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Brain targeting efficiency of antimigrain drug loaded mucoadhesive intranasal nanoemulsion

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ABSTRACT

Zolmitriptan (ZT) is a well-tolerated drug in migraine treatment suffering from low bioavailability due to low amount of the drug that reaches the brain after oral and nasal delivery. Development of new nasal mucoadhesive nanoemulsion formulation for zolmitriptan may success in delivering the drug directly from the nose to the brain to achieve rapid onset of action and high drug concentration in the brain which is required for treatment of acute migraine. ZT mucoadhesive nanoemulsion were prepared and characterized for drug content, zeta potential, particle size, morphology, residence time and permeation through the nasal mucosa. The selected formula was tested in-vivo in mice for its pharmacokinetics in comparison with intravenous and nasal solution of zolmitriptan. Results showed that addition of chitosan as mucoadhesive agent in 0.3% concentration to the nanoemulsion enhanced its residence time and zetapotential with no significant effect on the globule size. All tested formulations showed higher permeability coefficients than the zolmitriptan solution through the nasal mucosa. In-vivo studies showed that the mucoadhesive nanoemulsion formulation of zolmitriptan has higher AUC_{0-8} and shorter T_{max} in the brain than the intravenous or the nasal solution. This was related to the small globule size and higher permeability of the formulation.

1. Introduction

Migraine headache is the most common neurological vascular headache disease which causes a throbbing and pulsating pain around the head. It usually includes abnormal sensitivity of arteries in the brain resulting in triggers which often lead to rapid changes in the artery diameter. As a result, other arteries in the brain and scalp dilate resulting in terrible pain in the head (Niranjan et al., 2015).

Zolmitriptan (4S-4-({3-[2-(dimethylammino)ethyl]-1H-indol-5-yl}methyl-1,3-oxazolidin −2-one) is second generation triptan which is an effective, well-tolerated treatment of acute migraine associated with menses, migraine with aura (Palmer and Spencer, 1997). It has a selective action on serotonin (5HT1B/1D) receptors and is very effective in reducing migraine symptoms. It is also effective in treatment of acute cluster headache (Cittadini et al., 2006; Mahakalkar and Upadhye, 2013)

Zolmitriptan (ZT) works by stimulating serotonin receptors in the brain which is a natural product in the brain that causes brain blood vessels to narrow. Zolmitriptan mimics this action of serotonin by stimulating its receptors, thus it acts peripherally inhibiting blood vessels dilatation and inflammation of cranial vessels.

Zolmitriptan is available commercially as a conventional tablet (ZOMIG®), an oral disintegrating tablet (ZOMIG-ZMT®) and a nasal spray (ZOMIG® nasal spray), in doses of 2.5 and 5 mg (Bankim et al., 2013; Patil et al., 2015). The oral administration of zolmitriptan showed many drawbacks, such as slow onset of action, low bioavailability (40%), nausea and incomplete pain relief with recurrence of headaches, short half-life (1–2 h) and first-pass metabolism (Ahonen et al., 2004; Goadsby and Yates, 2006; Mittal et al., 2014).

In addition, considerable ratio of migraine patients suffers from gastric stasis, severe nausea and vomiting during the migraine attack. The matters which causes erratic absorption of the drug from the gastrointestinal tract with delayed gastric emitting which makes the oral treatment is ineffective (Egla and Abd Al hammid, 2017; Vyas et al., 2005). Intranasal zolmitriptan has proved earlier onset of action than the oral formulation especially in acute cluster

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headache (Charlesworth et al., 2003). However clinical studies showed that zolmitriptan half-life and bioavailability after nasal administration do not significantly differ from those obtained after oral intake of the drug (Bigal et al., 2003; Goadsby and Yates, 2006; Mittal et al., 2014).

Recently, nose to brain delivery has become a novel noninvasive technique for transporting therapeutic agents directly to the brain depending on the unique connection provided by the olfactory and/or trigeminal nerve system present between the olfactory epithelium and the brain, bypassing the BBB (Pires et al., 2009) in addition to other intranasal rout benefits such as avoiding extensive hepatic and intestinal metabolism and better patient compliance due to ease of delivery and non-invasiveness (Mistry et al., 2009; Pandey et al., 2016; Stevens et al., 2011). However, the nasal transport of the drug from the nose to the brain is affected by many factors such as rapid clearance of the drug from the nose by the nasal mucosal membrane cilia (Kolsure and Rajkapoor, 2012; Raza et al., 2007), drug concentration, dosage form, and others (Hongbing et al., 2008). Modification of the dosage form in which the drug is delivered into the nasal cavity along with using absorption enhancer within the formula are two of the most important approaches used to enhance direct transfer of the drug from the nose to the brain. (Charlton et al., 2007; Dalpiaz et al., 2008; Hongbing et al., 2008)

Nanoemulsions are thermodynamically stable, isotropic, clear dispersions containing oil and water phases, stabilized by an interfacial film of surfactant and/or cosurfactant molecules (Rodrigues et al., 2015). Briefly, they are emulsions with droplet size on the order of 100 nm. The major differences between classical emulsions, nanoemulsions and microemulsions are in droplet size range and stability characteristics. Nanoemulsions are attractive for aforementioned applications because they are relatively the least sensitive to physical and chemical changes (Gupta et al., 2016; Pandey et al., 2016).

Nanoemulsion (NE) formulations enhance nose-to-brain drug delivery since they are able to protect the encapsulated drug from biological and/or chemical degradation, and increase its extracellular transport (Mahajan et al., 2014). They also provide higher surface area and can be formulated in different formulations such as liquids, sprays, foams, creams, ointments and gels (Sarker, 2005).

The objective of this work was to formulate nano-sized mucoadhesive drug delivery system of zolmitriptan in order to enhance its transport from nose to brain and have rapid onset of action to increase its efficiency in acute migraine management.

2. Methods

2.1. Materials

Capryol PGMC, Capmul MCM EP, Maisine 35-1, and Captex 200-P were obtained as a gift from GATTEFOSSE, France. Kolliphor® RH 40 (Polyoxyl 40 hydrogenated castor oil) and Kolliphor® El (Polyoxyl 35 hydrogenated castor oil) were purchased from Sigma (Sigma-Aldrich). Chitosan (MW:100,000–300,000 Da, Acros Organics, New jersy, USA). Tween 80, Brij 35, Ploxamer 188, Oleic acid, IPM, and Olive oil and other analytical reagents were purchased from El-Gomheria Co., Cairo, Egypt.

2.2. Spectrophotometric determination of zolmitriptan (ZT) in methanol

Stock solution of ZT in methanol was prepared by dissolving ZT in methanol into 100 mL volumetric flask to give the final concentration of 1 mg/mL. This solution was scanned against methanol at the UV range 200–400 nm using UV–vis Schimadzu spectrophotometer (Model UV-1601, Japan). Serial dilutions were done and the calibration curve was constructed in the range from 50 to 800 μg/mL.

For confirmative study, oils, surfactant and cosurfactants interferences with ZT estimation were studied using methanol as reference by measuring separately the absorbance of the oil, surfactant, and co-surfactants into which the maximum amount of ZT was dissolved at ZT ⩘max against methanol.

2.3. Solubility studies

1 Excess amounts of ZT was added into screw capped vials to 2 g of each of the following oils: (Capryol PGMC, Maisine 35-1, Capmul MCM EP, Oleic acid, IPM, and Olive oil), surfactants: (Kolliphor® RH 40, Kolliphor® El, Tween 80, Brij 35) and co-surfactants: (Transcutol-P, PEG 400, Captex 200-P, and Poloxamer 188).

The contents of each vial were mixed using vortex (BV1000 BenchMixer™) then shacked for 48 h using shaker (PSU-20i Orbital Multi-Platform Shaker) at room temperature. After equilibrium, solutions were centrifuged using laboratory centrifuge (Remi Laboratory Centrifuge *R*32A, Remi Equipment, Bombay, India) at 5000 rpm for 15 min and filtered by Whatman filter (0.45). From each supernatant, 0.5 mL was taken and diluted with 5 mL methanol then measured spetrophotometrically for ZT concentration. Each experiment was done in triplicate. The oil, surfactant and co-surfactant into which ZT has maximum solubility were selected for construction of the pseudo-ternary phase diagrams.

2.4. Pseudo-ternary phase diagrams construction

Based on solubility studies, Capryol PGMC was selected as the oil phase, Kolliphore® RH40 as the surfactant and Transcutol®-P as the cosurfactant along with distilled water as the aqueous phase for construction of the pseudo-ternary phase diagram.

Three ratios of the surfactant: cosurfactant (Smix) were used 1:1, 2:1, and 3:1 along with the oil in different ratios; 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9 for construction of three phase diagrams in order to investigate the one has the maximum region of NE formation (Shah et al., 2014). Addition of water was done drop wise using the water titration method with mixing by a vortex until formation of clear transparent emulsion stopped with physical change appearance (usually occurs as turbidity,

Table 1
Composition and physicochemical characterization of prepared NE systems.

Oil (%w/w)	Smix (2:1) (%w/w)	Water (%w/w)	Globule size (nm)	PDI%	% T	Turbidity after centrifugation
10	30	60	180.53 ± 2.34	0.14 ± 0.02	89.65 ± 2.13	Phase separation
10	34	56	125.76 ± 3.72	0.23 ± 0.01	92.34 ± 1.85	turbid
10	38	52	76.62 ± 2.84	0.17 ± 0.04	97.68 ± 2.34	clear
10	42	48	67.57 ± 1.86	0.25 ± 0.01	99.46 ± 1.57	clear
10	46	44	61.27 ± 2.73	0.22 ± 0.03	99.67 ± 1.38	clear
10	50	40	54.63 ± 3.24	0.026 ± 0.03	100.08 ± 1.63	turbid

Values are expressed as mean ± SD, n = 3.