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Design Development and Evaluation of Agomelatine Microemulsion for Intranasal Delivery

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ABSTRACT

The purpose of this study was to develop and optimize microemulsion containing agomelatine for intranasal delivery. Agomelatine, an antidepressant drug, has absolute bioavailability of only 5% due to high first pass metabolism. Agomelatine microemulsion and were prepared by titration method. Ternary phase diagram gave the microemulsion region and the concentration of oil; Smix and water were selected from ternary phase diagram. Based on solubility study, oleic acid, tween 80 and propylene glycol were selected as oil, surfactant and co surfactant respectively. Microemulsions were prepared using water titration method. 1:1% v/v ratio (Tween 80: Propylene glycol) was selected for formulation development. The prepared microemulsions were optimized optical transparency, viscosity measurement, phase separation, determination of pH, measurement of globule size, measurement of zeta potential, drug content, *In vitro* diffusion study, stability studies. The optimized batch was further characterized for optical transparency, viscosity measurement, phase separation, determination of pH, measurement of globule size, measurement of zeta potential, drug content, *In vitro* diffusion study, stability studies.

Keywords: Depression, Intranasal, Microemulsions, Agomelatine

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INTRODUCTION

Depression as estimated by WHO, depression shall become the second biggest illness in terms of morbidity by another decade in the world, already one out of every twelve men and five women have depression. With newer medication, and better facilities, treating depression has become easier, and most people respond very well to treatment, and return to optimum functioning very soon. Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. Today, depression is estimated to affect 350 million people. The World Mental Health Survey conducted in 17 countries found that on average about 1 in 20 people reported having an episode of depression in the previous year. Depressive disorders often start at a young age; they reduce people's functioning and often are recurring. For these reasons, depression is the leading cause of disability worldwide in terms of total years lost due to disability. The demand for curbing depression and other mental health conditions is on the rise globally. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. Depression usually starts between the ages of 15 and 30, and is much more common in women. [1].

The word microemulsion was originally proposed by Schulman et al. (1959). They prepared a quaternary solution of water, benzene, hexanol, and k-oleate which was stable, homogenous and slightly opalescent.. Basically a coarse (or macro) emulsion was prepared and the system was then titrated to clarify by adding a co-surfactant (second surface active substance). When the combination of the four components was right, the system cleared spontaneously. Most of the work reported by Schulman dealt with four component systems. Hydrocarbons (aliphatic or aromatic), ionic surfactants, co surfactants (generally 4–8 carbon chain aliphatic alcohol) and an aqueous phase. Schulman had previously published extensively in the field of monolayers and applied what he had learnt in that field to explain the formation of microemulsions. The surfactant and co-surfactant, when properly selected, form a mixed film at the oil/water interface, resulting in an interfacial pressure exceeding the initial positive interfacial tension.[2, 3] Microemulsions are thermodynamically stable isotropic systems in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate

surfactant or its mixture. The short to medium chain alcohols are generally considered as co surfactants in the microemulsion system. The presence of surfactant and co surfactant in the system makes the interfacial tension very low. Therefore microemulsions form spontaneously, with an average droplet diameter of 10 to 140 nm. Microemulsions offer several advantages like high solubilization of lipophilic drugs, stability, ease of preparation and stabilization of hydrolytically susceptible compounds. Microemulsions provide a large surface area for better absorption of drugs due to smaller globule size. Various drugs such as Sumatriptan, Zolmitriptan, Cabergoline, Clonazepam, Nimodipine, Tacrine, and Diazepam have been successfully delivered through nasal route in the form of microemulsion and it resulted in improved drug absorption. In order to formulate a nasal formulation with desirable performance, it is advisable to focus on maximizing the residence time in the nasal mucosa and thus ensuring efficient absorption of drug. Use of mucoadhesive polymers in the nasal formulations is expected to increase the residence time and thereby enhance the absorption of the drug. [3-12]

MATERIALS AND METHODS

Agomelatine was obtained as a gift sample from Enaltec Labs, Igatpuri, Nashik, India. Tween 80 and propylene glycol were purchased from Research-Lab Fine Chem. Industry – Mumbai.

Construction of pseudo ternary phase diagram-

Pseudo-ternary phase diagrams were constructed using water titration method at ambient temperature (25°) to determine the ME regions. Pseudo ternary phase diagram was plotted for each Smix 1:1, 1:2 and 2:1 using the CHEMIX Software (Version 7.00). [13]

Formulation of Microemulsion-

Based on the phase diagram, the optimum Smix ratio was selected and the drug loaded microemulsiom were prepared by dissolving the drug in the oil-Smix mixture, and then titrated with water on the magnetic stirrer at 150 RPM for 10 min. Agomelatine was added to the specific amount oil then surfactant and co-surfactant with varying percentage, and then an appropriate amount of water was added to the mixture drop by drop with constant stirring on magnetic stirrer. Microemulsions containing agomelatine were obtained spontaneously on stirring the mixtures. All microemulsions were stored at appropriate temperature. Four formulations containing different concentration of oil, Surfactant/co-surfactant were prepared with the help of selected region area of pseudo ternary phase diagram. Each formulation was prepared according to the procedure explained above and then these formulations were evaluated. [14, 15]

Evaluation of Microemulsion-

The Microemulsion was evaluated for the following characteristics: [7, 8, 9, 14, 15, 16]

a. Optical Transparency-

Optical transparency of the formulation was determined by inspecting the sample in clear and transparent container under the presence of light against reflection into the eyes.

b. Viscosity Measurement-

The Viscosities of microemulsions were measured using a Brookfield rotational viscometer (LV2, Brookfield Inc., USA) at 24.9˚ at 10 rpm.

c. Phase Separation-

Microemulsion system were subjected to centrifugation (Remi Motor, Mumbai) at 3000 rpm for a period of 2 h and examined for any evidence of phase separation.

d. Determination of pH

A 10% dispersion of formulation was prepared in distilled water and pH was determined by using pH meter which was prior standardized with standard buffers of pH 4 and pH 7.

e. Measurement of Globule Size

The average globule size of the microemulsions was determined by Zetasizer Nano-ZS (Malvern Instruments, UK). Measurements were carried at an angle of 90˚ at 25˚. Microemulsion was diluted with double distilled water to ensure that the light scattering intensity was within the instrument's sensitivity range. All the measurement was carried out at 25˚. The polydispersity index of the formulation was determined by the same instrument. The width of the size distribution was indicated by the polydispersity index (P.I)

f. Measurement of zeta potential-

The zeta potential was determined to verify stability of microemulsion due to charge interaction. Zeta potential was measured by using Zetasizer Nano-ZS (Malvern Instruments, UK). The measurement was performed at 25°.

g. Drug Content-

A definite volume of formulation was taken in a 10 ml volumetric flask and diluted with methanol. The resultant solution was sonicated for 3 min at ambient temperature and the absorbance of the resultant solution was measured at λmax of 234 nm against blank.

h. *In vitro* diffusion study-

In vitro diffusion was carried out by modified franz diffusion cell. A glass cylinder with both ends open, 10 cm height, 3.7 cm outer diameter and 3.1 cm inner diameter was used as diffusion cell. A sheep nasal mucosa was fixed to one end of the cylinder with the aid of an to result as a diffusion cell. 1 ml of microemulsion was taken in the cell (donor compartment) and cell was immersed in a beaker containing 100 ml of pH 6.4 Phosphate buffer as receptor compartment. The entire surface of the cell was in contact with the receptor compartment which was agitated using magnetic stirrer and a temperature of 37±1° was maintained. Samples 10 ml of the receptor compartment were taken and with same amount replaced to maintain sink condition. The sample was analyzed for agomelatine at 234 nm against blank using UV Spectrophotometer. Amount of agomelatine released at various time intervals was calculated with the help of calibration curve with phosphate buffer and plotted against time.

i. Stability Studies-

The microemulsions were subjected to stability study at 40º C± 20 C, 75 % RH±5% RH for 6 mo. The samples were evaluated for transparency, drug contents, pH, and *in vitro* drug release for 6 mo period.

RESULT AND DISCUSSION

Pseudo Ternary Phase Diagram-

Plotting of pseudo ternary phase diagram for formulation of microemulsion with Smix ratio (1:1, 1:2, 2:1). Pseudo ternary phase diagram shown in following fig. 1 respectively.

Percent composition of selected ratio of microemulsion formulation-

Pseudo ternary phase diagram of ratio 1:1 gave the clear transparent microemulsion as compare to 1:1 and 2:1 ratio. So 1:1 ratio was selected for further final preparation as shown in Table 1 & figure 2.

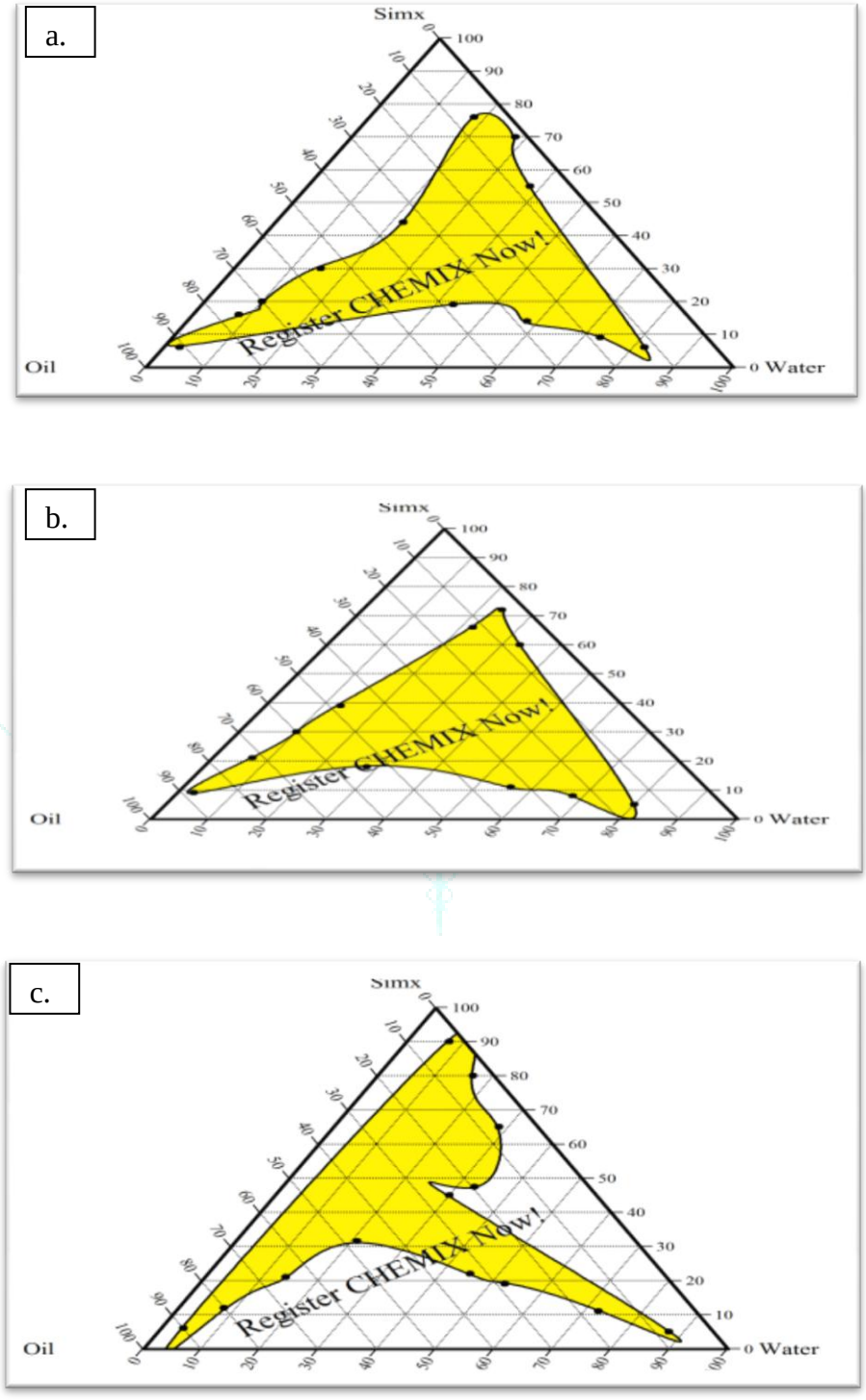

Figure 1: Pseudo ternary phase diagram

Table 1: Composition of microemulsion

Ingredients	ME1	ME2	ME3
Agomelatine	1.25	1.25	1.25
Oleic Acid	5	14	10
Tween 80	37.5	33	35
Propylene Glycol	37.5	33	35
Water	20	20	20

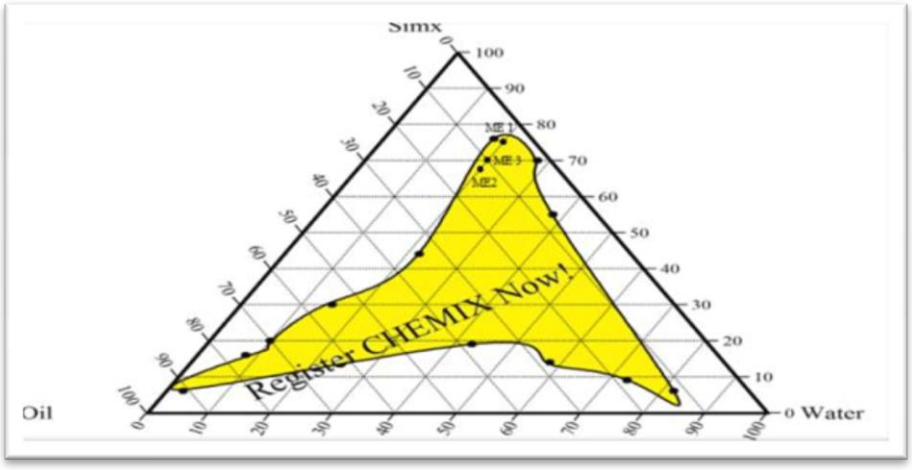

Figure 2: Pseudo ternary phase diagram of ratio 1:1

Evaluation of Microemulsion-

Evaluation of Microemulsion-

a. Optical Transparency-

Optical transparency of the formulation was determined by inspecting the sample in clear and transparent container (glass beaker) under the presence of light against reflection into the eyes. All the formulations observed clear and transparent formulation microemulsion shown in Table 2 and fig. 3.

Table 2: Optical Transparency

Formulation	Transparency
ME1	Transparent
ME2	Transparent
ME3	Transparent

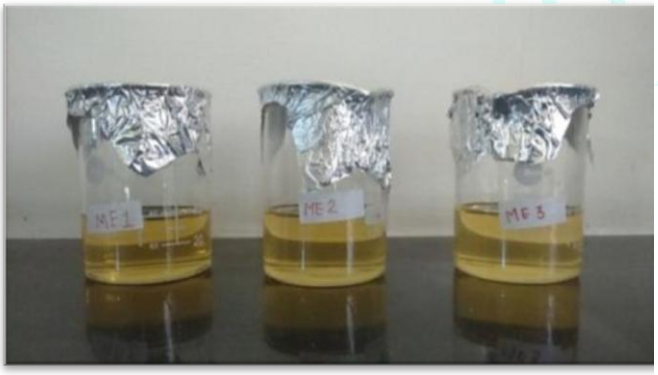

Figure 3: Optical Transparency of all Three Formulations

b. Viscosity Measurements-

The Viscosities of all the formulations Microemulsions were measured using a Brookfield rotational viscometer (LV2, Brookfield Inc., USA) at 24.9° at 10 rpm. Formulation with higher viscosity has a better contact time thus increases the absorption. At the same time, high viscosity enhanced the permeability of drug and shown in Table 3.

Table 3: Viscosity Measurement

Formulations	Viscosity (cps) (±SD)
ME1	245.9 ± 0.81
ME2	236.9 ± 0.86
ME3	248.3 ± 0.67

c. Phase Separation-

Microemulsion system were subjected to centrifugation (Remi Motor, Mumbai) at 3000 rpm for a period of 2 h and examined for any evidence of phase separation and shown in Table 4.

d. Determination of pH-

pH of various microemulsion are shown in the following table no. 17 which was found to be in range of 4.93 to 5.10. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5 and shown in Table 5.

e. Measurement of Globule Size-

The globule size of the microemulsion formulation of optimized batch was found to be 122.0 nm. The polydispersity index of formulation was determined by zetasizer. The width of the size distribution was indicated by polydiserpersity index, which shown in fig. 4 and Table 6.

Table 4: Phase Separation

Formulations	Phase Separation
ME1	No Phase Separation
ME2	No Phase Separation
ME3	No Phase Separation

Table 5: Determination of pH

Formulations	pH (±SD)
ME1	4.93 ± 0.91
ME2	5.02 ± 0.45
ME3	5.10 ± 0.46

Table 6: Globule Size Analysis

Formulations	Globule Size (nm)	PDI
ME1	291.8	0.571
ME2	195.7	0.463
ME3	122.0	0.203

f. Measurement of Zeta Potential-

It should be negative or neutral. Which indicate that droplets of micro emulsion having no charge, that is system is stable. It is determined by using Zetasizer. Zeta potential is essentially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation. To retain the stability of microemulsions it should be zero or neutral. The zeta potential was determined to verify stability of microemulsion due to charge interaction. Zeta potential was measured by using Zetasizer Nano-ZS (Malvern Instruments, UK). The measurement was performed at 25° which shown in fig. 4 and Table 7.

Table 7: Measurement of Zeta Potential

Formulations	Zeta Potential
ME1	-14.1
ME2	-30.0
ME3	-32.9

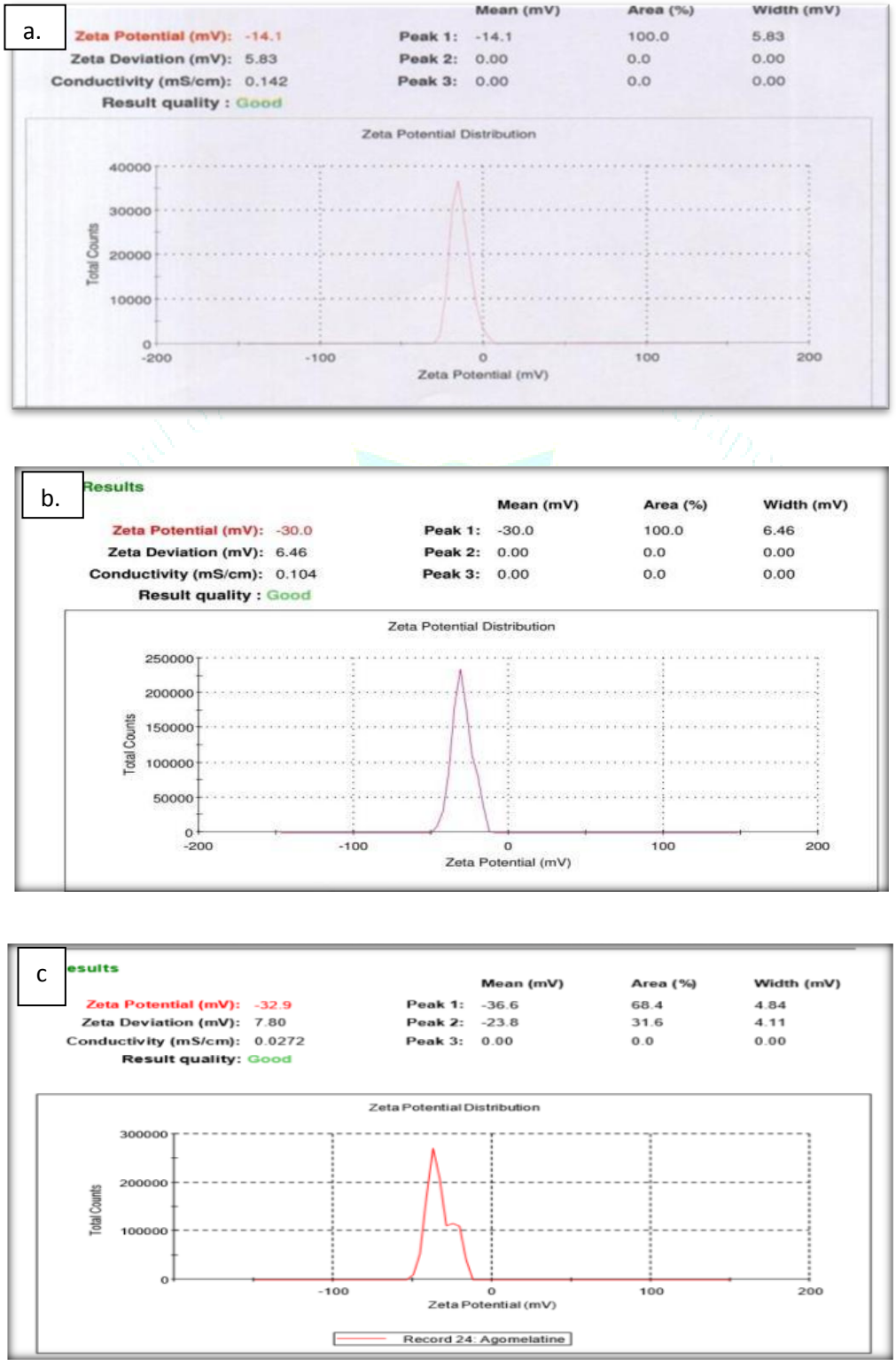

Figure 4: Representation of the obtained data for Zeta potential of microemulsion

(a) ME1; (b) ME2; (c) ME3

g. Drug Contents-

The percentage drug content of all prepared microemulsion formulations was found to be in the range of 81.65 to 88.85 %. The ME3 Formulation drug content was found to be 88.85% and shown in Table 8.

h. *In vitro* diffusion study-

Out of the 3 formulations maximum release after 1 ho was found for ME3 formulation. This indicates release of 83.09% drug availability, shown in fig. 5 and Table 9.

Table 8: Drug Content

Formulations	Drug Content % (±SD)
ME1	85.45 ± 0.56
ME2	81.65 ± 0.62
ME3	88.85 ± 0.75

Table 9: *In-Vitro* Diffusion Study

Time in min.	ME1	ME2	ME3
5	15.25 ± 0.54	13.52 ± 60	11.78 ± 0.64
10	19.66 ± 0.78	19.47 ± 0.60	20.54 ± 0.62
15	25.45 ± 0.66	24.63 ± 0.64	28.12 ± 0.57
20	29.02 ± 0.55	30.84 ± 0.67	35.75 ± 0.65
25	36.85 ± 0.65	36.63 ± 0.64	41.95 ± 0.74
30	40.65 ± 0.63	42.14 ± 0.60	49.35 ± 0.67
35	47.12 ± 0.55	49.82 ± 0.67	54.15 ± 0.56
40	52.88 ± 0.67	54.37 ± 0.59	60.52 ± 0.62
45	57.78 ± 0.65	60.46 ± 0.41	66.74 ± 0.64
50	64.61 ± 0.59	65.91 ± 0.69	71.03 ± 0.51
55	71.43 ± 0.61	71.73 ± 0.44	78.13 ± 0.59
60	78.46 ± 0.58	76.12 ± 0.52	83.09 ± 0.54

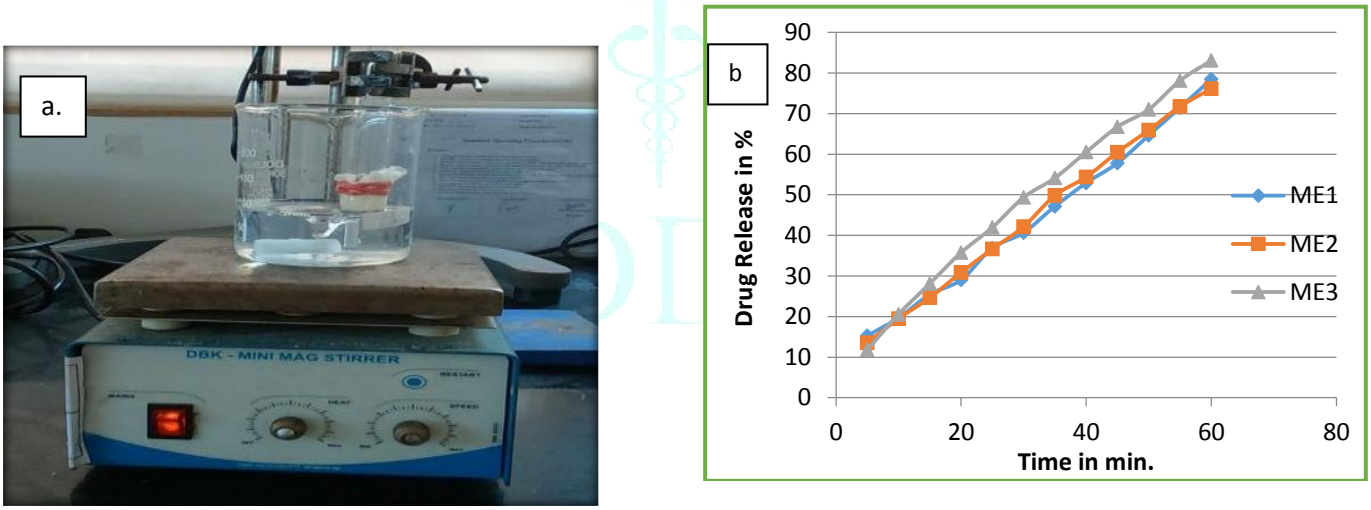

Figure 5: *In Vitro* diffusion Study (a) *In Vitro* diffusion Study assembly; (b) *In Vitro* drug release

i. Stability Studies-

The microemulsions were subjected to stability study at 40º ± 20 C, 75 % RH±5% RH for 6 mo respectively. The samples were evaluated for transparency, drug contents, pH, and *in vitro* drug release every month for 6 mo period and shown in Table 10.

Table 10: Stability Studies

Sr. No.	Observation	Before Accelerated Stability Testing	After Accelerated Stability Testing
			180 days
1.	Visual appearance (Transparency)	Transparent	Transparent
2.	Drug content (%) (± SD)	88.85 ± 0.75	86.95 ± 0.50
3.	pH (±SD)	5.10 ± 0.46	5.20 ± 0.52
4.	In vitro drug release (±SD)	83.09 ± 0.54	81.01 ± 0.46

Formulation ME 3 was found to be transparent and stable up to 6 mo have there is no significant change in drug content, visual appearance.

Finally, it can be summarized that the microemulsion of agomelatine can be one of the promising tool in improve bioavailability, increases the rate of absorption due to the small globule size and by avoiding first pass metabolism and direct transport into systemic circulation for effective and longer treatment required for antidepressant action with increased stability.

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REFERENCES

1. Iyer K, Khan ZA. Depression–A Review. Inter Sci Congress Association 2012; 1(4):79-87.
2. Dhuria SV, Hanson LR, Frey IWH. Intranasal Delivery to The Central Nervous System: Mechanisms and Experimental Considerations. J of Pharm Sci 2010; 99(4):1654-1673.
3. Jaiswal PL, Darekar AB, Saudagar RB. A Recent Review on Nasal Microemulsion for Treatment of CNS Disorder. Inter J of Current Pharm Res 2017; 9(4):5-13.
4. Jaiswal PL, Darekar AB, Saudagar RB. A Recent Review on Nasal Microemulsion for Treatment of CNS Disorder. Inter J of Current Pharm Res 2017; 9(4):5-13.
5. Kakad JK, More PK, Gondkar SB, Saudagar RB. A Recent Review on Nasal Drug Delivery System. World J of Pharm Res 2015; 4(2):269-281.
6. Pagar SA, Shinkar DM, Saudagar RB. A Review on Intranasal Drug Delivery System. J of Adv Pharm Ed & Res 2013; 3(4):333-346.
7. Mahajan HS, Rasal AD, Microemulsions for Nasal Drug Delivery Systems: An Overview. Inter J of Pharm Sci and Nanotech 2013; 5(4):1825- 1831.
8. Katiyar BS, Katiyar SS, Mishra PS and Sailaja DL, Microemulsions: A Novel Drug Carrier System. Inter J of Pharm Sci Review And Res 2013; 20(2):138- 148.
9. Muzaffar F, Singh UK, Chauhan L. Review on Microemulsion as Futuristic Drug Delivery. Inter J of Pharm and Pharm Sci 2013; 5(3):39- 53.
10. Madhav S, Gupta D. A Review on Microemulsion Based System. Inter J of Pharm Sci and Res 2011; 2(8):1888- 1899.
11. Vispute M, Sayyad N, Khan T, Shaikh S. An Overview on Exploring Nasal Microemulsion for Treatment of CNS Disorders. Inter J of Pharm Sci and Res 2013; 4(4):1294-1311.
12. Patadiya H, Agarwal J, Chaudhary S, Shah H. Microemulsion Based Nasal To Brain Delivery of Drug Acting on CNS. Inter J of Pharm Resand Bio-Sci 2015; 4(2):472-491.
13. Sinko PJ: Martin's Physical Pharmacy and Pharmaceutical Sciences. 6th ed. Wolters Kluwer/ Lippincott wilkins; 2011.p. 17-53.
14. Thakkar HP, Patel AA, Chauhan NP. Formulation and Optimization of Mucoadhesive Microemulsion Containing Mirtazapine for Intranasal Delivery. Chronicles of Young Scientists 2014; 5(1):25- 32.
15. Darekar AB, Jaiswal PL, Saudagar RB. Design Development and Evaluation of Duloxetine Hydrochloride Microemulsion for Intranasal Delivery. Eur J of Biomedand Pharma Sci 2018; 5(2):679-684.
16. Bhise SB: Laboratery Manual of Biopharmacutics and Pharmacokinetics: Published by Trinity Publishing House; 2010. p. 64.