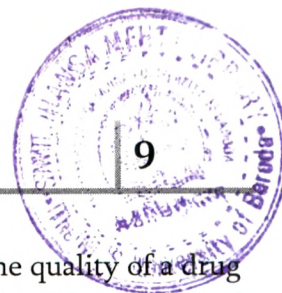


Stability Study Of Drug Loaded MSNs

Materials and Methods



Stability Study of Drug Loaded MSNs

9.1 Significance

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The stability of active components is a major criterion in determining the design and evaluation of dosage form. Several forms of instability can lead to the rejection of a drug formulation. Determination of stability broadly covers the physical, chemical and biological stability.

The uniform size and shape of pores, large surface areas, and high thermal and hydrothermal stability of mesoporous MSNs are well documented¹⁻⁶. Drug molecules are likely to be adsorbed or chemically bound to mesopores (silanol group) of MSNs⁷. Hence it is necessary to check the physical stability of the drug molecules.

9.2 Method of sample preparation and evaluation

Physical stability of drug loaded MSNs was evaluated by performing accelerated stability study:

- (a) $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity.
- (b) $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ of relative humidity.

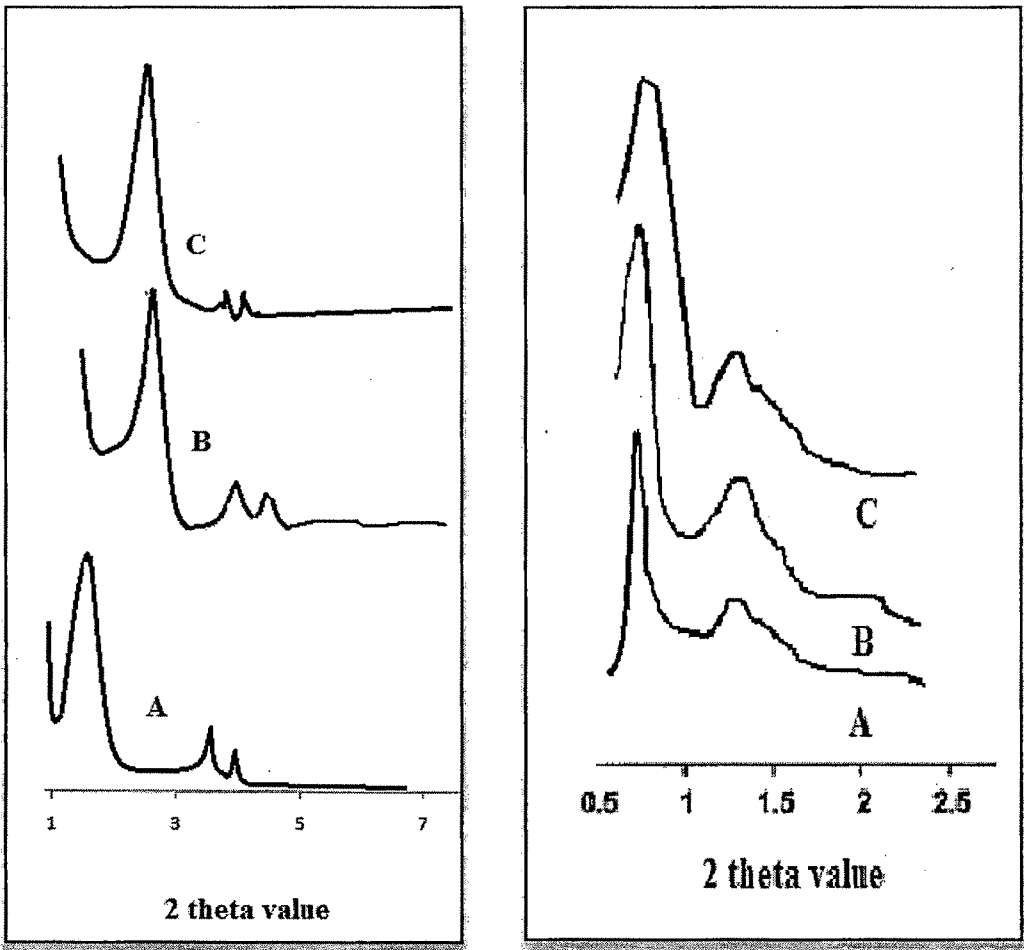
About 400 mg of drug (MTX and DTB) loaded MSNs (MCM-41 and MSU-H) were hermetically sealed in glass vials and stored for six months at different experimental conditions as stated above. The samples were withdrawn at predetermined time intervals of 2, 4, and 6 months and were evaluated by TEM, DSC and XRD instrumental techniques.

Results and Discussion

9.3 Storage stability of drug loaded MSNs

Higher dissolution rates of the selected drugs were due to the drugs were bound to silanol groups of the mesopores and the lack of the drug in a crystalline form⁷, so storage stability studies were conducted in order to verify the physical stability of selected drugs i.e. MTX and DTB.

It is important to check the effect of temperature, as the temperature increases molecule energy and motion with possible breakage of the interactions between MSNs and drug molecules^{8, 9}. The eventual presences of crystalline form of drugs were monitored by XRD and DSC, physical stability of MSNs was checked by TEM.



a) MTX + MCM-41

b) MTX + MSU-H

Figure 9.1: XRD pattern of MTX loaded MSNs in 30 °C ± 2 °C and 65% ± 5% relative humidity after A) 2 months, B) 4 months C) 6 months

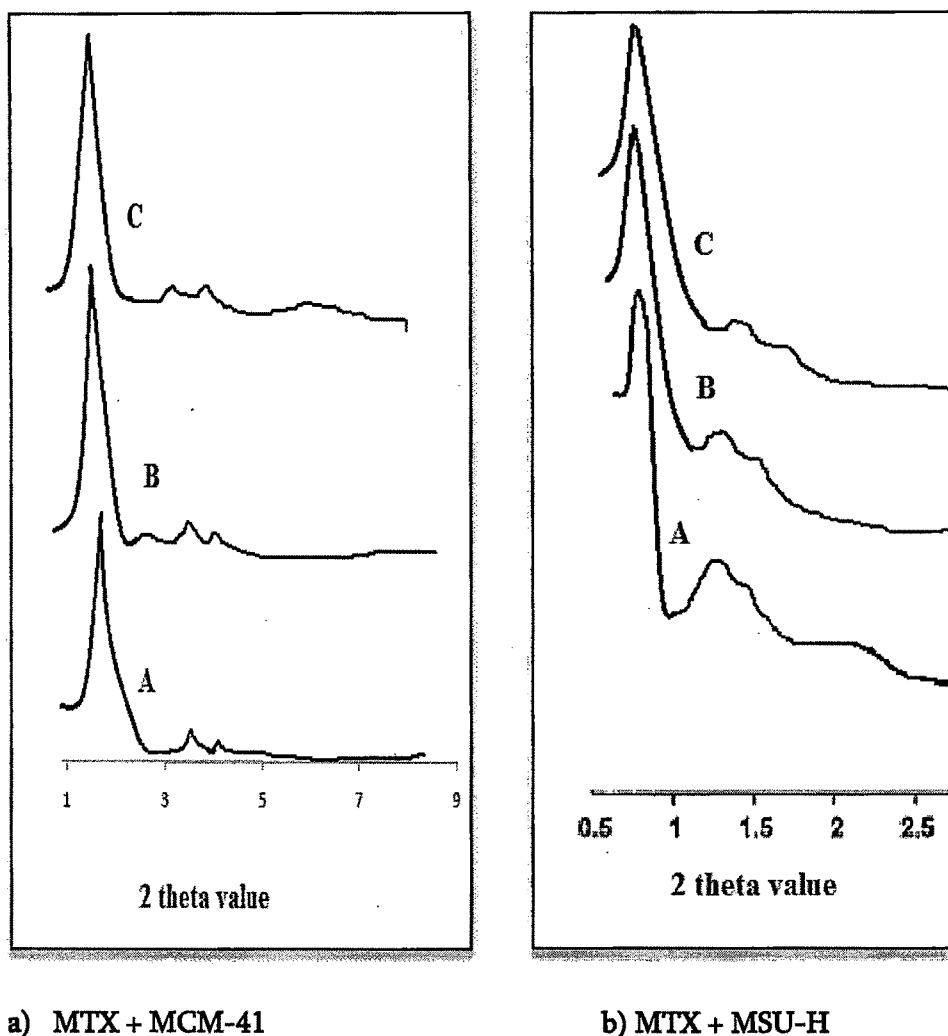


Figure 9.2: XRD pattern of MTX loaded MSNs in $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

XRD patterns of MTX loaded MCM-41 and MSU-H MSNs are shown in Fig. 9.1 and 9.2. Drug loaded samples were previously stored in two different conditions i.e. at $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity and $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity. The XRD patterns of all samples were recorded after 2, 4 and 6 months. Fig. 9.1-a and Fig. 9.2-a XRD were of MTX loaded MCM-41 and showed the presence of reflections with angle 2θ in the range of $2\text{--}8^{\circ}$, typical of MCM-41¹⁰. More importantly XRD of the selected samples do not show peaks relative to the crystalline drugs i.e. MTX, clearly indicating that MTX loaded MCM-41 samples are stable in tested conditions. Whereas Fig. 9.1-b and Fig. 9.2-b show the

XRD of MTX loaded MSU-H MSNs under prescribed conditions for 2 months, 4 months and 6 months. None of these patterns show the characteristic peaks of drug MTX suggesting the stability of MTX loaded MSU-H MSNs.

Similar findings were observed for the DTB loaded MCM-41 and MSU-H MSNs. XRD diffractograms of DTB loaded MCM-41 and MSU-H MSNs shown in Fig. 9.3 and 9.4. These diffractograms do not show the characteristic peaks of crystalline DTB, confirming the physical stability of DTB within the mesopores.

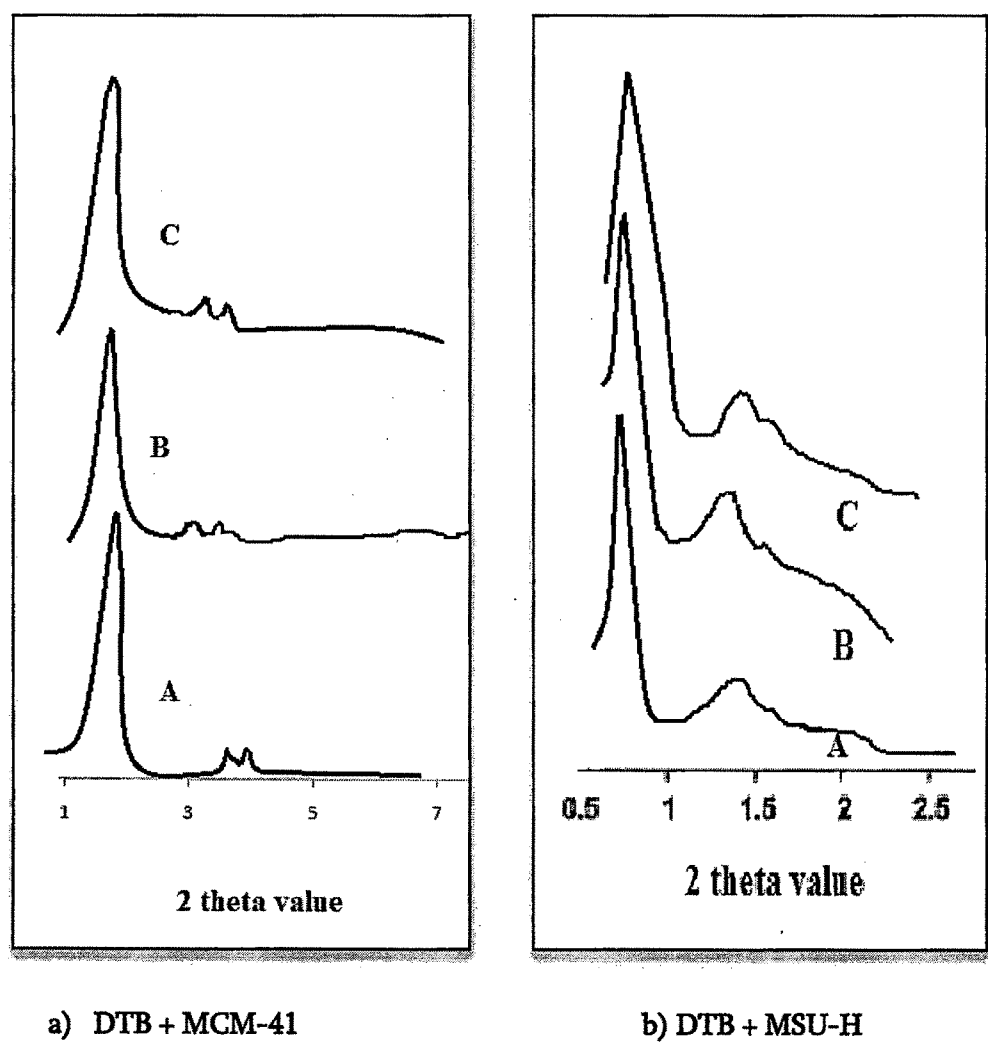


Figure 9.3: XRD pattern of DTB loaded MSNs in $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

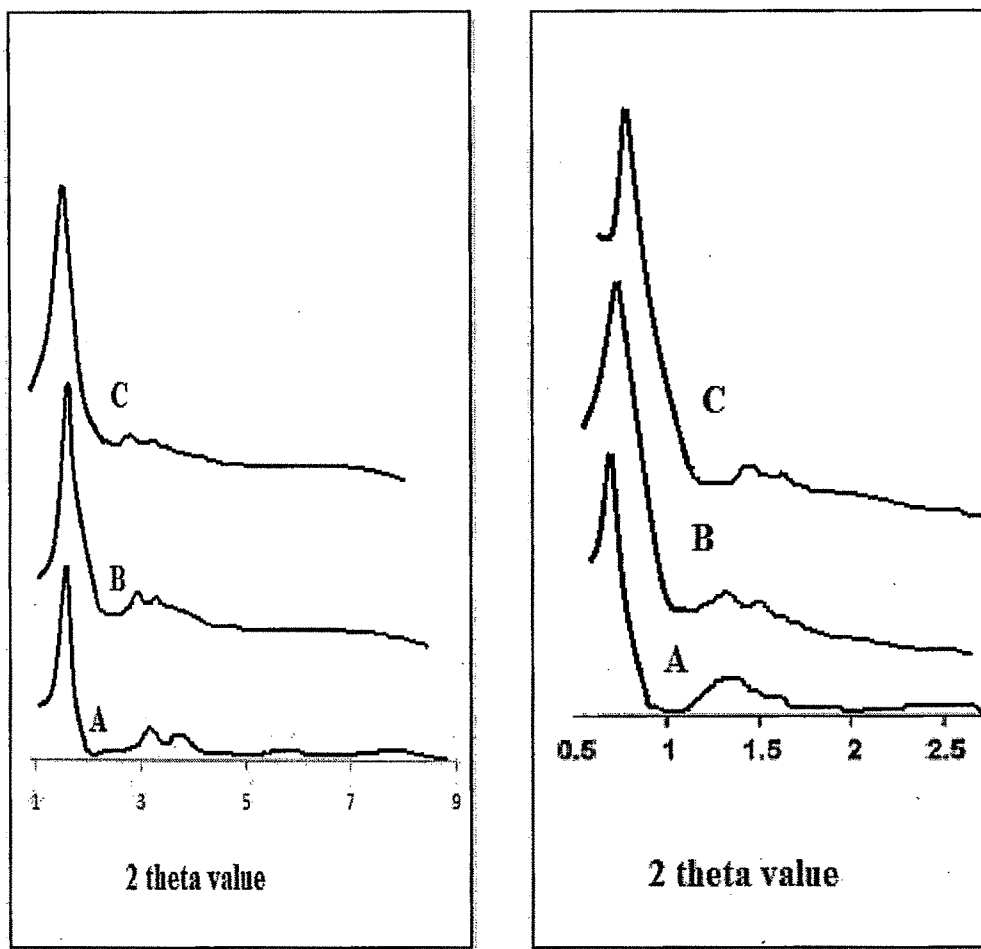


Figure 9.4: XRD pattern of DTB loaded MSNs in $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

The physical storage stability of both the drug loaded MSNs i.e. MCM-41 and MSU-H was checked by high resolution TEM images. The physical structure and the mesoporosity of MCM-41 and MSU-H MSNs were checked. In all tested conditions both the MSNs show good physical stability. Figure 9.5 to 9.12 revealed the structural integrity of drug loaded MCM-41 and MSU-H MSNs after 2, 4 and 6 months at $30\text{ }^{\circ}\text{C}$ and $40\text{ }^{\circ}\text{C}$.

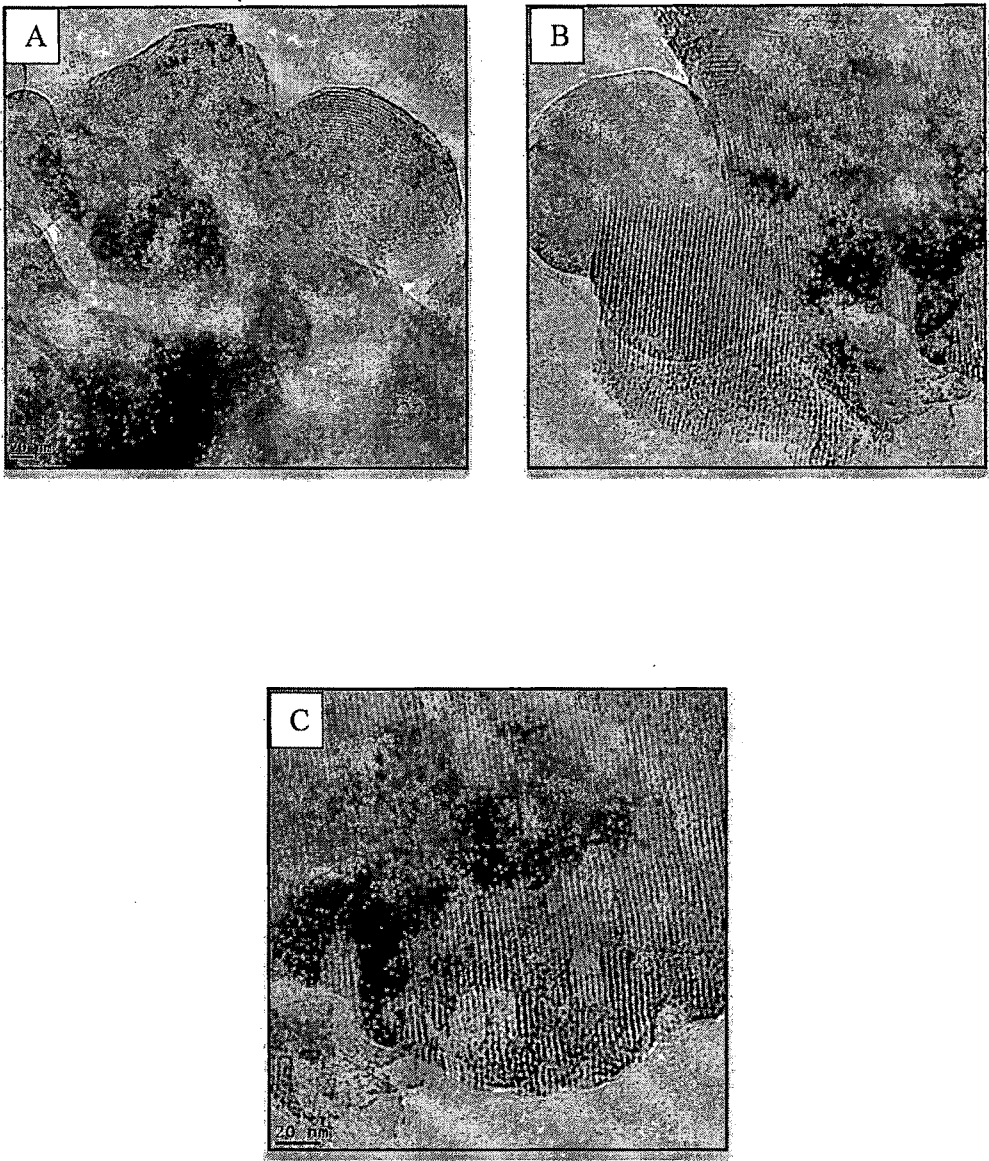


Figure 9.5: TEM images of MTX loaded MCM-41 MSNs in 30 °C ± 2 °C and 65% ± 5% relative humidity after A) 2 months, B) 4 months C) 6 months

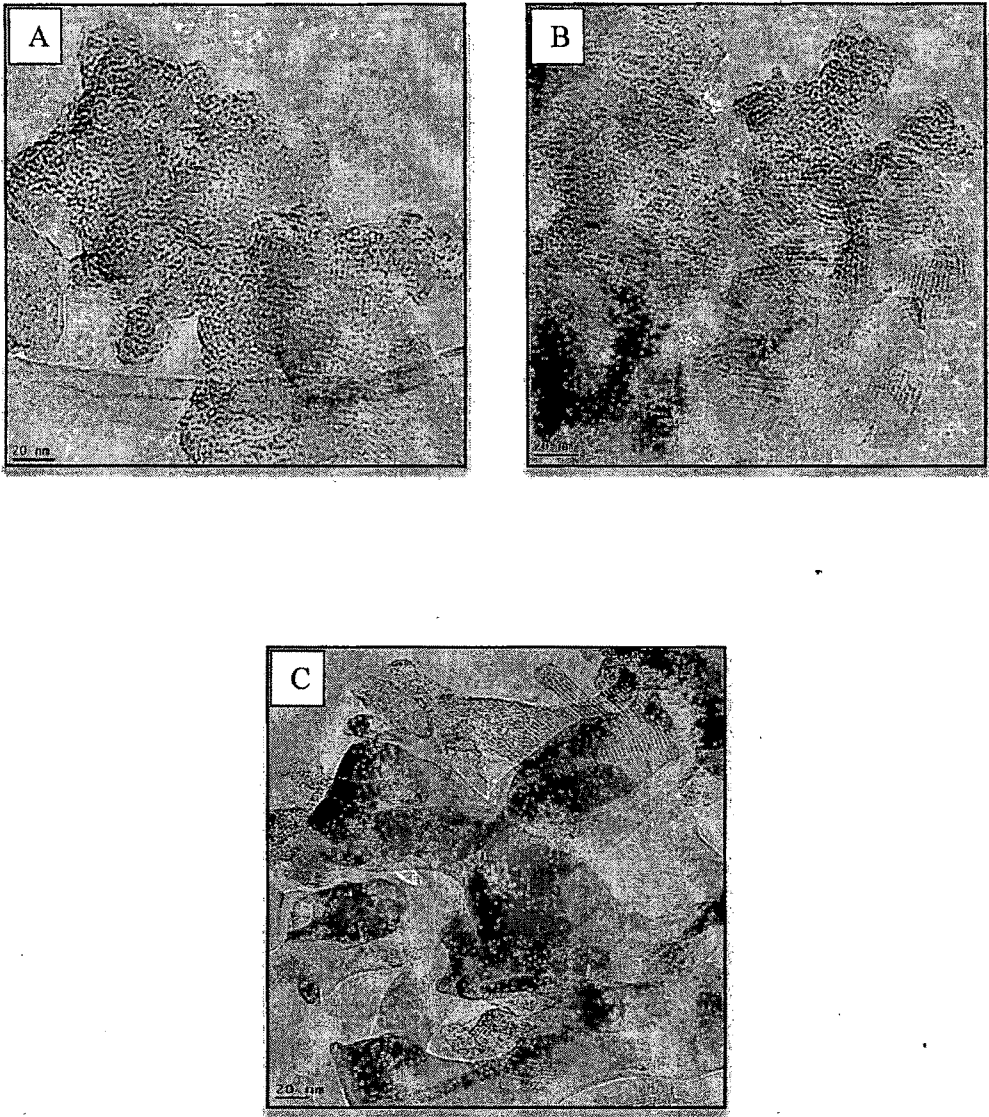


Figure 9.6: TEM images of MTX loaded MCM-41 MSNs in $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

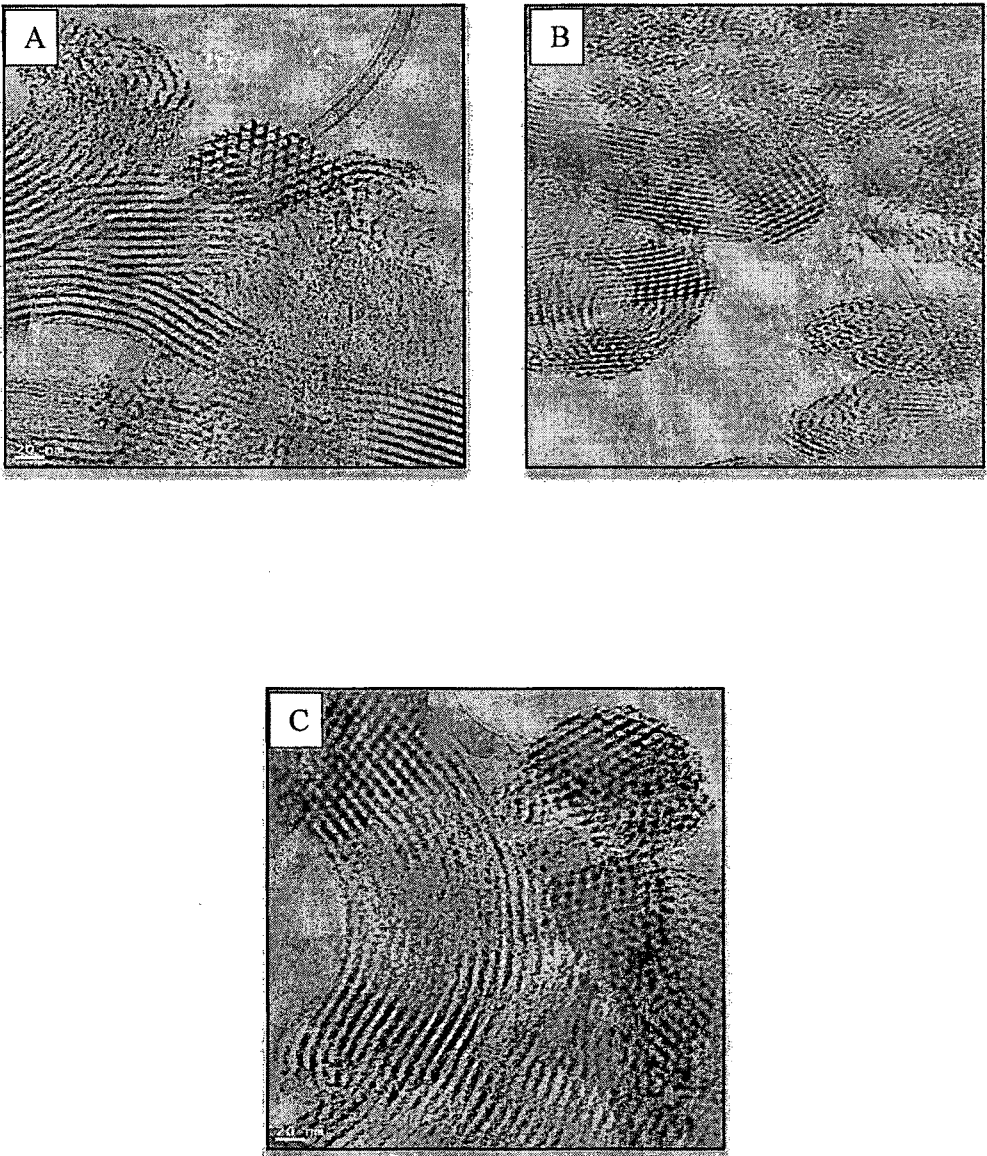


Figure 9.7: TEM images of MTX loaded MSU-H MSNs in $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

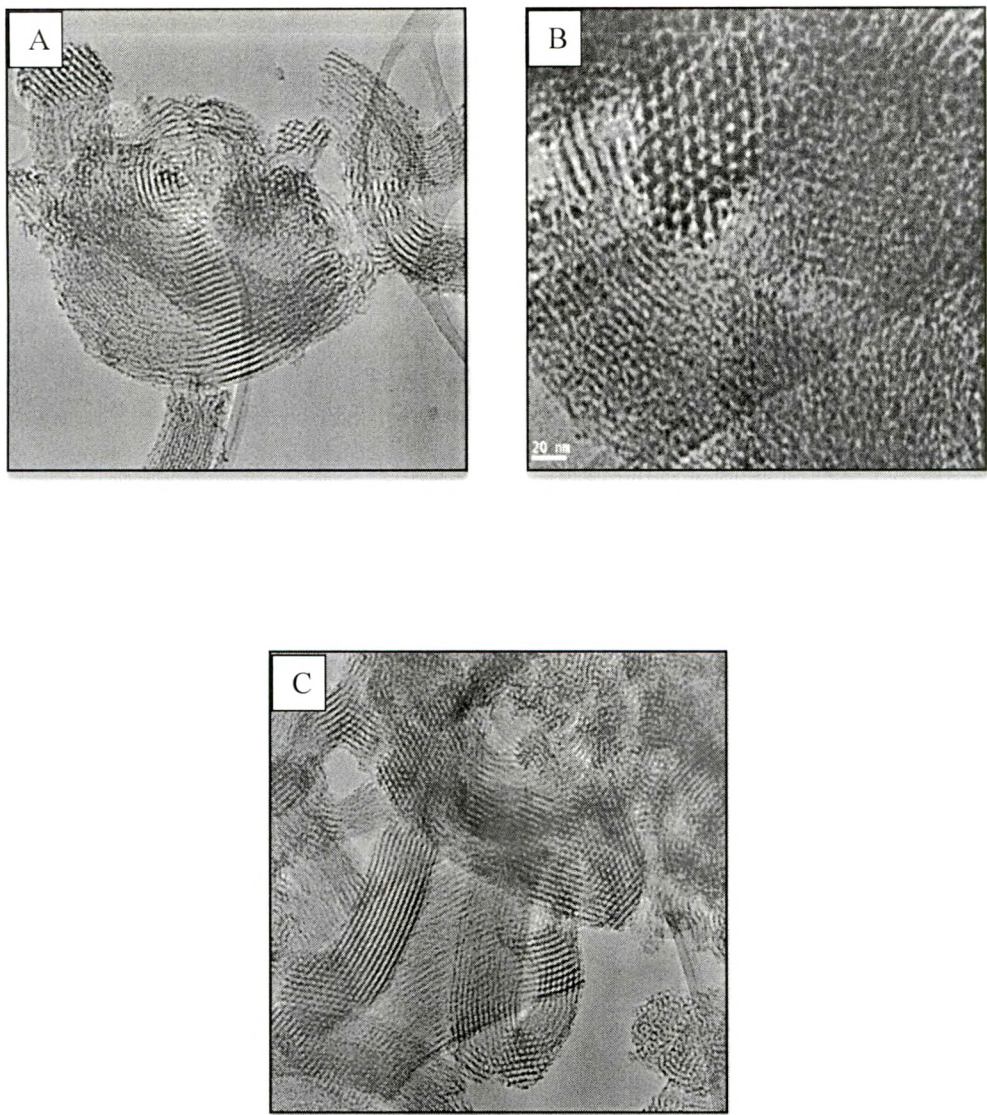


Figure 9.8: TEM images of MTX loaded MSU-H MSNs in $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

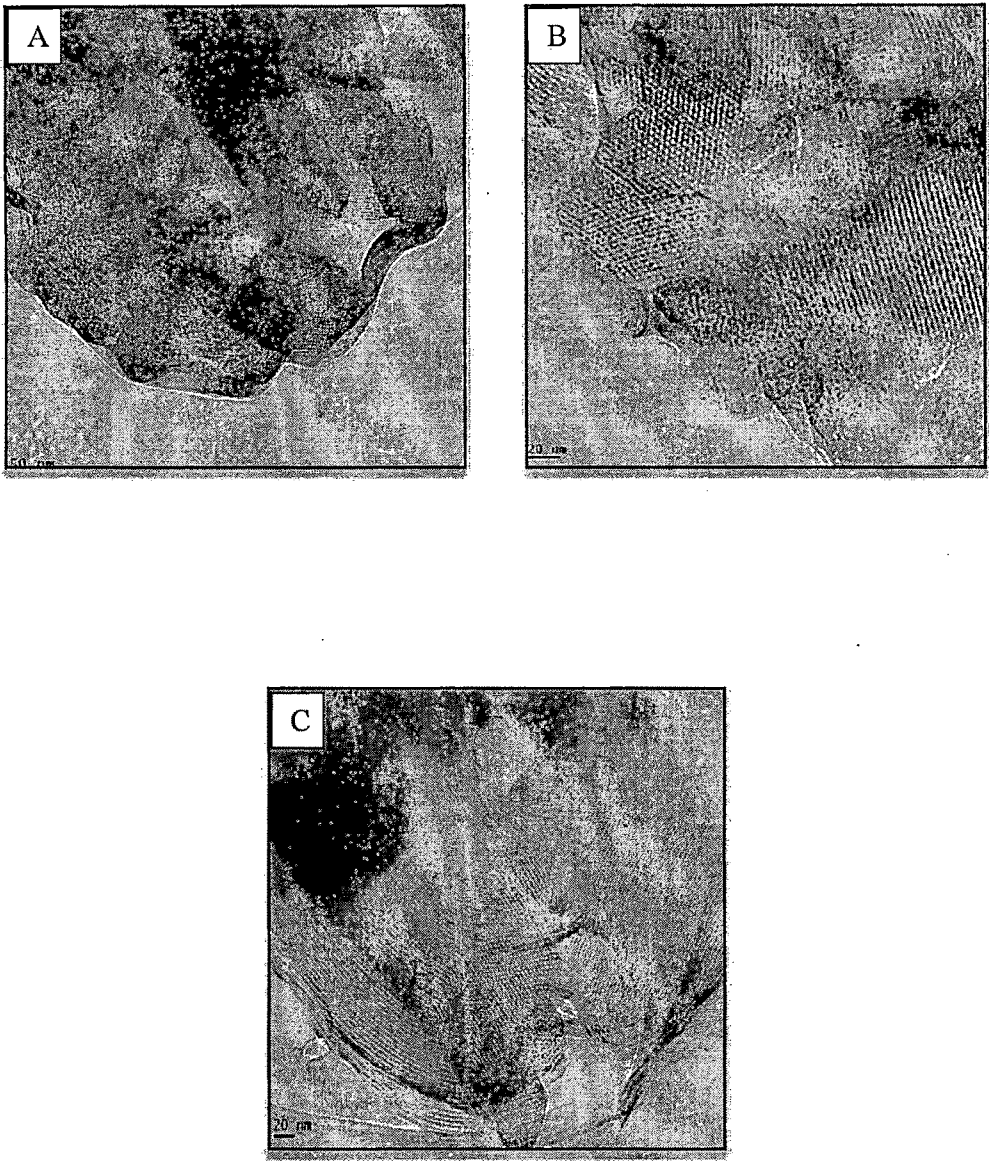


Figure 9.9: TEM images of DTB loaded MCM-41 MSNs in $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

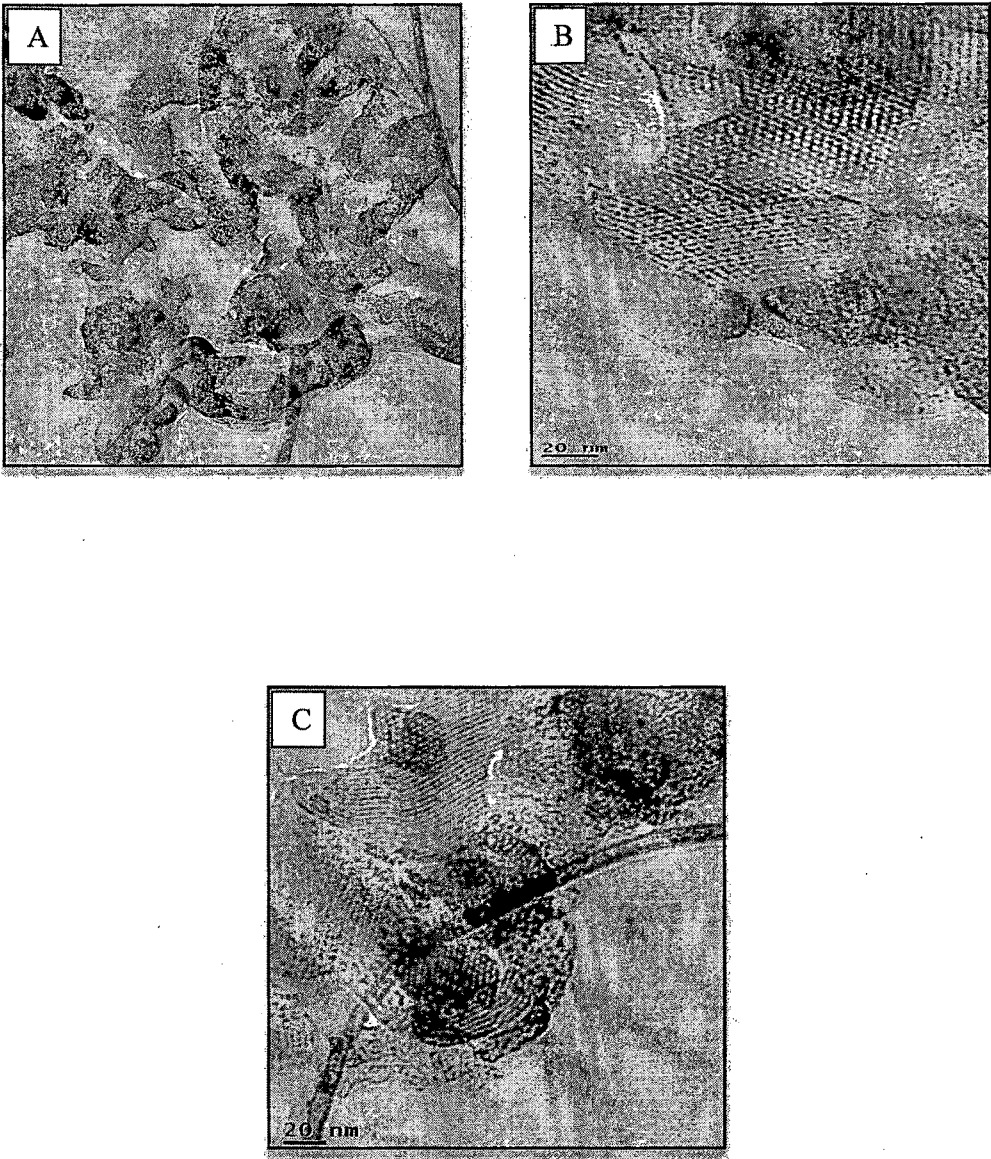


Figure 9.10: TEM images of DTB loaded MCM-41 MSNs in $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

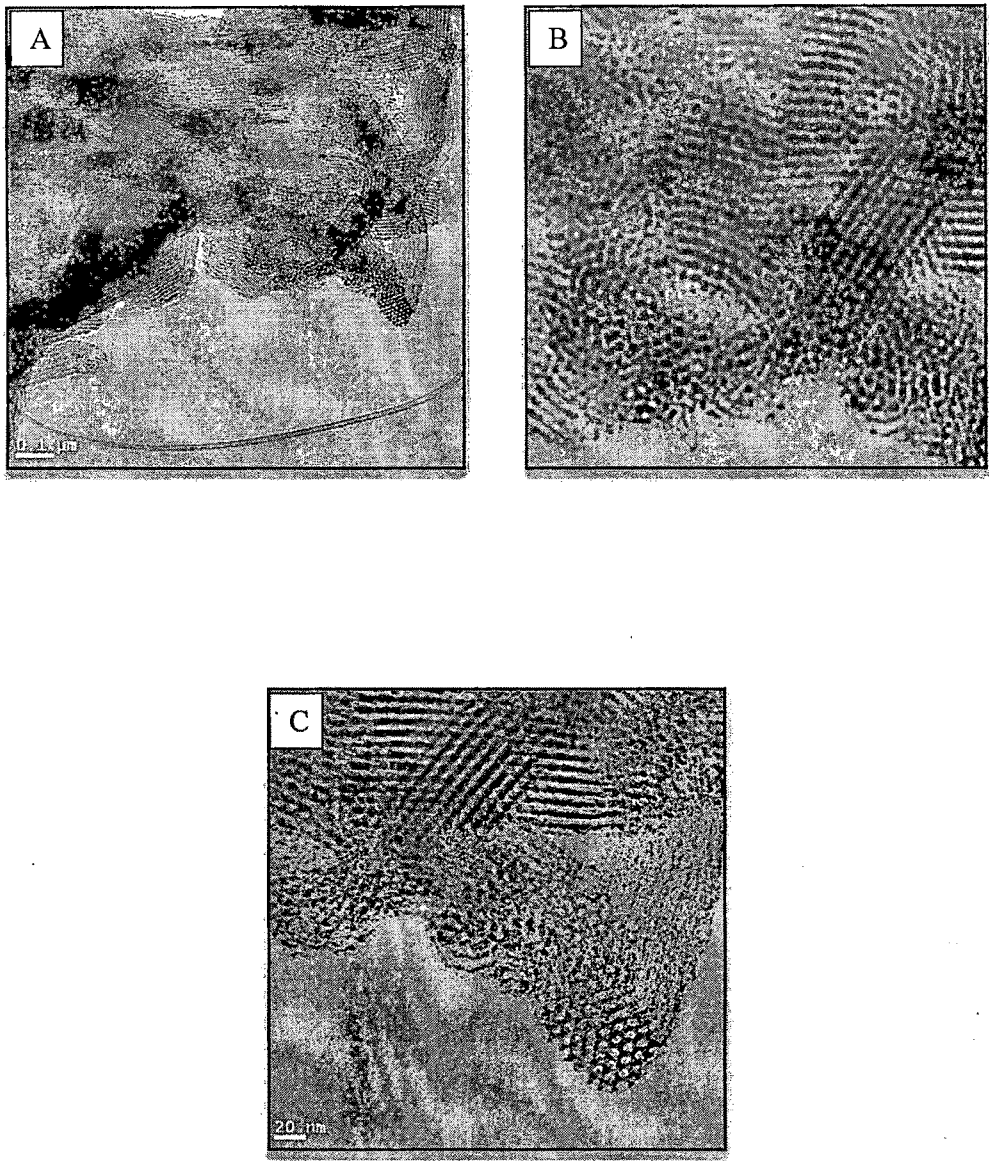


Figure 9.11: TEM images of DTB loaded MSU-H MSNs in $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

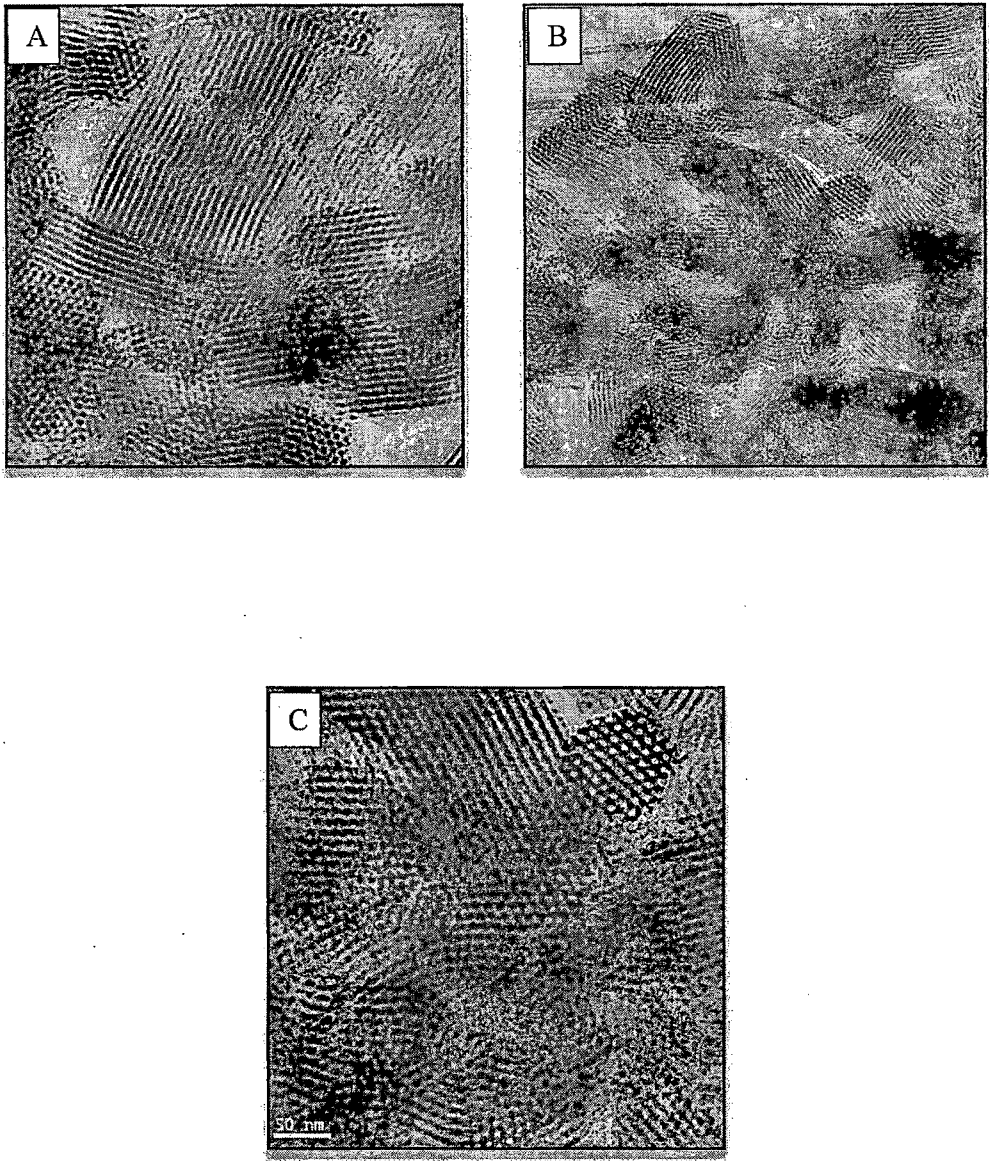


Figure 9.12: TEM images of DTB loaded MSU-H MSNs in $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

DSC thermograms of MTX and DTB loaded MSNs were recorded under experimental storage conditions for both the MSNs. Fig. 9.13-a to 9.16-a represent the thermogram recorded with $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity. The stability of both the drugs within the MSNs was established as MTX and DTB melting peaks could not be detected in any of the thermogram. DSC thermograms as shown in Fig. 9.13-b to 9.16-b for the MCM-41 and MSU-H MSNs samples were recorded when samples were stored at $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity. Thermograms recorded in both the conditions represent a characteristic peak around $100\text{ }^{\circ}\text{C}$ due to loss of humidity and the absence of melting peak relative to MTX and DTB. The absences of melting peak of respective drug indicate that the drug molecules are physically stable within the pores of MSNs. This fact was in accordance with XRD pattern of MSNs.

It was evident from XRD, TEM and DSC studies that MCM-41 and MSU-H are stable carriers for MTX and DTB. In spite of the presence of humidity and the possibility of partial drug dissolution in the water adsorbed on the solid surface of MSNs, no nucleation and subsequent drug crystallization occurs due to perfect match of small pore diameter and the drug molecule size. This is because recrystallization of molecules included in pores occurs only when the pore size is more than 20 times the diameter of the molecules. However, when the drug molecule is confined in a mesopores, its recrystallization is prevented both by the presence of temperature and high humidity¹².

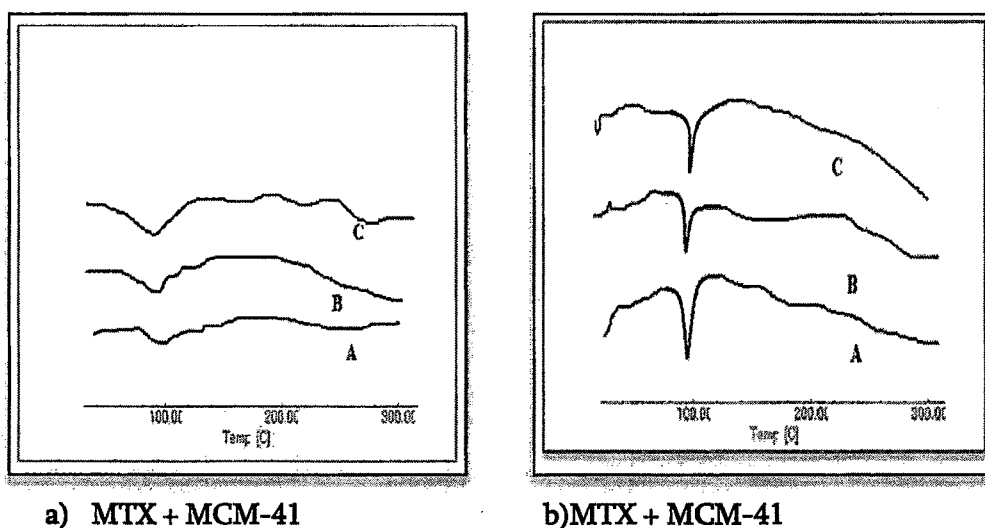


Figure 9.13: DSC of MTX loaded MCM-41 (a) $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $65\% \pm 5\%$ relative humidity for A) 2 months, B) 4 months C) 6 months (b) $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity after A) 2 months, B) 4 months C) 6 months

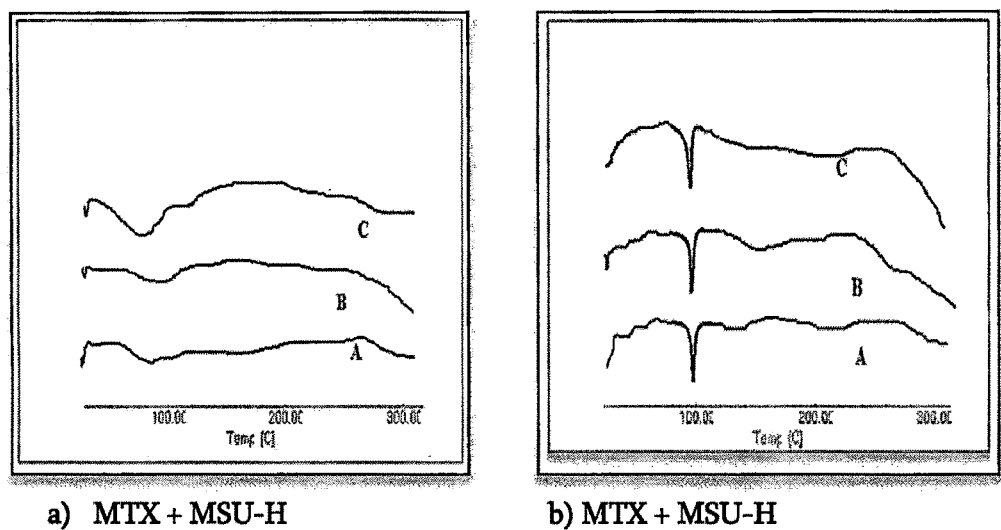


Figure 9.14: DSC of MTX loaded MSU-H (a) 30 °C ± 2 °C and 65% ± 5% relative humidity for A) 2 months, B) 4 months C) 6 months (b) 40 °C ± 2 °C and 75% ± 5% relative humidity after A) 2 months, B) 4 months C) 6 months

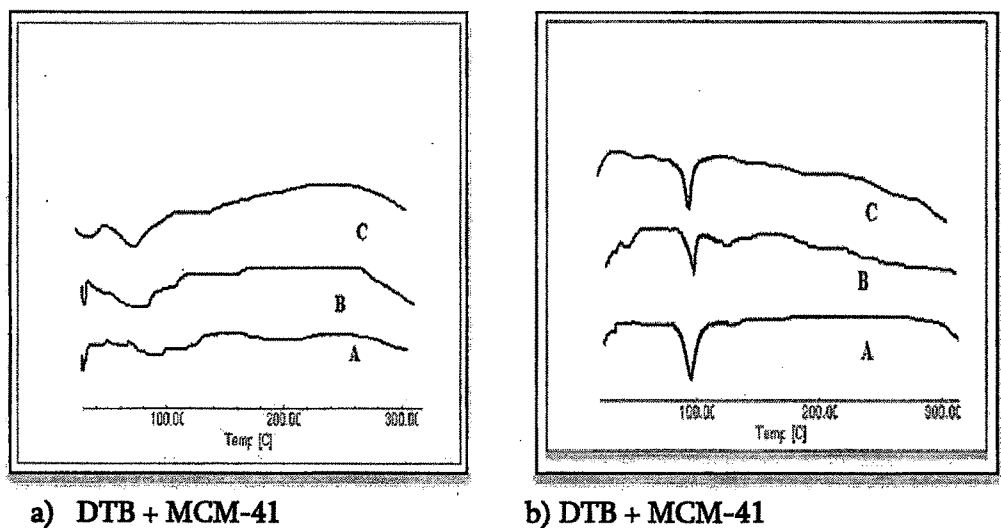


Figure 9.15: DSC of DTB loaded MCM-41 (a) 30 °C ± 2 °C and 65% ± 5% relative humidity for A) 2 months, B) 4 months C) 6 months (b) 40 °C ± 2 °C and 75% ± 5% relative humidity after A) 2 months, B) 4 months C) 6 months

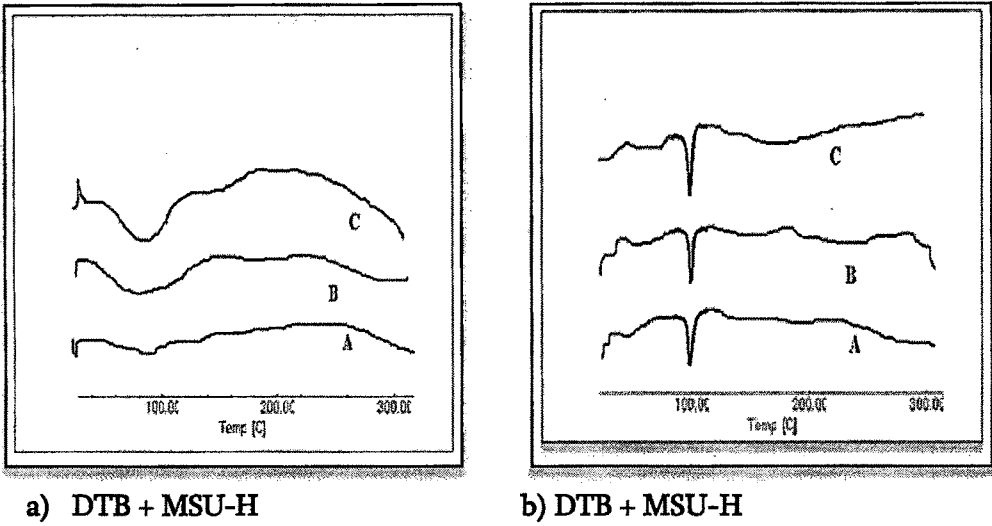


Figure 9.16: DSC of DTB loaded MSU-H (a) 30 °C ± 2 °C and 65% ± 5% relative humidity for A) 2 months, B) 4 months C) 6 months (b) 40 °C ± 2 °C and 75% ± 5% relative humidity after A) 2 months, B) 4 months C) 6 months

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