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Development and evaluation of Zotepine loaded mucoadhesive microemulsion for intranasal delivery

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ABSTRACT

Mania and bipolar illness are the major problems in the schizophrenia treatment, zotepine, atypical antipsychotic drug used for this condition. The aim of present investigation was to develop mucoadhesive microemulsion of zotepine for intranasal delivery by phase titration method. The developed formulations were evaluated for its size, zeta, PDI and invitro release studied. The optimized formulation, containing 5% Oleic acid, 40% Tween 80: PEG400 (3:1) and 55% water. The globule size (53.1±0.31), zeta potential (-32.1±0.2),PDI (0.13±0.23).0.5% chitosan was added to the optimized formulation to prepare mucoadhesive formulation.

Keywords: Zotepine; Microemulsion; pseudoternary phase diagram; solubility;

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INTRODUCTION:

Schizophrenia is a severe mental disease and chronic condition having world-wide occurrence of 23 million people approximately. [1] It is associated with three types of symptoms which are positive symptoms such as hallucinations, delusions, thought disorder, negative symptoms such as abnormal emotions, inability to enjoy pleasure and cognitive symptoms such as, inability to use learned skills, Inability to focus or pay attention. [2] Antipsychotic drugs are used for the treatment of cognitive symptoms and both positive and negative of schizophrenia [3]

Zotepine (ZME) is a second-generation antipsychotic drug which appears to act as a dopamine type 1 (D1), type 2 (D2), serotonin (5-HT)-2A receptor antagonist and noradrenaline reuptake inhibitor [4] Zotepine having broad efficacy and improves positive and negative symptoms of Schizophrenia.

Oral administration of drug is more convenient and well accepted. However, upon oral administration drug undergoes hepatic first pass effect. [5] Presently, ZME oral formulation is available in tablet which has oral bioavailability of 7-13%. Disadvantages of oral dosage form includes poor bioavailability, and slow transport along gastrointestinal tract. [6]

Hence, in order to improve bioavailability of formulation alternative routes of administration should be preferred. In last three decades the intranasal drug delivery system is emerging delivery option for targeting to brain. It offers high absorption of drug, it increases the bioavailability of drug, reduction of drug dose in drug dose and avoidance of hepatic first pass effect and improved patient compliance. [8,9,10,11] In recent years targeting the brain through intranasal microemulsion based delivery systems have been studied extensively. [12]

In the present study, we developed zotepine loaded mucoadhesive microemulsions through intranasal drug delivery to brain.

MATERIALS:

Zotepine was received from Sun Pharmaceuticals limited, Hyderabad, India as gift sample, Capmul MCM was from Abitec corporation Ltd. Mumbai, India Cremophor RH 40 was received as free sample from Gattefose SAS, France. Oleic acid, Tween 80 PEG 400, PEG600 was purchased from Sd fine chemicals. Chitosan, sunflower oil, castor oil from sigma Aldrich, Bangalore, India.

METHODS:

Screening of oil

Zotepine solubility in various oils was find out by adding an excess amount of drug in 5ml capacity vials containing two ml of the different oils, and then mixed using cyclomixer, then the vials were stirrer on water bath shaker at 25ºC for 48 h. After equilibrium, vials were centrifuged at 10000 rpm for 10 min [13]. The supernatant was filtered through a membrane filter (0.45µm). The concentration of zotepine was determined in oils using UV spectroscopy. The study was carried in triplicate.

Screening of Surfactants

Cremophor RH 40 and Tween 80 were screened. In water, surfactant solution of 2.5ml was prepared, to this add 5% with vertexing. If a one phase clear solution was obtained, the add the oil until the solution became turbid.

Screening of Cosurfactants

Tween 80 was combined with cosurfactant PEG400, at a Smix ratio of 1:1,2:1,3:1 the pseudoternary phase diagrams were made. Different weight ratios of oil and Smix, 9:1,8:2,7:3,6:4,5:5,4:6,3:7,2:8 ,1:9, were taken so that maximum ratios were Perform to define the boundaries of phases precisely formed in the phase diagrams. [14,15] The pseudo ternary graphs are plotted by using CHEMIX software.

Preparation of microemulsion containing Zotepine

ZME formulations were prepared by water titration method [16] by different the ratios of oil, Surfactant, co-surfactant, and water; keeping the zotepine drug concentration of constant.

25 mg drug was mixed with oil (Oleic acid), and to that surfactant mixture (Tween80:PEG400) was added and mixed thoroughly for 5 minutes at room temperature. The mixture was titrated with water drop wise until a transparent and stable ZME was formed. ZMMEs were prepared by adding 0.5% w/w chitosan solution in 1% acetic acid to microemulsion formulation, were represented in Table 1.

Characterization of Formulation

Zeta potential, Globule size and Polydisperse index

Zeta potential, Globule size, PDI and measurements were performed by using Zetasizer (Nano-ZS90, Malvern, Worcestershire, UK) by taking 1ml of formulation into polystyrene cuvettes for globule size and PDI and disposable folded capillary Cell for zeta potential at 25ºC respectively.

Transmittance (%T)

Transparence of microemulsion was determined by percentage transmittance measurement through UV Spectrophotometer. Percentage transmittance of samples was measured at 650nm with purified water taken as blank and triplicate were performed for each formulation [17]

Drug content

ZME and ZMME drug content was determined by taking equivalent to 25mg of zotepine and diluted using methanol. Samples were prepared in triplicate and the absorbance was measured at 278 nm using UV-Visible Spectrophotometer.

Viscosity

The viscosity of microemulsion was determined using Brookfield viscometer. Viscosity determinations were performed at 40 rpm at 25 ± 0.3ºC.

pH

The pH of microemulsion was determined by using a calibrated digital pH meter at room temperature by taking 5 ml of microemulsion individually in a beaker.

Scanning electron microscopy

1 ml of the mucoadhesive microemulsion of zotepine formulation was placed on the stub. This specimen was observed with a scanning electron microscope, SEM micrographs of the microemulsion surfaces were observed. [18]

Stability studies

The optimized ZME was stored at three different temperature ranges for 3 months i.e., refrigerating condition (2– 8ºC), room temperature and elevated temperature (40 ± 2), shelf life of the stored microemulsion system was evaluated by phase separation, rheological behavior, emulsifying time, electrical conductivity, pH, percentage transmittance [19]

Statistical Analysis

Experimental data from more than triplicate are shown as means ± standard deviations (SD).

RESULTS AND DISCUSSION:

In the development of microemulsion systems for poorly soluble drugs, drug loading in the formulation is very critical factor, which is dependent on the drug solubility in various components used in the formulation. Hydrophilic drugs are preferably solubilized in w/o microemulsions, whereas o/w systems seem to be a better choice for lipophilic drugs. The amount of the formulation should be minimized to deliver the therapeutic dose of the drug. Solubility of the drug in the oil phase is an important measure for the selection of the oil, it influences to maintain the drug in solubilized form in the microemulsion formulation. If the surfactant or cosurfactant is influence to drug solubilization, there could be a risk of precipitation. Thus, an understanding of factors that influencing drug loading ability while maintaining the capability of the system to undergo monophasic dilution with water and minimizing the propensity for drug precipitation or crystallization in diluted systems is essential to the development of stable and appropriately less-volume microemulsion systems for drug delivery applications.

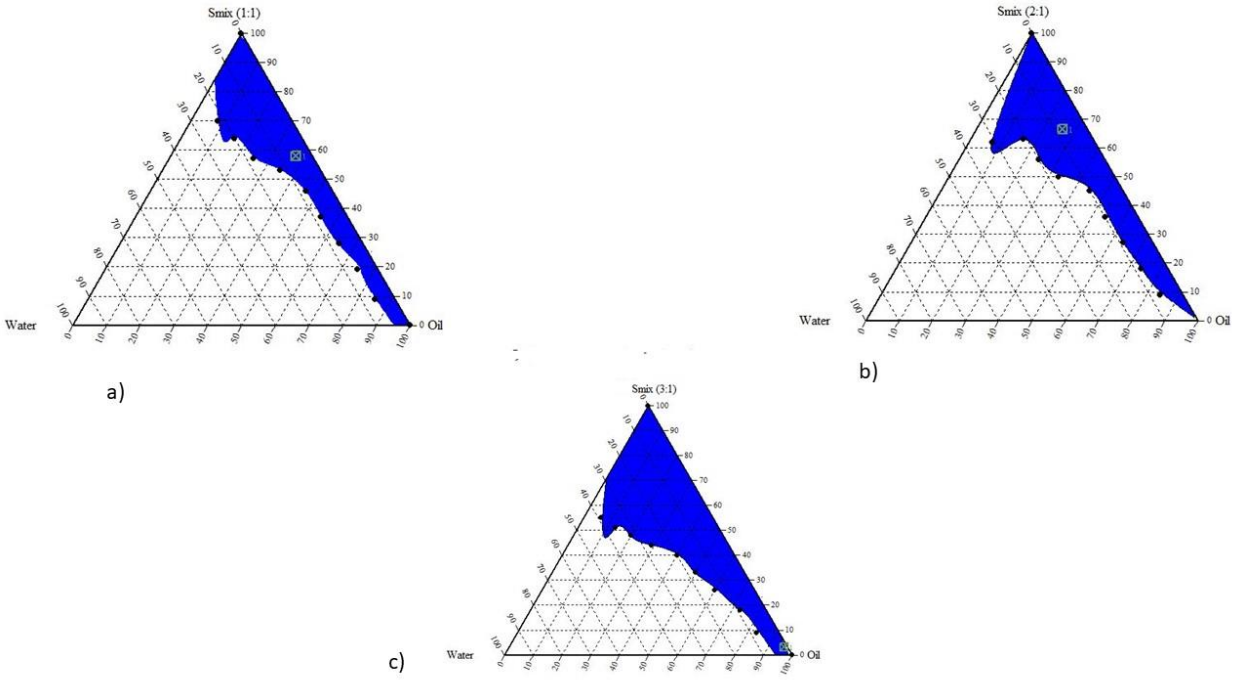

Fig. 1. Pseudo ternary phase diagram using oleic acid as oil, Tween 80 as surfactant, PEG400 as cosurfactant and water, ratio of S mix (Tween 80: PEG400) a) 1:1, b)2:1 c)3:1

Oleic acid was selected as Oil Phase, Smix was Tween 80: PEG400 (3:1), water from the Pseudo ternary phase diagrams (Fig 1). The solubility of zotepine in different oils was determined (Table I). The solubility of zotepine was found to be highest in Oleic acid (130.12±1.12 mg/ml) as compared to other oils.

Table I. Solubility of zotepine in different Oils at 25°C (mean ±SD, n=3)

S. No	Solvent	Solubility (mg/ml)
1	Capmul MCM	137.54±1.13
2	Tween 80	264.23±1.24
3	Cremophore R	122.3±1.54
4	Oleic acid	430.29±0.25
5	Castor oil	150.21±1.23
6	Olive oil	130.12±1.12
7	PEG 400	221.34±1.52
8	Sunflower oil	101.12±0.38
9	PEG600	99.43±0.23

The microemulsions were selected so that all the formulations contain increasing concentrations of oil and Smix Table II.

Table II: composition of microemulsion containing Zotepine

Formulation	Oil (%)	Smix (%)	Water (%)	Chitosan (%)
ZME1	5	35	60	-
ZME 2	7.5	35	57.5	-
ZME 3	10	35	55	-
ZME 4	5	40	55	-
ZME 5	7.5	40	52.5	-
ZME 6	10	40	50	-
ZME 7	5	45	50	-
ZME 8	7.5	45	47.5	-
ZME 9	10	45	45	-
ZME 10	5	50	45	-
ZME 11	7.5	50	42.5	-
ZME 12	10	50	40	-
ZME 13	5	60	35	-
ZME 14	7.5	60	32.5	-
ZME 15	10	60	30	
ZMME	5	40	55	0.5

Note: Zotepine 25 mg in all formulations

Characterization of formulation

Characterization of the ZME and ZMME are shown in Table III. The globule size was of 53.1 ± 0.31nm and 88.8±0.45nm, Zeta potential measurements of −32.1±0.2 and 12.5±0.47 mV on the globules of ZME and ZMME indicated that the system is physically stable and PDI of 0.13 ± 0.23 and 0.22±0.12 for ZME and ZMME, respectively, indicate that the ME approached a monophasic stable system. This microemulsion system can more efficiently deliver a drug due to the presence of a larger surface area. pH was of 6.51 and 6.67 for the ZME and ZMME. A formulation whose pH is in this range may help in reduce the irritation give upon administration. Formulation was stable for 3 months.

Table III: Characterization of Formulations. Data shown as mean ± SD (n=3)

Formulation	Globule Size (nm)	Zeta size (mV)	PDI	pH	Viscosity (mPa-s)
ZME1	91.1±0.18	-22.5±0.3	0.21±0.12	6.56	169
ZME 2	67.3±1.12	-21.9±0.7	0.20±0.31	6.39	179
ZME 3	48.1±0.14	-28.1±0.6	0.17±0.14	6.41	195
ZME 4	53.1±0.31	-32.1±0.2	0.13±0.23	6.51	154
ZME 5	41.3±0.26	-26.4±0.5	0.22±0.26	6.45	200
ZME 6	49.8±0.33	-21.2±1.4	0.19±0.31	6.42	181
ZME 7	45.4±0.56	-28.6±1.8	0.18±0.46	6.43	188
ZME 8	125.3±0.34	-2.7±1.2	0.21±0.27	6.34	201
ZME 9	114.4±0.67	-24.8±1.4	0.16±0.34	6.31	256
ZME 10	126.3±0.39	-27.8±1.3	0.17±0.25	6.42	235
ZME 11	119.4±0.52	-23.6±0.2	0.18±0.44	6.25	227
ZME 12	105.3±0.30	-24.5±0.9	0.13±0.72	6.43	210
ZME 13	72.6±0.44	-25.3±0.7	0.15±0.36	6.32	193
ZME 14	82.7±0.18	-27.7±0.3	0.18±0.64	6.60	242
ZME 15	75.8±0.23	-25.6±0.64	0.20±0.61	6.62	182
ZMME	88.8±0.45	12.5±0.47	0.22±0.12	6.67	230

Scanning electron microscopy

Optimized formulation SEM results depicted that pure drug Zotepine is having rough surface, after converting in to microemulsion it has smooth surface, SEM micrographs of plain drug and Microemulsions are shown in Figure 2.

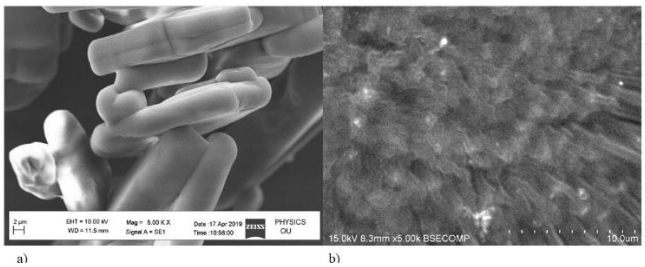

Figure 2.SEM image of a) Pure zotepine b) Optimized formulation

CONCLUSION:

The zotepine microemulsion formulations for intranasal delivery were developed by water titration method. The Mucoadhesive microemulsion and microemulsion formulation showed small globule size and good zeta potential and uniform distribution of globules after 3 months of stability studies, SEM studies shown formation of globules. According to this study, Microemulsion formulation is potential; it may be increase bioavailability of formulation and avoids hepatic first pass effect. Hence, the present study concluded that intra nasal administration of may be considered as replacement to oral administration

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