Chapter 9 (Part- A)

Stability Study for Oral SMEDDS

Management of Dyslexia and ADHD

9.1 Introduction

The optimized formulation was subjected to stability studies as per International Conference on Harmonization (ICH) guidelines. This study was performed to assess the stability profile of the optimized SMEDDS formulation. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products varies with time under the influence of a variety of environmental conditions such as temperature, humidity and light. It is also useful to determine the shelf life of the formulation and recommend the storage conditions. When a pharmaceutical dosage form is altered, the stability of the drug may be changed. A stable dosage form maintains its physical integrity and does not adversely influence the chemical integrity of the active ingredient during its life on the shelf. Hence, a stability study must include a product characterization and study of the product stability during storage.

9.2 Stability Study of Modafinil SMEDDS

Stability study of Modafinil loaded SMEDDS was performed as per ICH guidelines to see the effect of temperature and humidity on dosage form during the storage time period of three months under the room temperature (RT) and at accelerated conditions (40°C ± 2°C and 75% ± 5% RH).(1) Dosage form was evaluated for drug content which will be helpful to determine the stability of drug in the formulation. The stability study was carried out at room temperature and at accelerated temperature up to 3 and 6 months respectively. All the studies were performed in triplicate.

9.2.1 Parameters for Stability Study

The various parameters evaluated to check stability of the formulations were as follow:

- Physical appearance: By Visual inspection
- Emulsification efficiency: By self-emulsification time
- Drug content : By RP-HPLC
- % Transmittance of reconstituted SMEDDS: By UV-Visible spectrophotometer
- Zeta potential, Globule size and PDI of the globules of the reconstituted SMEDDS: By Malvern zeta sizer.

9.3 Result and Discussion

Table 9.1 Stability Study for SMEDDS at RT and Accelerated Conditions

Temperature	Parameters	0 month	1 month	2 months	3 months	6 months	12 months
At Room Temperature	Visual Inspection	Clear	Clear	Clear	Clear	Clear	Clear
	Self emulsification time (sec)	19.33 ± 0.57	20.66 ± 2.08	21.33 ± 1.52	23.66 ± 2.08	19.54 ± 2.23	20.66 ± 2.42
	Assay	99.61 ± 0.17	99.39 ± 0.28	99.11 ± 0.23	98.94 ± 0.16	98.73 ± 1.07	98.02± 1.27
	% Transmittance	99.63 ± 0.47	99.41 ± 0.45	99.43 ± 0.64	99.29 ± 0.36	98.74 ± 1.01	97.57 ± 1.03
	Globule size (nm)	18.97 ± 0.17	18.86 ± 0.28	19.12 ± 0.23	19.17 ± 0.16	21.63 ± 1.07	23.17± 1.27
	PDI	0.187 ± 0.06	0.169 ± 0.09	0.214 ± 0.11	0.194 ± 0.06	0.214 ± 0.56	0.237±0.216
	Zeta Potential (mV)	-2.73 ± 0.14	-2.69 ± 0.21	-2.71 ± 0.36	-2.73 ± 0.43	-2.67 ± 0.81	-2.82 ± 0.74
Accelerated conditions: 40°C ± 2°C /75% RH ± 5%	Visual Inspection	Clear	Clear	Clear	Clear	Clear	-
	Self emulsification time (sec)	19.33 ± 0.57	22.56 ± 1.15	26.33 ± 1.47	25.66 ± 1.64	20.43 ± 2.03	-
	Assay	99.61 ± 0.17	99.29 ± 0.38	99.06 ± 0.86	98.89 ± 0.41	97.08 ± 1.43	-
	% Transmittance	99.63 ± 0.47	99.36 ± 0.34	99.42 ± 0.14	99.31 ± 0.83	98.02 ± 1.26	-
	Globule size (nm)	18.97± 0.17	19.21± 0.82	19.15± 0.76	19.23± 0.58	21.43 ± 1.27	-
	PDI	0.187± 0.06	0.227± 0.13	0.218± 0.21	0.224± 0.18	0.146± 0.28	-
	Zeta Potential (mV)	-2.73 ± 0.14	-2.71 ± 0.51	-2.73 ± 0.33	-2.68 ± 0.36	-2.51 ± 0.69	-

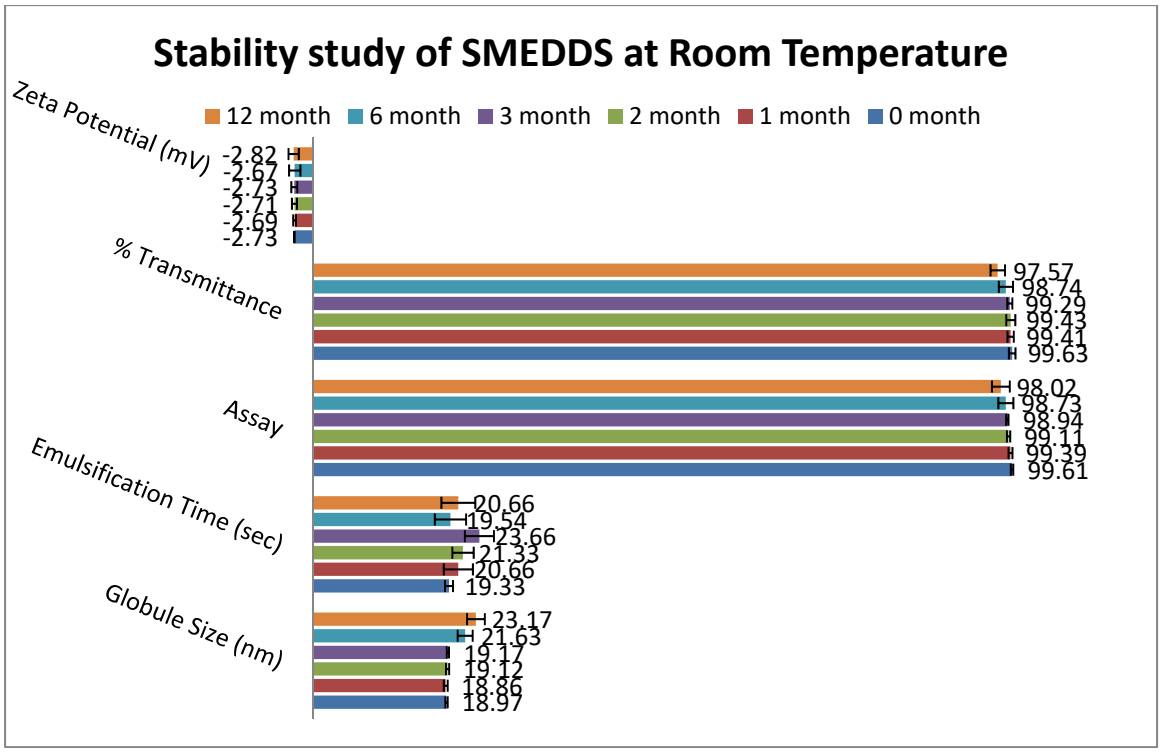


Fig. 9.1 Stability Study of Modafinil loaded SMEDDS at Room Temperature

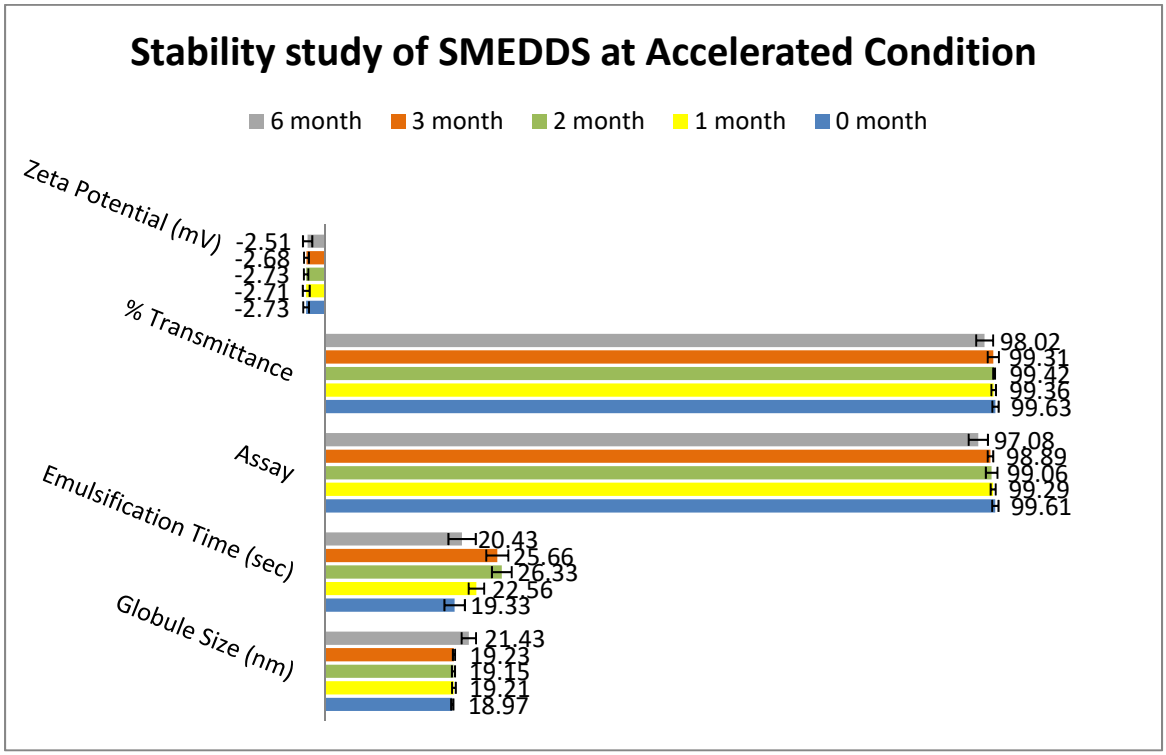


Fig. 9.2 Stability Study of Modafinil loaded SMEDDS at Accelerated Conditions

Selected SMEDDS formulations were evaluated for thermodynamic stability study, were subjected to different stress tests like centrifugation and freeze-thaw test. If the SMEDDS formulations are stable in this condition, metastable formulations thus are to be avoided and frequent tests need not be performed during storage. No phase separation and no significant change in globule size ($p>0.05$) of the optimized Modafinil during thermodynamic stability study was observed. Therefore, SMEDDS formulations were analyzed for self-emulsification time, assay, % transmittance, globule size, PDI and zeta potential. Optimized SMEDDS formulation was found to be thermodynamically stable. Table 9.1, Fig. 9.1 (stability at room temperature) and Fig. 9.2 (stability at accelerated conditions) represented stability study of Modafinil loaded SMEDDS. Physical appearance didn't change during real time and accelerated stability studies (40°C ± 2°C temperature / 75%± 5%RH). PDI was not encountered in the bar chart because it remained < 0.250 during stability study which reveals that SMEDDS showed uniform particle size distribution even at different stability intervals. SMEDDS remained clear at all the storage conditions i.e. no signs of drug precipitation or cloudiness. This indicates that drug remained in the solubilize form at room temperature as well at accelerated stability conditions (40°C±2 °C/75 ±5 % RH).

Self emulsification time and percentage transmittance didn't show any significant change ($P<0.05$). Moreover, there is no significant decrease in Modafinil concentration was observed at the end of 6 months for SMEDDS formulation at accelerated condition and also after 12 months at room temperature, indicating that drug remains chemically stable in the optimized SMEDDS formulation. Also, the globule size, zeta potential didn't show any significant change ($P>0.05$) during real time and accelerated stability study. Hence, the system was found to be capable of producing stable microemulsion on dilution with uniform globule size and no significant change ($p>0.05$) in zeta potential indicate that it didn't show any change in the excipients property. Thus, Modafinil loaded SMEDDS was found to be stable under room temperature as well as at the accelerated condition (40°C ± 2 °C/75 ± 5 % RH) for 12 months and 6 months respectively.

Chapter 9 (Part- B)

Stability Study for NTB Microemulsion

Management of Dyslexia and ADHD

9.4 Stability Study of ME and MME

Stability study for Vinpocetine loaded ME and MME were performed as per ICH guidelines to see the effect of temperature and humidity on dosage form during the storage time period of three months under the room temperature and at accelerated conditions (40°C ± 2°C /75%RH ± 5%). (1) Vinpocetine loaded ME and MME were filled in glass vials and kept at the specified storage conditions. Duplicate samples were withdrawn at 0,1,2,3,6 months and 0,1,2,3,6,12 months to evaluate their physical and chemical stabilities at accelerated condition and at a room temperature respectively. The physical stability was evaluated visually for any such physical changes (clarity, phase separation and/or drug precipitation), and the mean globule size was analyzed by Malvern zeta sizer after suitable dilution with water. Chemical stability was expressed as the content of drug determined and was determined by UV spectrophotometric method. All the studies were done in triplicates.

9.5 Parameters for Stability Study

The various parameters evaluated to check the stability of the formulations were listed in section 9.2.1. Beside this parameters one more parameters i.e. pH was analyzed by pH meter.

9.6 Result and Discussion

Table 9.2 Stability Study at Room Temperature and Accelerated Conditions for ME

Temperature	Parameters	0 month	1 month	3 months	6 months	12 months
At Room Temperature	Visual Inspection	Clear	Clear	Clear	Clear	Clear
	pH	5.51 ± 0.07	5.49 ± 0.16	5.52 ± 0.11	5.74 ± 0.1	5.43 ± 0.09
	Assay (%)	99.14 ± 0.51	99.04 ± 0.81	98.09 ± 0.92	98.44 ± 0.64	97.85 ± 1.45
	% Transmittance	99.24 ± 0.15	99.01 ± 1.09	99.43 ± 0.84	98.02 ± 0.61	97.44 ± 0.35
	Globule size (nm)	19.01 ± 1.11	20.05 ± 1.08	21.1 ± 1.31	19.07± 1.02	21.24 ± 1.36
	Zeta Potential (mV)	-11.24 ± 0.62	-10.89 ± 1.12	-11.57 ± 0.7	11.02 ± 1.23	-10.35 ± 1.25
Accelerated Conditions: 40°C ± 2°C/75%RH ± 5%	Visual Inspection	Clear	Clear	Clear	Clear	-
	pH	5.51 ± 0.07	5.34± 0.11	5.3 ± 0.06	5.5 ± 0.17	-
	Assay (%)	99.14 ± 0.51	99.11 ± 0.60	98.33 ± 1.78	98.88 ± 2.86	-
	% Transmittance	99.24 ± 0.15	98.77 ± 1.23	98.32 ± 0.92	98.09 ± 1.64	-
	Globule size (nm)	19.01 ± 1.11	21.07 ± 0.98	20.01 ± 1.21	21.33 ± 0.93	-
	Zeta Potential (mV)	11.24 ± 0.62	11.04 ± 1.34	11.73 ± 1.69	-11.8 ± 1.79	-

Poor physical stability is ultimately revealed by phase separation and can be visually analyzed. Excipients used for preparation of microemulsion like unsaturated lipids may degrade on storage and affect stability of microemulsion. Degradation of lipid can alter the microemulsion chemically and/or physically for e.g. Clarity, color change and cloudiness of emulsion, surface property as well zeta potential of the emulsion. Therefore, physicochemical property of the microemulsion are required to be monitored. Simultaneously, robustness of microemulsion to dilution was examined by

10 and 100 times diluted MME and ME with water. The diluted microemulsions were store for 10 hrs and observed for any sign of phase separation and/or drug precipitation.

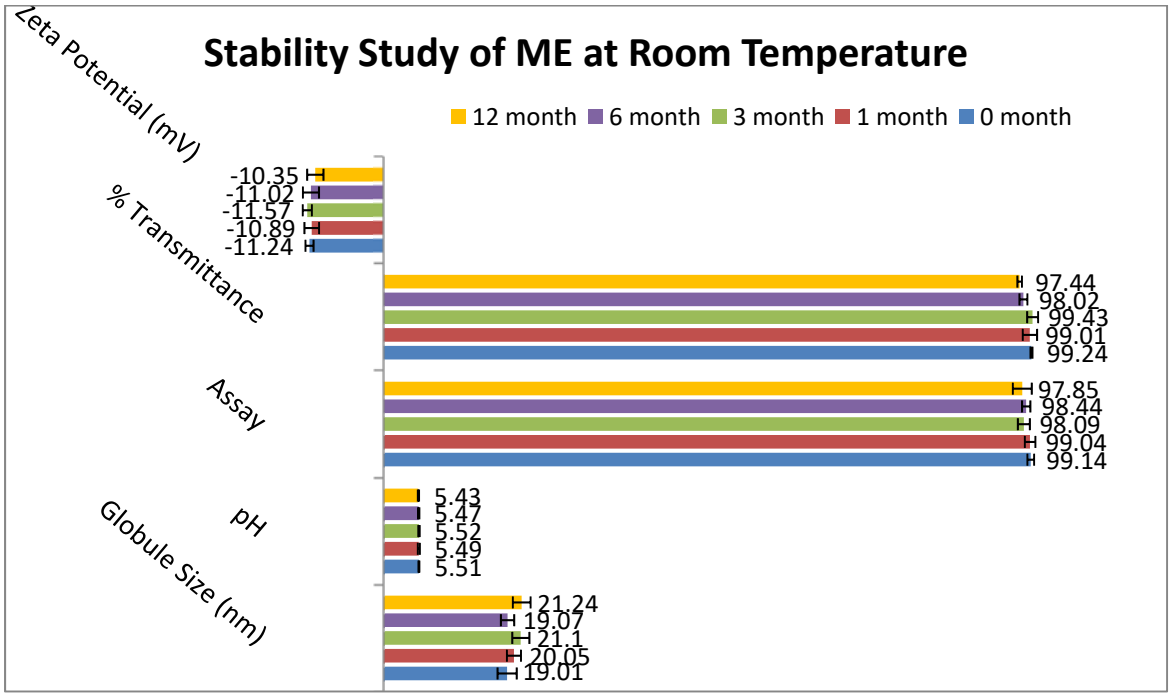


Fig. 9.3 Stability Study of ME at Room Temperature

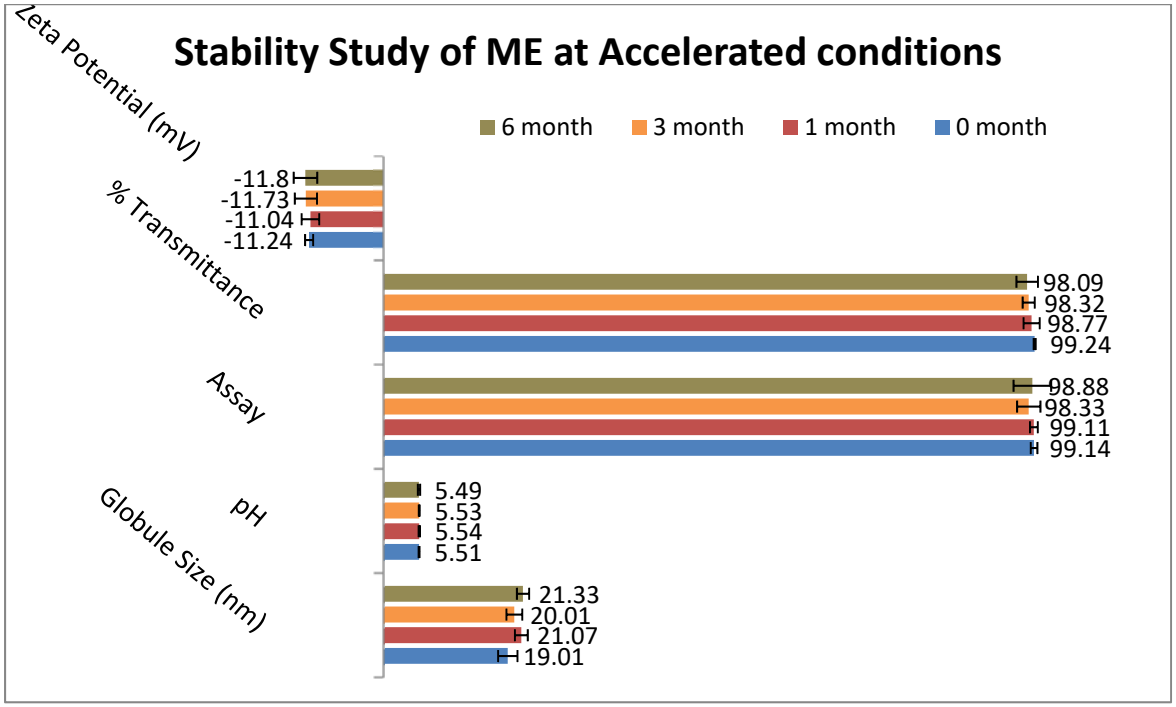
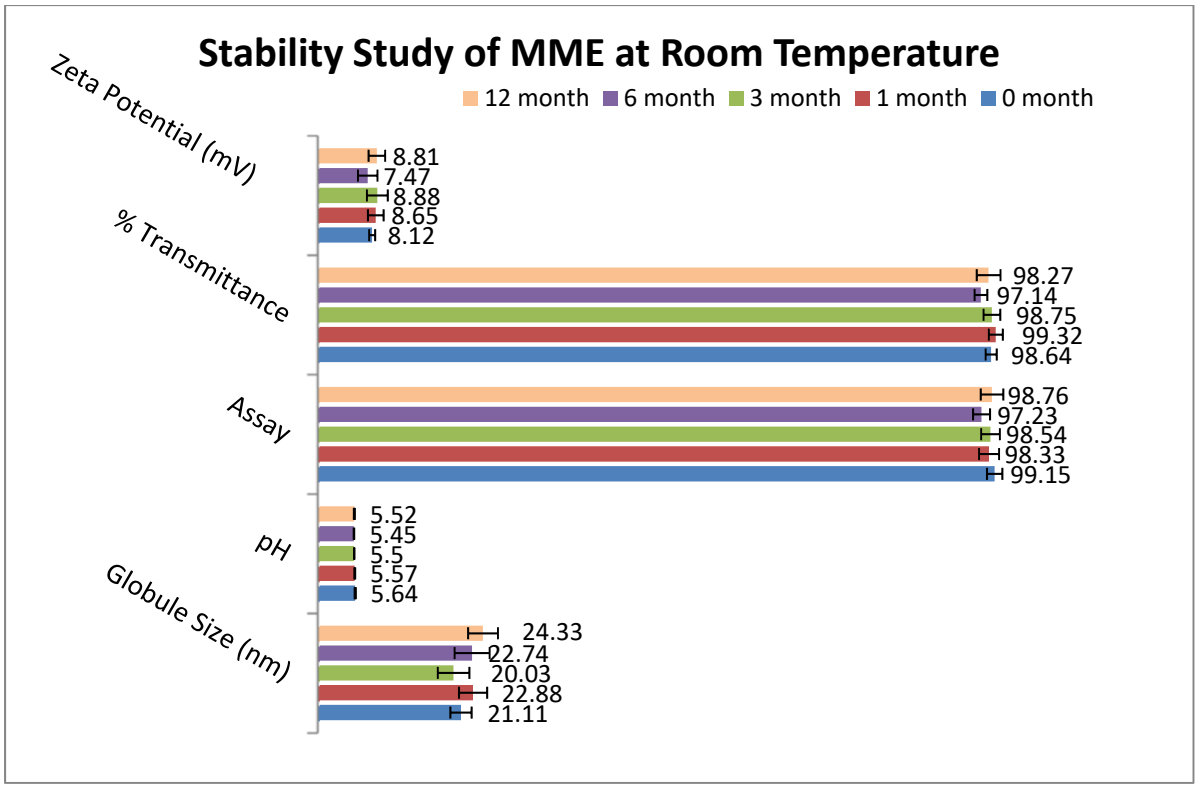


Fig. 9.4 Stability Study of ME at Accelerated Conditions

Table 9.3 Stability Study at Room Temperature and Accelerated Conditions for Mucoadhesive Microemulsion (MME)

Temperature	Parameters	0 month	1 month	3 months	6 months	12 months
At Room Temperature	Visual Inspection	Clear	Clear	Clear	Clear	Clear
	pH	5.64 ± 0.09	5.52 ± 0.06	5.50 ± 0.03	5.45 ± 0.04	5.52 ± 0.08
	Assay (%)	99.15 ± 1.12	98.33 ± 1.46	98.54 ± 1.37	97.23 ± 1.24	98.76 ± 1.65
	% Transmittance	98.64 ± 0.81	99.32 ± 1.02	98.75 ± 1.22	97.14 ±0.93	98.27 ± 1.74
	Globule size (nm)	21.11 ± 1.56	22.88 ± 2.06	20.03 ± 2.31	22.74 ± 2.56	24.33 ± 2.18
	Zeta Potential(mV)	8.12 ± 0.44	8.65 ± 1.15	8.88 ± 1.53	7.47 ± 1.43	8.81 ± 1.21
Accelerated Conditions: 40°C ± 2°C / 75%RH ± 5%	Visual Inspection	Clear	Clear	Clear	Clear	-
	pH	5.64 ± 0.09	5.52 ± 0.11	5.54 ± 0.08	5.49 ± 0.17	-
	Assay (%)	99.15 ± 1.12	98.17 ± 1.13	98.04 ± 1.32	96.17 ±2.08	-
	% Transmittance	98.64 ± 0.81	99.19 ± 1.18	97.12 ± 1.15	97.47 ± 1.2	-
	Globule size (nm)	21.11 ± 1.56	21.88 ± 1.47	23.03± 1.14	24.87± 1.32	-
	Zeta Potential (mV)	8.12 ± 0.44	8.84 ± 1.25	7.72 ± 1.29	8.56 ± 1.31	-



9.5 Stability Study of MME at Room Temperature

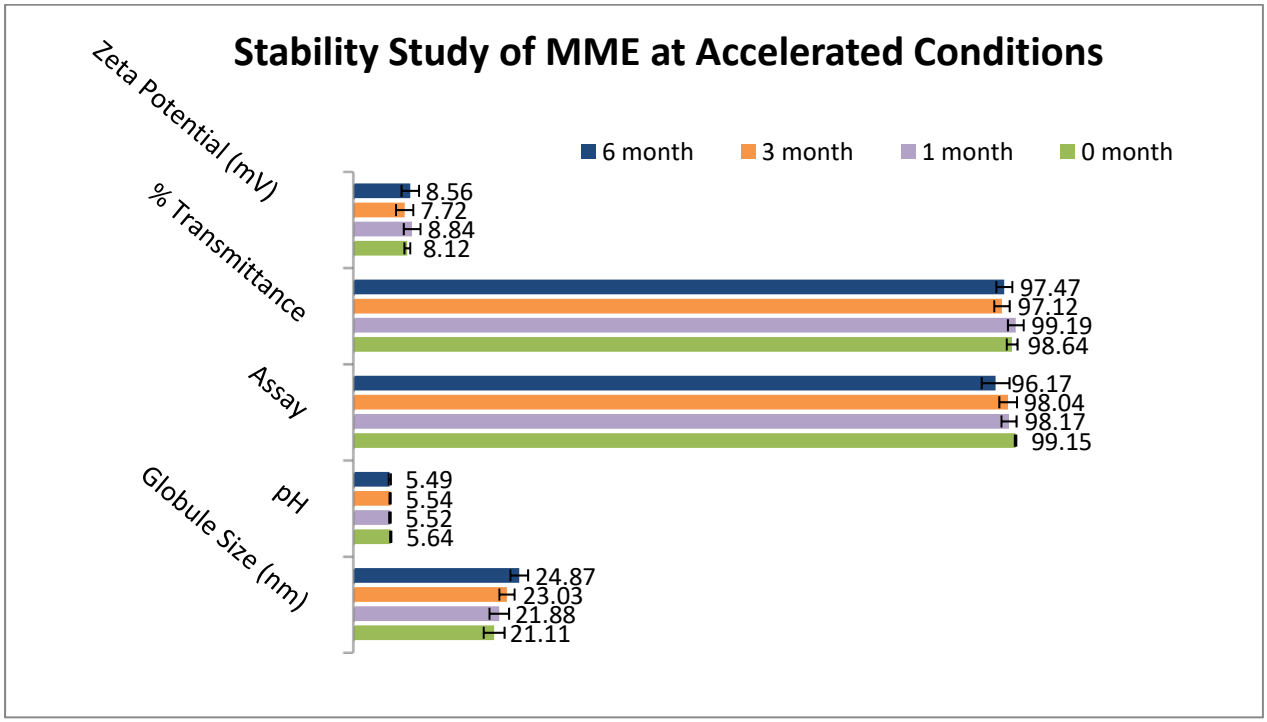


Fig. 9.6 Stability Study of MME at Accelerated Conditions

The result did not show any phase separation or precipitation of drug when kept for 10 hrs, after 10 and 100 times dilution. This suggests that MME and ME were robust to dilution. From the table 9.1 and table 9.2, no significant change ($p>0$) in pH represent that the formulation is stable for both real time and accelerated stability period. Both formulations didn't show any change in physical appearance during real time and accelerated stability studies (40°C ± 2°C / 75% ± 5%RH) concluded from Table 9.2, Table 9.3 and Fig. 9.3 to 9.6. Both ME and MME remained stable and clear at both storage conditions. This indicates that the drug remained in the solubilize form at accelerated stability conditions (40±2 °C/75 ±5 % RH) as well at room temperature. There was no significant ($p>0.05$) decrease in Vinpocetine concentration (drug content) in both ME and MME formulation. Some of the property of microemulsion will start to change long before phase separation is visually seen. An increase in particle size is suggestive of physical instability, since this observed the coalescence or flocculation, which is initialization of phase separation. Zeta potential is important to measure, as its value governs stability of product. Higher surface charge observed by high zeta potential will generally be apt to stabilize emulsion due to higher repulsion of the globules from each other. Increase in globule size and changes in zeta potential are both point out of physical stability. Globule size and zeta potential were observed for both ME as well as MME formulation at different time laps of 0, 1, 2, 3,6 months for accelerated study and 0,1,2,3,6,12 months for real time study respectively. Data from Table 9.2, Table 9.3 show that the globule size is continuously increased over the stability period but not significantly and are still in the required range whereas zeta potential was remained constant in the range and same as in the previous study which represents that the system is physically stable at both conditions. The overall stability of all the formulation under the given conditions was found out to be in acceptable range.The value of percentage transmittance of formulation were remain same and no significant difference were observed though periodic change in size represent that the system was physically stable. Results of the study represent that formulation didn't produce any considerable changes in drug content, globule size, zeta potential and pH, indicate that formulation remained stablealong with the excipients without any significant physicochemical changes.

Thus, from the results of physicochemical stability study it can be concluded that the ME and MME are stable with globule size of required range for nasal administration, zeta potential value of stable formulation, % transmittance indicates the clarity of microemulsion, pH confirms water continuous microemulsion system with stability of drug in formulation. These all results represent that Vinpocetine loaded ME and MME were found to be stable under room temperature for 12 months as well as at the accelerated condition (40 ± 2 °C/75 ± 5 % RH) for 6 months.

9.7 Reference

1. ICH Harmonised Tripartite Guideline Stability Testing of New Drug Substances And Products Q1A(R2)