NOSE TO BRAIN DELIVERY OF ZIPRASIDONE MICROEMULSION: DESIGN AND CHARACTERIZATION

Amarjitsing Premsinh Rajput*, Patil Vikas Prakash, Chaudhari Pankaj Motilal, Chaudhari Swapnil Prakash,
Baviskar Dheeraj Tukaram

Department of Pharmaceutics, KVPS's Sanstha's Institute of Pharmaceutical Education, Boradi, Tal-Shirpur, Maharashtra,
India

*Corresponding Author Email: amarjit.rajput@yahoo.com

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ABSTRACT

Nasal administration offers an interesting promising alternative technique to the parenteral route for achieving systemic drug effects. Now a day many drugs have better systemic bioavailability through nasal route as compared to oral administration. Microemulsion is dispersed, macroscopically homogenous thermodynamically stable, optically transparent, single phase system, formed by spontaneous solubilisation of two immiscible liquid, in the presence of surfactants. Microemulsion offers number of advantages than drug formulation for nasal drug delivery. Ziprasidone is lipophilic, benz-isothiazoyl-piperazine derivative, used in the treatment of schizophrenia, mania and mixed states associated with bipolar disorder. The microemulsion was prepared by precipitation method. The characterization of microemulsion formulation includes determination of viscosity, pH, drug content, refractive, conductivity measurement, zeta potential analysis and particle size analysis. *In-vitro* drug permeation studies were done by using Keshary Diffusion cell. All ME formulations were shown fast drug permeation 99.50 % for ME 2 within 1 h and 99.40 % for ME 6 within 100 minutes since the ME 2 which is optimized on the basis of *in-vitro* study. Nasal mucoadhesive drug delivery system is designed with an aim to target the drug and to maintain the dosage form at its absorption site for a rapid onset of time. This will result in the enhancement of the absorption of the drug, which will in turn reduce the presystemic metabolism; increase the bioavailability of the drug, initiate rapid onset of action and thus will decrease the dosing frequency and dose related side effects of the drug. For this purpose in microemulsion system is preferred over conventional solution system.

Keywords: Microemulsion, Ziprasidone, Cremophore RH 40, Particle size, *In-vitro* permeation study.

INTRODUCTION

Nasal administration offers an interesting promising alternative technique to the parenteral route for achieving systemic drug effects. Now a day many drugs have better systemic bioavailability through nasal route as compared to oral administration. Biotechnological advancement has lead to the development of a new large number of protein and peptide drugs for the treatment of several diseases.^{1,2} The interest in nasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action.³ Schizophrenia is considered to be neurodevelopment disorder. This implies that structural and functional change in the brain is present even in some patients, or that they develop during childhood and adolescence, or both. The treatment of CNS disorders are challenging because of a variety of formidable obstacles for effective and persistent delivery of drugs. Even though the drugs used for the treatment of CNS disorders are potent, their clinical failure is often not due to lack of drug efficacy but mainly due to short comings in the drug delivery approach. Hence, scientists are exploring the novel approaches so that delivery of the drugs can be enhanced and / or restricted to the brain and CNS. Many advanced and effective approaches to the CNS delivery of drugs have emerged in recent years. Intranasal drug delivery is one of the focused delivery option for brain targeting as brain and nose compartments are connected to each other via olfactory / trigeminal route via peripheral circulation. Realization of nose to brain transport and the therapeutic viability of the route can be traced from the ancient times and has been successfully investigated for rapid and effective transport in last two decades. Intranasal drug delivery delivers drug directly to the brain circumventing BBB and reduces drug delivery to the non targeted sites. This may result in reduction

in dose, systemic dilution and first pass metabolism of the drug.⁴ Microemulsions or micellar emulsions are defined as single optically isotropic and thermodynamically stable multi component fluids composed of oil, water and surfactant (usually in conjunction with a cosurfactant). The droplets in a microemulsion are in the range of 1 nm - 100 nm in diameter. Microemulsion have various textures such as oil droplets in water, water droplets in oil, bi continuous mixtures ordered droplets or lamellar mixtures with a wide range of phase equilibrium among them and with excess oil and / or water phases. This great variety is governed by variations in the composition of the whole system and in the structure of the interfacial layers.^{5,6}

Objectives

- To enhance solubility of Ziprasidone by microemulsion technique.
- To deliver Ziprasidone via nasal route for the effective treatment of CNS disorder (schizophrenia).
- To formulate microemulsion with the help of ternary phase diagram.
- To study characterization of microemulsion for their viscosity, drug content, particle size, zeta potential and *in-vitro* permeation study.
- To carry out *in-vitro* diffusion studies microemulsion across cellulose acetate membrane using Keshary Diffusion Cell.

MATERIAL AND METHODS

All the chemicals were obtained from commercial supplier and used as received: Ziprasidone (Lupin Pharmaceutical Limited, Mumbai, India), Iso-propyl myristate, Cremophor EL, Cremophor RH 40, Lutal E 400 (BASF India Limited, Mumbai, India), Oleic acid, Span 20, Tween 80 (Research Laboratory, Mumbai, India), Propylene glycol (Loba Chemie, Mumbai, India), Disodium hydrogen phosphate, Potassium

hydrogen phosphate, Sodium chloride (Merck Chemical Limited, Pune, India) and Castor oil (Rajesh Chemicals, Indore, Madhya Pradesh, India). All the other reagents and chemicals were used of analytical grade.

Preparation of Microemulsion

The phase diagrams were constructed at Km value: 0.5, 1 and 2. The Km value at which the higher microemulsion region was obtained is selected for the further studies. On the basis of solubilization capacity, concentration and hydrophilicity the eight formulations ME1 to ME8 were selected from this microemulsion region. The composition of the formulation is shown in Table 1.

Formulation Selection

- Formation of microemulsion was determined by visual observation. A clear isotropic single-phase system were classified as microemulsion.⁷
- The opaque systems showing birefringence with oily streaks, fan shaped textures when viewed by cross-polarized light microscopy were classified as systems containing lamellar crystals (LCs).
- The system consisting of two-phases when viewed by phase-contrast microscopy and showing no birefringence under a cross polarizer was classified as a coarse emulsion.
- For each percentage of oil selected, the formula that used the minimum concentration of Smix for its microemulsion formation was selected from the phase diagram.
- Phase diagrams were constructed from data gathered by the titration method. Phase diagram were constructed to define the extent of the microemulsion regions i.e. proportion in which the three/four essential components must be mixed to form a transparent, clear, single phase, homogeneous and stable microemulsion.

Evaluation Parameters of Microemulsion

Physicochemical parameters of microemulsion

It is important to study the physical parameters of the microemulsion system containing Ziprasidone HCl. Physical parameters are estimated to test their suitability for the future use as nasal microemulsion. The physical parameters such as viscosity, pH and refractive index were studied.

Determination of Viscosity

Viscosity is an expression of the resistance of a fluid to flow, the higher the viscosity, the greater is the resistance. Viscosity measurements can indicate the presence of rod-like or worm-like reverse micelle. For Non-Newtonian system the viscosities of microemulsion were measured with Brookfield digital viscometer (LV3, Brookfield Inc., USA) equipped with spindle No.3. The viscosities of prepared MEs were measured at (6, 12, 30 and 60 rpm). The measurement was done at ambient temperature. After stabilization viscosity of the formulations were recorded.

Determination of pH

The pH value conventionally represents the acidity or alkalinity of an aqueous solution and it is expressed as,

$$\text{pH} = -\log_{10} [\text{H}^+]$$

Where, [H⁺] is the hydrogen ion concentration in moles/litre.

pH of all formulations was determined by using digital pH meter. The pH meter was calibrated before each use with standard pH 4.0, 7.00 and 10 buffer solutions.⁸ The 25 ml of

prepared ME were taken and immersed glass electrode and allowed to stabilize. After stabilization the pH of the formulation was recorded.

Determination of Refractive Index

If a light enters a less dense substance, it is refracted away from the interface rather than toward it. The relative value of this effect between two substances is given by refractive index n ,

$$n = \frac{\sin i}{\sin r} \quad (1)$$

Where i = Angle of incident ray,
 r = Angle of refracted ray

Refractive index of the system is measured by using an Abbe's refractometer by placing 1 drop of solution on the slide.⁹

Determination of Drug content

The 0.1 ml microemulsion formulation was added in 10 ml volumetric flask diluted with 7.4 PBS to make the volume up to 10 ml and analyzed spectro-photometrically at 267 nm.

Determination of Conductance

In order to get a first approximation of the structure of microemulsions, electrical conductivity measurements can be used. The conductivity of all the formulations was determined using digital conductivity meter 304. The conductivity cell used is Type CD - 10, and the cell constant is 1 ± 10 %. The electrode was dipped in the microemulsion sample until equilibrium was reached and reading becomes stable¹⁰. The conductivity cell was calibrated using standard KCl solution.¹⁰

Determination of Particle size (Globule Size)

The globule size of prepared microemulsion was analyzed by laser light scattering technique using Malvern Zetasizer (Nano-ZS, Malvern Instruments, UK. Dynamic light scattering (DLS), sometimes referred to as Photon Correlation Spectroscopy (PCS) is a non-invasive, well-established technique for measuring the size of molecules and particles typically in the micron and nano region. Typical applications of Dynamic Light Scattering are the measurement of the size and size distribution of particles in emulsions and molecules dispersed or dissolved in a liquid.

Determination of Zeta Potential

The zeta potential of the microemulsion droplet surface was determined by electrophoretic mobility in an apparatus such as a Malvern Zetasizer ZS (Malvern Instruments, UK) equipped with suitable software and calibrated with the supplied standard. The microemulsion is diluted in double distilled water, needed in order to obtain the scattering intensity allowing optimal particle detection. The sample count rate should be between 100 to 1000 KCps, in homodyne detection (if heterodyne detection is used, the contribution of the reference beam should be deduced). Three consecutive measurements are performed at 25°C using a constant cell drive of 150 mV. The electrophoretic mobility is converted into zeta potential values through the Smoluchowsky equation, using the dielectric constants and viscosity of dispersion medium.

In- vitro Drug Permeation Study

The *in-vitro* release studies of topical ME formulations was carried out by means of diffusion cells. In the present study, *in vitro* drug release of prepared microemulsion from various formulations was studied by using Keishery-Chein type diffusion cell using cellophane membrane.¹¹ The cellophane membrane was soaked in diffusion medium for 1 h before use. In the present study, appropriate diffusion medium (phosphate buffer pH 7.4) was present in receptor compartment. The drug contained in microemulsion (1 mg)

was kept in the donor compartment and it was separated from the receptor compartment by an appropriate membrane. The donor and receptor compartment were held together by using clips of strong grip. The receptor compartment containing dissolution medium was maintained at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ by circulating the water in outer jacket from organ bath to mimic the *in-vivo* condition. Adequate samples (1 ml) were withdrawn at specific interval 10, 20, 30...up to 100 minutes and replaced with fresh medium. These samples were diluted with mobile phase and analyzed by UV method.

Table 1: Compositions of Microemulsion Formulations ME1-ME8

Batch Code	Components		
	Oil % w/w	Water % w/w	Smix % w/w
ME1	5	20	75
ME2	10	21	69
ME3	15	14	71
ME4	20	16	64
ME5	25	15	60
ME6	30	15	55
ME7	35	14	51
ME8	40	11	49

Table 2: Composition of IPM / Cremophor EL/ Cremophor RH40/ Water (Smix 1: 2)

Smix: Oil	Smix (% w/w)	Oil (%w/w)	Water (% w/w)
1 : 9	75.00	8.33	16.67
2 : 8	68.37	17.10	14.53
3 : 7	60.87	26.09	13.04
4 : 6	53.10	35.39	11.50
5 : 5	45.45	45.45	9.09
6 : 4	36.70	55.00	8.26
7 : 3	28.04	65.42	6.54
8 : 2	18.87	75.47	5.66
9 : 1	9.52	85.71	4.76

Table 3: Composition of IPM / Cremophor EL/ Cremophor RH40/ Water (Smix 1: 1)

Smix: Oil	Smix (% w/w)	Oil (%w/w)	Water (% w/w)
1 : 9	65.22	7.25	27.54
2 : 8	55.56	13.89	30.56
3 : 7	44.87	19.23	35.90
4 : 6	34.09	22.72	43.18
5 : 5	32.89	32.89	34.21
6 : 4	27.78	41.67	30.56
7 : 3	25.86	60.34	13.79
8 : 2	17.86	71.43	10.71
9 : 1	9.43	84.90	5.66

Table 4: Composition of IPM / Cremophor EL/ Cremophor RH40/ Water (Smix 2: 1)

Smix: Oil	Smix (% w/w)	Oil (%w/w)	Water (% w/w)
1 : 9	71.42	7.94	20.63
2 : 8	64.51	16.13	19.35
3 : 7	57.38	24.59	18.03
4 : 6	50.42	33.61	15.96
5 : 5	42.37	42.37	15.25
6 : 4	34.48	51.72	13.79
7 : 3	25.86	60.34	13.79
8 : 2	17.39	69.57	13.04
9 : 1	9.43	84.91	5.66

Table 5: Determination of Viscosity

Sr. No.	Batch code	Speed			Mean (cps)
		6	12	30	
1.	ME 1	2.672	2.671	2.678	2.6692
2.	ME 2	2.347	2.348	2.350	2.3572
3	ME 3	2.476	2.480	2.478	2.2342
4.	ME 4	2.116	2.112	2.118	2.0214
5.	ME 5	1.801	1.802	1.804	1.7215
6.	ME 6	1.596	1.598	1.592	1.6024
7.	ME 7	1.459	1.451	1.457	1.5222
8.	ME 8	1.350	1.341	1.347	1.3688

Table 6:- Determination of pH

Sr. No.	Batch Code	pH
1.	ME 1	6.4
2.	ME 2	6.3
3.	ME 3	6.2
4.	ME 4	6.2
5.	ME 5	6.3
6.	ME 6	6.5
7.	ME 7	6.8
8.	ME 8	6.8

Table 7: Determination of Drug Content

Sr. No.	Batch Code	Drug content
1.	ME 1	99.23± 0.05
2.	ME 2	99.93± 0.06
3.	ME 3	99.65± 0.06
4.	ME 4	100.06± 0.1
5.	ME 5	98.63± 0.07
6.	ME 6	99.21± 0.09
7.	ME 7	98.23± 0.08
8.	ME 8	99.65± 0.06

Table 8: Determination of Conductance

Sr. No.	Batch Code	Conductance (ms/cm)
1.	ME 1	0.73±0.002
2.	ME 2	0.64±0.010
3.	ME 3	0.52±0.002
4.	ME 4	0.36±0.010
5.	ME 5	0.21±0.030
6.	ME 6	0.24±0.002
7.	ME 7	0.13±0.020
8.	ME 8	0.34±0.010

Table 9: Determination of Particle size

Sr. No	Batch Code	Particle size (nm)	PDI
1.	ME 1	301.6	0.416
2.	ME 2	158.1	0.218
3.	ME 3	170.8	0.167
4.	ME 4	198.9	0.138
5.	ME 5	212.1	0.232
6.	ME 6	211.8	0.038
7.	ME 7	230.2	0.189
8.	ME 8	316	0.205

Table 10: Zeta potential value of microemulsion formulation

Batch Code	Mean zeta potential (mV)	Zeta Deviation (mV)	Area of Peak (%)	Width (mV)
ME 1	45.5	-	-	-
ME 2	40.5	7.63	100	7.63
ME 3	31.3	-	-	-
ME 4	27.3	-	-	-
ME 5	30.5	-	-	-
ME 6	25.1	10.1	100	10.1
ME 7	30.5	-	-	-
ME 8	31.2	-	-	-

Table 11: Comparative in-vitro permeation study of all ME formulations

Time (min)	ME 1	ME 2	ME 3	ME 4	ME 5	ME 6	ME 7	ME 8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	38.60	37.10	38.00	38.60	38.30	37.10	36.40	35.00
20	48.20	43.70	42.40	43.40	43.20	40.50	43.10	41.10
30	58.20	55.30	46.00	48.40	47.50	53.20	49.90	44.60
40	66.30	74.60	55.10	52.90	54.00	66.20	55.90	49.60
50	71.60	84.30	59.10	59.30	60.80	71.30	61.10	54.10
60	78.00	99.50	64.00	66.40	68.00	82.10	68.00	58.00
70	83.20	99.00	70.90	74.70	73.10	90.90	74.90	66.30
80	86.60	98.70	77.20	80.70	78.60	97.50	82.30	71.50
90	90.60	98.40	84.70	86.70	84.10	99.40	90.30	74.10
100	94.80	98.10	90.70	92.90	91.20	94.30	96.30	80.90

Figure 1: Pseudoternary Phase diagram of IPM/ Cremophor EL / Cremophor RH40/ Water at $K_m = 0.5$

Figure 2: Pseudoternary Phase diagram of IPM/ Cremophor EL / Cremophor RH40/ Water at $K_m = 1$

Figure 3: Pseudoternary Phase diagram of IPM/ Cremophor EL / Cremophor RH40/ Water at $K_m = 2$

Figure 4: Conductance Vs Water concentration (% w/w) of microemulsion system

Figure 5: Zeta potential of ME 2 microemulsion formulations

Figure 6: Zeta potential of ME 6 microemulsion formulations

Figure 7: Comparative in-vitro permeation study of all ME formulations

RESULT AND DISCUSSION

Formulation Studies of Microemulsion

A microemulsion of Ziprasidone was successfully prepared using titration method followed by construction of pseudo ternary phase diagram. The selection of surfactant and co-surfactant mixture was on the basis of HLB values, drug solubility, safety and stability profile. Surfactants cremophor EL were selected for the study along with co-surfactants like Cremophor RH 40. Thus highly viscous and clear microemulsion gel was obtained. It was found that, this

system is less stable difficult to incorporate into the nasal cavity.¹²

Characterization of Microemulsion Formulation

Physicochemical parameter of microemulsion formulation

Physical parameters are estimated to test their suitability for the future use as nasal microemulsion. The various parameters such as viscosity, pH and refractive index were studied.

Determination of Viscosity

The viscosities of all formulations are as shown in Table 5.

Determination of pH

The pH of all formulation was in the range of 6.2 to 6.8. The pH partition theory explains absorption and distribution of drug. The results are as shown in Table 6.

Determination of Drug content

All the results indicate that the drug was uniformly distributed amongst the different microemulsion formulation. All the formulation meets the pharmacopeial requirement which permit the $\pm 5\%$ deviation. The results are as shown in Table 7.

Determination of Conductance

In this work, the conductivity measurements were performed without deliberate incorporation of an electrolyte although the presence of electrolyte in a nonionic microemulsion is necessary to provide ions for a charge transport. However, the addition of salt may result in phase separation. The conductivity of sample was smaller than 10 % w/w water. Above 10 % w/w, a drastic increase in conductivity was observed and furthermore a sharp increase of conductivity was found at higher water content. The results are shown in Table 8.

Determination of Particle Size

All the formulation shows particle size in the micron range. Particle size in nano or in micron range gives good transparency and good stability to the formulation. Particle size in micro meter shows soothing effect and irritation to nasal mucosa after instillation into eye and good penetration of drug through the nasal epithelial layer. The results are shown in Table 9.

Determination of Zeta Potential

The zeta potential value of all ME formulation was found to be in between (25.1 and 45.5) given in Table 10. The values of this parameter are important because the charge of the internal phase provides information on the efficacy of the induced electrical barrier. This charge depends upon on the interface.

In vitro Permeation Study

In vitro diffusion from various formulations was studied by using cellulose membrane having pore size 45 μm . From the Table 11, the formulation ME 2 which shows highest permeability (99.50 %) within 1 h among the all formulation tested. In the formulation ME 1 the concentration of oil 5 % w/w and high concentration of Smix due to increased level of concentration at above CMC the drug release acts as long acting. In the ME 2 the oil concentration 10 % and water concentration 21 % which shows that water concentration two fold higher than that of oil and CMC which maintain droplet size as minimum as possible due to low interfacial tension between two phase which minimized by Smix. Drug release from oil as early as possible and it gives rapid onset of action. In other formulation ME 3 to ME 5 the oil concentration increase but at level of CMC the release rate decreases due Smix concentration and higher the interfacial tension. ME 6 which shows release 99.40 % release in 100 minutes. Release rate minimum as compared due to concentration of water (11 % w/w) which less and phase

inversion may occurs at interference but Smix 49 %w/w which higher than oily phase which affect on release rate.

CONCLUSION

Nasal cavity is novel route of drug administration. Its application is not only local but also systemic drug delivery. On the basis of systemic delivery, the microemulsion formulation is used for rapid onset of action for insoluble drugs. Although spray, medicated powders, solution and gel used for nasal delivery but it gives action after long period of time or no dose specification. Microemulsions are dispersed, macroscopically homogenous thermodynamically stable, optically transparent, single phase system, formed by spontaneous solubilisation of two immiscible liquid, in the presence of surfactants. Microemulsion offers number of advantages than drug formulation for nasal drug delivery. Ziprasidone is lipophilic, benz-isothiazoyl-piperazine derivative, used in the treatment of schizophrenia, mania and mixed states associated with bipolar disorder. Ziprasidone HCl has a potent selective antagonist activity for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), 1 and 2 adrenergic and H₁ histaminergic receptors. This research work is aimed to formulate and evaluate the nasal microemulsion for rapid onset of action. Preformulation studies include drug identification by melting point, UV spectroscopy, FTIR and DSC. Compatibility study by TLC and FTIR analysis revealed that all excipients (IPM, Cremophor EL and Cremophor RH40) used in thesis were compatible with Ziprasidone. Formulation studies of microemulsion were done by construction of pseudo-ternary phase diagram to determine the microemulsion existence region and preparation of microemulsion formulation with selection of composition (oil: 5-40 %; Smix: 49-75 %; Water 11-21 % w/w). Characterization of microemulsion formulation include determine of viscosity, pH, drug content, refractive, conductivity measurement, zeta potential analysis (ME 2: 40.5; ME 6: 25.1) and particle size analysis (ME2: 258.1 nm; ME6: 211.8). *In vitro* drug permeation studies were done by using Keshary Diffusion cell. All ME formulations were shown fast drug permeation 99.50 % for ME 2 within 1 h; and 99.40 % for ME 6 within 100 minutes. Since the ME 2 which is optimized on the basis of vitro study. Nasal mucoadhesive drug delivery system is designed with an aim to target the drug and to maintain the dosage form at its absorption site for a rapid onset of time. This will result in the enhancement of the absorption of the drug, which will in turn reduce the presystemic metabolism; increase the bioavailability of the drug, initiate rapid onset of action and thus will decrease the dosing frequency and dose related side effects of the drugs. For this purpose in microemulsion system is preferred over conventional solution system.

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