Summary and Conclusion

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In order to circumvent solubility-limited bioavailability, new approaches of drug delivery systems are being increasingly investigated. In the present study, two mesoporous silica nanomaterials (MCM-41 and MSU-H MSNs) with different pore diameter were investigated for their potential to improve the solubility of the poorly soluble drugs, methotrexate and dasatinib.

The results of this study demonstrated the successful entrapment and release of selected drugs (MTX and DTB) in MCM-41 and MSU-H MSNs, confirming the potential of MSNs as a drug carrier for poorly soluble drugs. MCM-41 MSNs have a high MTX and DTB loading efficiency, up to 47.8% and 48% respectively. Whereas MSU-H MSNs having an entrapment efficiency of 49.7% and 50.1% for MTX and DTB respectively. MSU-H MSNs show high loading efficiency in comparison to MCM-41 MSNs, mainly due to their large pore size. Large pores may facilitate the easy diffusion of the drug molecules into the mesopores. This finding is in accordance with data obtained from *in-vitro* dissolution study. It was found that the drug dissolution from MSU-H MSNs was more in comparison to MCM-41 MSNs. The *in-vitro* drug release studies showed that the dissolution rate of the drugs from both the MSNs was significantly faster as compared to bulk drug and marketed formulation.

The MTX dissolution profile from MCM-41 and MSU-H at pH 7.4 was compared to that of MTX from commercial formulation. The dissolution profiles indicate that after the 10 min, more than 60% MTX was released from MCM-41 MSNs whereas only 26% MTX was released from the commercial tablet formulation while more than 85% MTX was released from MSU-H MSNs and 57% MTX was released from the commercial formulation of MTX.

The dissolution profile of DTB loaded MCM-41 and MSU-H MSNs at pH 4 was compared to that of commercial formulation of DTB. The dissolution profile of DTB loaded MCM-41 MSNs suggest that after the 10 min, more than 70% DTB was released whereas only 32% of DTB release from the commercial formulation. The release profile of DTB loaded MSU-H suggest that more than 79% DTB was released while 52% DTB was released from the commercial formulation.

The dissolution improvement was associated with transformation of drug molecule from crystalline state to amorphous form, which typically dissolves at faster rate as compared to the crystalline form. The amorphous nature of the entrapped drugs and integrity of MSNs were confirmed by DSC, XRD and TEM. It was found that various other mechanisms are also involved in dissolution improvement of the drugs. Nano sized pores and presence of plenty of silanol groups facilitate the retention of the drug molecules within the mesopores of MSNs. Nano sized MSNs provide large surface area and pore distribution,

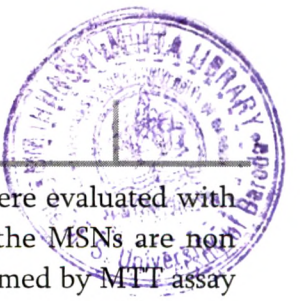
confirmed by BET surface area and BJH pore determination, provide better platform for drug retention. Decrease in particle size and increase in surface area of drug molecules lead to the solubilization enhancement. In addition, the weak interactions between MSNs and functional groups of the drug detected as by FTIR spectroscopy also contributes to rapid desorption of the drug from the carrier surface upon contact with the dissolution media.

The stability of drug molecules within the mesopores and the integrity of the mesostructure were determined by physical stability study. The drug molecules within the mesopores and mesoporosity of the MSNs showed good physical stability during the storage conditions.

Drug loaded samples were previously stored in two different conditions i.e. at 30 °C ± 2 °C and 65% ± 5% relative humidity and 40 °C ± 2 °C and 75% ± 5% relative humidity. The XRD patterns of all samples were recorded after 2, 4 and 6 months. XRD pattern of MTX and DTB loaded MCM-41 and MSU-H MSNs showed the diffraction peaks at 100, 110 and 200, confirming the intact mesoporosity of the MCM-41 and MSU-H MSNs. More importantly XRD of the selected samples (MTX and DTB loaded MCM-41 and MSU-H MSNs) do not show peaks relative to the crystalline drugs clearly indicating that MTX and DTB loaded MCM-41 and MSU-H MSNs samples are stable in tested conditions.

The physical storage stability of MTX and DTB loaded MCM-41 and MSU-H 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 and structural integrity of MTX and DTB loaded MCM-41 and MSU-H MSNs after 2, 4 and 6 months at 30 °C and 40 °C.

DSC thermograms of MTX and DTB loaded MCM-41 and MSU-H MSNs were recorded under experimental storage conditions for both the MSNs. The stability of MTX and DTB within MCM-41 and MSU-H MSNs was established as MTX and DTB melting peaks could not be detected in any of the thermogram. Thermograms recorded in both the conditions represent a characteristic peak around 100 °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 (MTX and DTB) indicate that the drug molecules are physically stable within the pores of MCM-41 and MSU-H MSNs. This fact was in accordance with XRD pattern of MSNs.



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The cytotoxicity of drug loaded MCM-41 and MSU-H MSNs were evaluated with K-562 and L-132 cell lines. The results suggest that the both the MSNs are non toxic to selected cell cultures. The cytotoxicity study was performed by MTT assay technique for the incubation time of 96h and the concentration up to 1000 µg/ml.

It was found that the cell viability of K-562 cells of MTX loaded MCM-41 and MSU-H MSNs was more than 80% and 85% respectively. Whereas more that 81% and 85% of cells were found to viable with L-132 cells of MTX loaded MCM-41 and MSU-H MSNs respectively. Cell cytotoxicity of DTB loaded MSNs of K-562 cells show the survival percentage more than 77% and 86% from MCM-41 and MSU-H MSNs respectively. Whereas more than 79% and 88% of L-132 cells were found to survive when treated with DTB loaded MCM-41 and MSU-H MSNs respectively.

It was found that when MSNs were exposed at higher concentration and for longer incubation time to the selected cells, natural biological rhythm of the cells gets affected. The results of cell cytotoxicity study show the decrease in cell viability with MCM-41 MSNs as compare to MSU-H MSNs. The smaller size, larger surface area and presence of cationic surfactant in trace amount are the factors which may impart the toxic behavior to MCM-41 MSNs.

It can be concluded from the study that MCM-41 and MSU-H MSNs can be used as drug carrier for MTX and DTB with enhanced dissolution and have the potential to be used as commercial formulation in future.