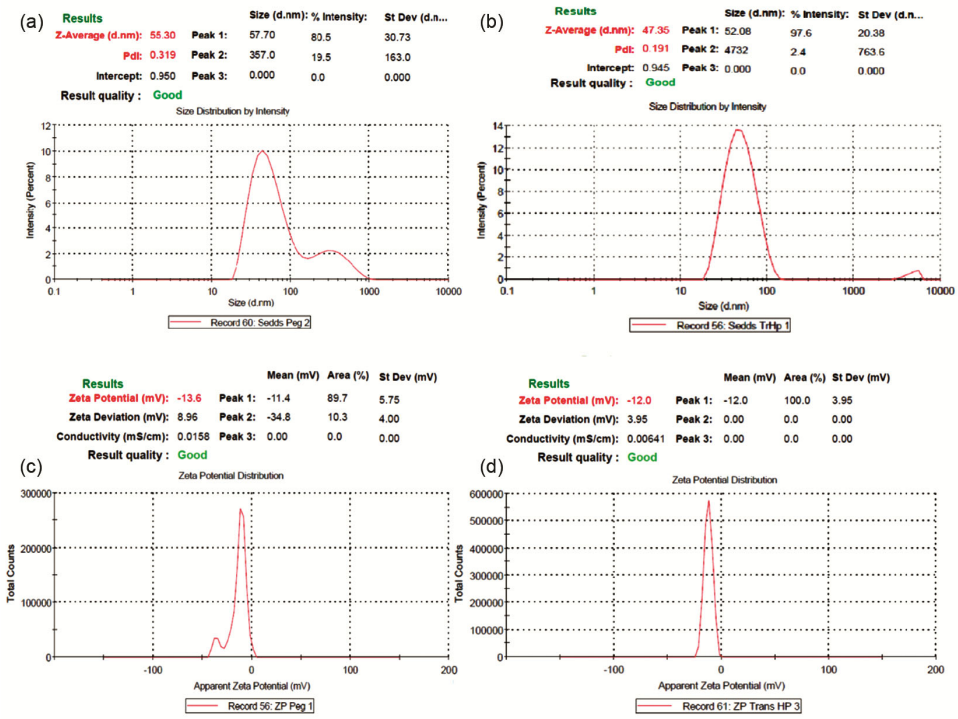

Fig. 3 — Globule size distribution (a) MP2, (b) MT2 and Zeta potential (c) MP 2 and (d) MT 2

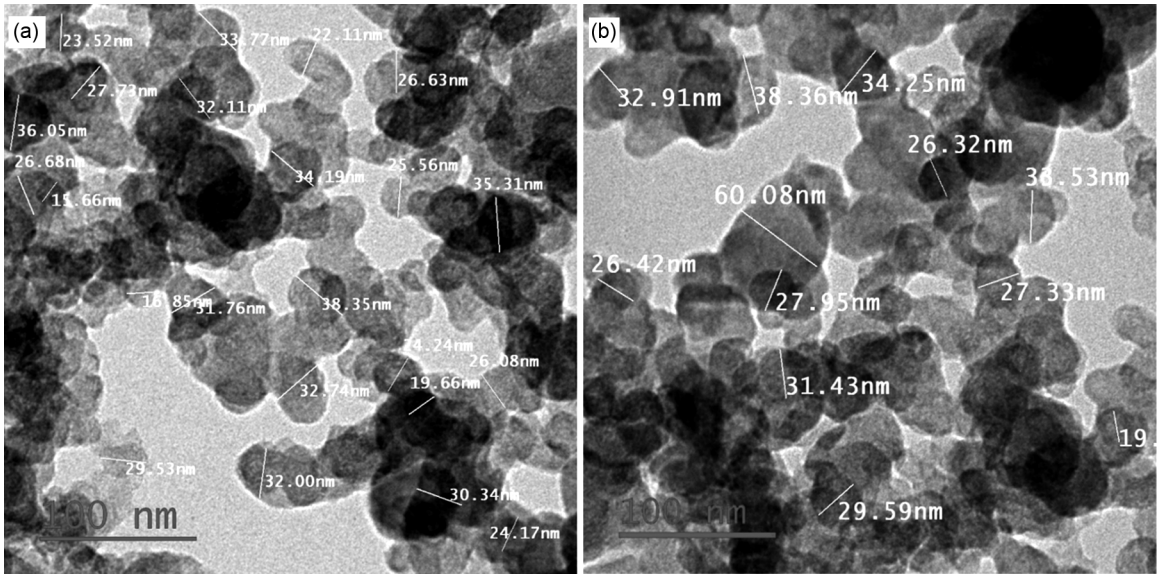

Fig. 4 — TEM photographs of (a) MP2 and (b) MT2

each other where the ZP is nearer to zero[24]. The Zeta potential value of polymeric nanoparticles or nanoemulsion in the said range was also ensured earlier to be physically stable.

Drug release studies

In vitro drug release and corneal permeation of SNEDDS concentrates (MP2 and MT2) and the pure drug (MCT) have been shown in Fig. 5. MP2 and MT2 exhibited significantly enhanced drug release compared to MCT. The presence of Transcutol in the formulation MT2 facilitated most of both the drug release (closer to 100 %) and corneal permeation (closer to 90 %). Small statistical deviation (< 1.2 %), similar pattern, and extent of drug release in-vitro and ex-vivo indicate good reproducibility. To discover the

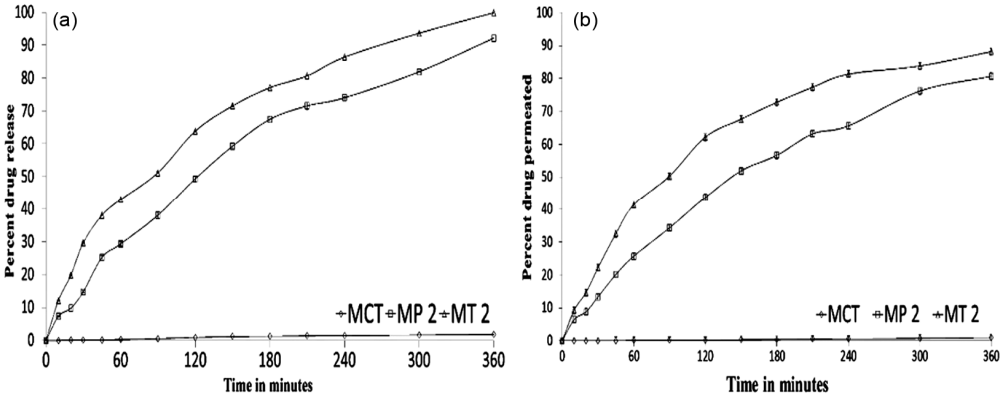

Fig. 5 — (a) In-vitro dissolution and (b) ex-vivo permeation of macitentan self-nanoemulsion for ocular delivery

Table 3 — In vitro release and ex vivo permeation parameters

Formulation	Korsmeyer Peppas		In vitro drug release		Ex vivo drug permeation	
	r^2	n	Js (μg/min) (mean±sd) (n=3)	$Pss*10^3$ (cm/min) (mean±sd) (n=3)	Js (μg/min) (mean±sd) (n=3)	$Pss*10^3$ (cm/min) (mean±sd) (n=3)
MT2	0.967	0.643	0.201 (0.0005)	1.82 (0.005)	0.313 (0.004)	2.84 (0.043)
MP2	0.990	0.752	0.174 (0.0023)	1.68 (0.023)	0.2003 (0.001)	1.93 (0.012)

dynamism of the drug release kinetic mechanism mathematical modeling was used $Mt / M = Ktn$, in which Mt / M is the cumulative percent drug release at time t, K is the constant and n is the diffusion exponent. The pure drug release in vitro and ex vivo lagged far behind with a mere release of about 2 %. The MP2, MT2 SNEDDS released above 50 % of the drug in 2 h in vitro as well in ex vivo corneal permeation. The SNEDDS formulations exhibited Korsemeyer-Peppas model where the n values (0643 and 0.752) indicated a partly diffusion and partly erosion-based release mechanism of the drug (in between 0.5 to 1.0) (Table 3).

Effect of Macitentan SNEDDS on ocular inflammation

Acute inflammation induced by Freund's adjuvant lasts for 14 days, and arachidonic acid inflammation elevates intraocular pressure. Cytokine-mediated acute inflammation in general is suggested to be induced in animal models by Carrageenan because the effect lasts not more than 24 h[26]. In the present study, carrageenan administered eye exhibited severe signs of inflammation with redness, frequent lacrimation, meibomian oozing, and puffiness of the conjunctiva. The absence of redness and inflammation in the standard normal eye was tagged as a negative control without carrageenan. Disappearance of inflammation and redness was observed within 1 h of the instillation of MT2 in the inflamed eyes in comparison to the normal negative control and positive control eyes. In positive control eyes (without MT2) inflammation of the conjunctiva was persistent even after 2 h (Fig. 6). As per the above results the developed stable SNEDDS of macitentan (MT2) could be useful for the management and control of ocular inflammation after topical administration.

The non-ionic surfactant mix provided a synergistic effect on the HLB value[21]. It enhanced the elasticity of oil-water interface with the deposition of surfactants ensuring the ultimate stabilization of oil-in-water micro/nanoemulsion. Larger monophasic zones exerting better performance were observed due to the presence of mixed surfactant systems. The great impact of appropriate surfactant/cosurfactant proportion and the level of oil was clearly observed in the illustration for achieving desirable properties[22].

Transcutol in the formulation (MT2) might have played a vital role for the improved diffusion process of drug majorly by increasing macitentan solubility, maintaining hydrated dynamics, and increasing thermodynamic driving force. Marked ex-vivo corneal permeability was achieved due to the interaction with the SNEDDS on the barrier permeability[27].

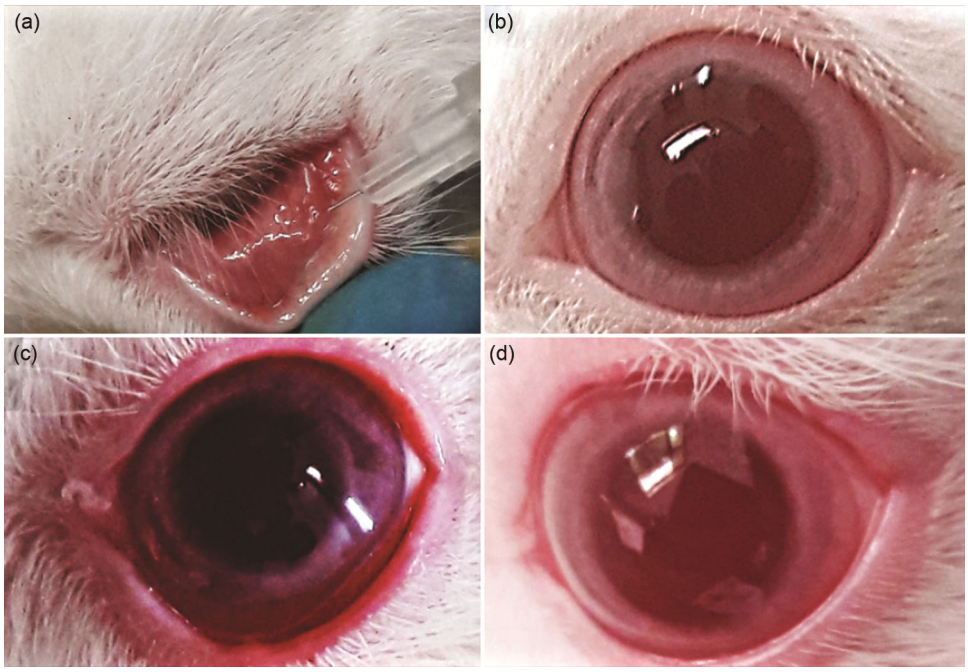

Fig. 6 — (a) Carageenan injection to the upper palpebral region of the eye for induction of acute conjunctival inflammation, (b) Normal untreated eye (negative control), (c) carrageenan-induced Inflamed eye without treatment (positive control), and (d) Recovered eye after ocular administration of MT2 self-nanoemulsion

Conclusion

Ocular delivery of macitentan SNEDDS have been developed successfully using a combination of oil, surfactant, and co-surfactant systems for improving the corneal permeability and controlling ocular inflammation. Formulation MT2 containing Transcutol HP has been optimized with respect to its globule size, PDI, and zeta potential with the highest corneal permeation of about 90 % in 6 h. After administration of MT2 symptoms of ocular inflammation in carrageenan-induced rabbit eye disappeared within 1 h whereas, acute inflammation has been continued for more than 2 h without drug treatment. Topical self-nanoemulsion of macitentan containing Transcutol may be used successfully for the prompt control of ocular inflammation with better patient compliance.

Conflict of Interest

The authors declare no conflict of interest.

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