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ORIGINAL ARTICLE

Amino modified Mesoporous silica nanoparticles as Drug carrier- Effect of Functionalization on Dissolution

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ABSTRACT
The current investigation was conducted with the purpose of dissolving rate and poorly water soluble medication Silymarin via encapsulation into mesoporous silica nanoparticles (MSNs). The blank MSNs and Differential scanning calorimetry, nitrogen sorption analysis, and Fourier transform infrared spectroscopy were used to thoroughly characterize surface decorated MSNs both before and after drug loading, X-ray diffraction. Chitosan (CH) was used for decoration on the surface of synthesized MSNs, and the impact of functionalization on dissolution was investigated. MSNs and surface decorated MSNs were characterized pre and post SLM loading. A significant increase in dissolution rate was found 92% in CH modified MSNs (SLM-CH-MSNs) as compare to SLM-MSNs was 79%. Thus, MSNs could serve as an effective platform for delivering of various poorly water soluble drugs.
Key words: Silymarin, Functionalized Mesoporous silica nanoparticles, Dissolution, Chitosan.

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INTRODUCTION

The use of nanotechnology-based drug delivery systems has gained increased attention in recent years because these systems are able to create stable and biocompatible formulations that deliver medications to target tissues at target times using target release rates while requiring the least amount of resources and offering the highest level of efficacy. [1–3]. MSNs have showed remarkable potential as an ideal drug delivery method due to their unique qualities such as uniform pore size, large surface area, typical honeycomb channeled structure, and significant loading and entrapment capacity. [4–6]. Many research attempts have been committed to change the chemical characteristics of MSNs by surface modification to have high loading and optimal release pattern for medication molecules [7,8]. In this regard, MSNs have been treated using polymeric polyethylene glycol [9] and 3-aminopropyl triethoxysilane (APTES) [10]. These surface-modified MSNs performed better than unmodified MSNs. Chitosan (CH), the second-most prevalent polysaccharide after cellulose, is commonly employed to create smart drug delivery systems [11,12]. Chitosan has been widely employed in drug delivery systems due to its unique qualities such as non-toxicity, biocompatibility, and biodegradability, among others. [13]. Low aqueous solubility is a common characteristic of biopharmaceuticals. Many drugs confront substantial hurdles in clinical use due to their low water solubility, preventing them from adopting a formulation strategy capable of producing large loads and rapid dissolving rates. Oral medication administration is the simplest technique to provide pharmaceuticals. [14-15]. Silymarin is a flavonoid chemical extract derived from the seeds of Silybum marianum (L.) Gaertn. Silymarin has four active ingredients: silybin, isosilybin, silychristin, and silydianin. The low water solubility of silymarin inhibits its oral absorption. To improve silymarin solubility, we synthesized both unmodified and surface modified mesoporous silica nanoparticles. Entrapment efficiency and dissolution were compared to unmodified and surface-modified MSN. Silymarin is a combination of flavonoid chemicals isolated from the seeds of Silybum marianum L. Gaertn. Silymarin contains active components such as silybin, isosilybin, silychristin, and silydianin. Silymarin's weak water solubility inhibits its oral absorption [16]. The aim of this work is to examine the rate of

medicine release of a poorly water soluble medicament. Drug release was compared to original MSN and chitosan-modified MSN. To boost the entrapment efficiency, drug loading and surface modification were performed. Silymarin drug-loaded MSN and CH-MSN were investigated utilizing FT-IR, SEM, nitrogen adsorption, XRD, and DSC.

MATERIAL AND METHOD

Materials

Silymarin were purchased from Yucca laboratories, Mumbai, tetraethyl ortho silicate, cetyl trimethyl ammonium bromide were purchased from Sigma Aldrich, (3-Aminopropyl) triethoxysilane were purchased from Tokyo chemical Lab, Ammonia solution, alcohol obtained from SD Fine Chemicals, Mumbai

Preparation of MSN

Blank mesoporous silica nanoparticles prepared by Sol-gel process. 81.6 ml of ethanol, 82 ml water and 41 ml of ammonia solution were added mix together. 5.4 g of CTAB were added in above solution and mixed by using sonicator. This mixture was stirred for 15 min using magnetic stirrer. Afterword 22.3 ml TEOS added drop wise and stirred for 2 hr. clear solution turns to opalescence that indicated the reaction was started and got the nanoparticles. Nanoparticles were washed by deionized water using cooling centrifuge. Dry powdered nanoparticles obtained after filtration and the drying overnight. Surfactant removed by calcination in muffle furnace by calcination process at 550^0 C for 4 hr.

Surface modification by Chitosan and drug loading

0.025 g of chitosan was dissolved in 25 mL acetic acid (1.5% v/v) and agitated for 4 hours. Then, 100 g of MSN was dissolved in 25 ml of acetic acid (1.5% v/v). The chitosan solution was combined with the Blank MSN solution and stirred for four hours. The substance was separated using centrifugation and then dried. The method was repeated with varied concentrations of chitosan[17]. Drug loaded in non-functionalized MSN and CH-modified MSN by solvent immersion method. Drug loading shown in Figure 1 and 2.

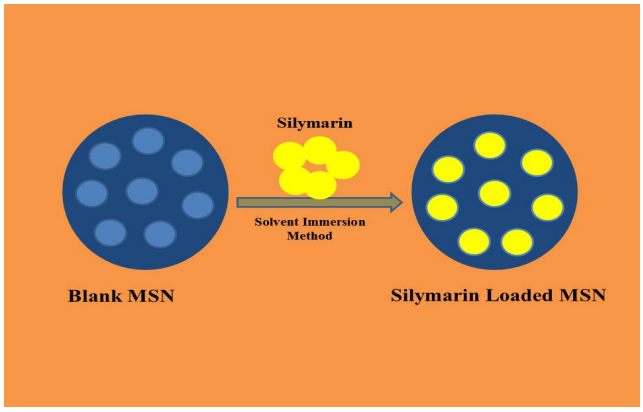


Figure1. Schematic representation of drug loading in non-modified MSN

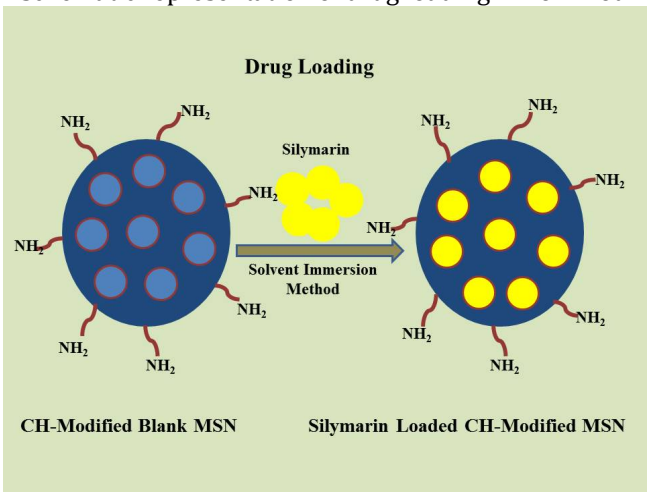


Figure 2. Schematic representation of drug loading for CH-modified MSN

Entrapment Efficiency and drug loading was studied for prepared MSN by using following formulae 1 and 2.

$$\text{Entrapment Efficiency \%} = \frac{\text{Total amount of drug in MSNs}}{\text{Total weight of sample}} \text{ X } 100 \quad (1)$$

$$\text{Drug loading capacity \%} = \frac{\text{Total amount of drug in MSNs}}{\text{Total amount of drug initially added}} \text{ X } 100 \quad (2)$$

Characterization and Evaluation of SLM loaded MSN, CH-functionalized MSNs

FT-IR

The FT-IR spectrum of prepared nanoparticles was recorded using Fourier Transform Infrared (FTIR) spectrophotometer. The sample was prepared by combining it with potassium bromide (KBr), triturating it in a glass mortar, and depositing it in a press pellet machine to produce a pellet. The pellet was inserted into the sample container (press pellet cell). The spectra was examined throughout a frequency range of 4000-400 cm-1. The obtained spectra were interpreted for functional groups.

XRD, DSC, SEM

XRD measurement of Silica nanoparticles were recorded with diffractometer of Brucker Axs Germany. The CuKå line at 1.54060 A served as the radiation source for the X-ray generator, which was operated at 40 kv and 30 mA. A mortar and pestle were used to grind the sample. An aluminum specimen container was filled with the crushed specimen.. The samples were scanned from 100 to 800. (20) at 250C. The morphology of synthesized MSNs was determined by SEM operated at an accelerating voltage of 15 kV. The samples were taken with a Hitachi SU 1510. Drug purity and physical state were assessed using Differential Scanning Calorimetric (DSC) analysis. The DSC analysis gives the interaction of various materials.

Nitrogen adsorption/desorption isotherm, Particle size and Zeta potential

Surface area, pore size and pore volume of the prepared mesoporous silica nanopatlicles at 300^0C for 8 h under vaccum were measured by nitrogen adsorption/desorption isotherm at -196.140C using Quantachrome Nova station instrument, version 11.05 analyser. (NLDFT)(Zhang Y. et al., 2012).Horiba S Z 100 was used for particle size and zeta potential investigation. Principle Laser diffraction quantifies particle size distributions by measuring the angular change in the intensity of scattered light as a laser beam passes through a dispersed particle sample. Zeta potential measurements are based on charges on particles in the formulation.

In vitro dissolution study

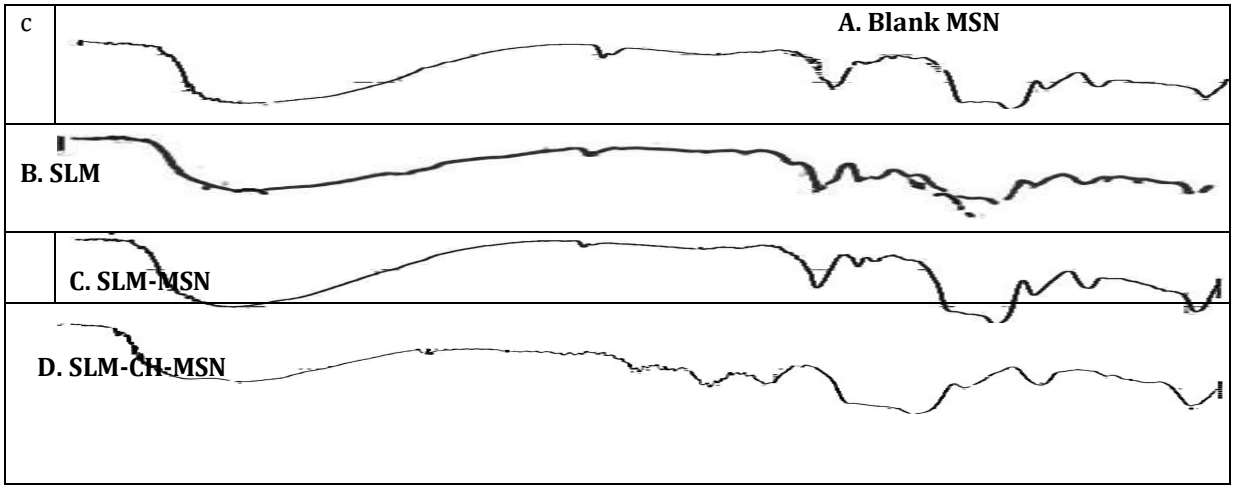
Dissolving tests were done using a USP II paddle technique (50 rpm, 37±0.5 ˚C, and 900 ml dissolving medium) using the TDT-08 dissolution tester Electrolab Mumbai. Aliquots of 10ml were removed at predefined time intervals, and a new amount of 10 ml dissolution media was added to maintain the volume of the dissolving medium. The samples were examined using a UV spectrophotometer at 287 nm.

RESULTS AND DISCUSSION

FTIR

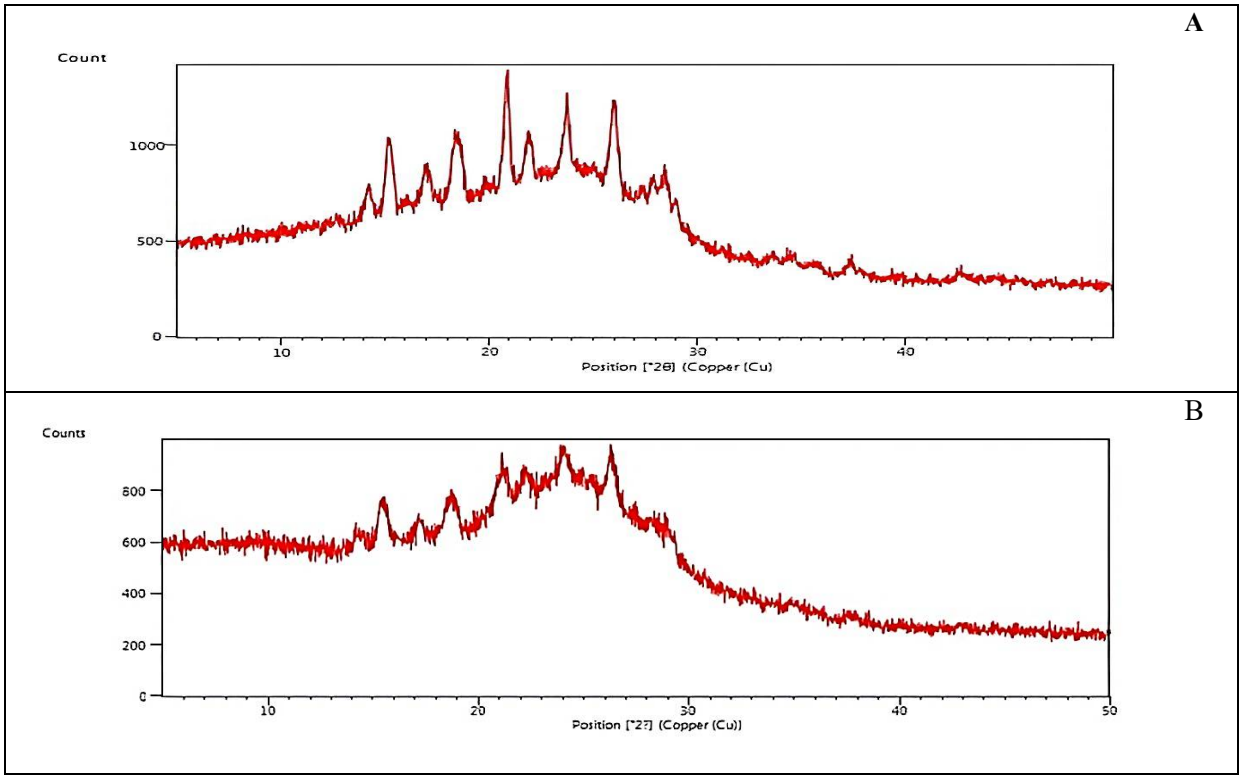
The IR spectrum of Silymarin and Silymarin loaded MSNs was determined in the range 400-4000 cm -1. The major IR peak observed for Silymarin is 3439.08 (-OH), 2937.59 (-CH), 1639.49 (-C=O), 1230.58 (-C-O-C), 1083.99 (-C-O) respectively. The Silymarin and Silymarin loaded MSN shows similar peaks at the respective wave number. It was predicted that there is no chemical interaction between the medication and the excipients. However, after surface functionalization, two new bands appear at 3215 (-NH 2) and 802 (-CH 2). This result is agreement with successful chitosan functionalization into drug loaded MSNs. Shown in figure 3.

Figure 3: FTIR of A) Blank MSN B)



X-ray diffraction (XRD) study, DSC, SEM

In figure 4A XRD pattern of SLM shows characteristic high intensity with prominent peaks of 2θ value at 21˚ and 25˚, which indicates that a silymarin is present in crystalline form. In figure 4B XRD pattern of SLM-MSN reveals the strength of diffraction peaks was lowered, indicating that the silymarin was successfully loaded into the blank MSNs. A very low intensity peaks 2θ value at 25 ˚ was observed. In figure 4C. XRD pattern of surface functionalized silymarin loaded MSNs shows that there is no present any characteristics Diffraction peaks revealed that chitosan molecules functionalized the surface of MSNs, confirming the presence of silymarin in amorphous form.



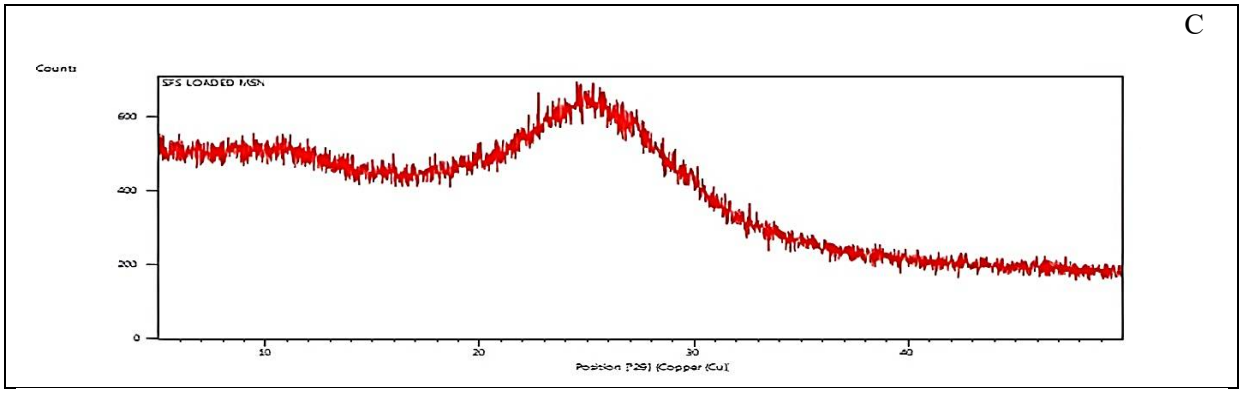


Figure 4: XRD of A) SLM B) SLM-MSN C) CH-SLM-MSN

The DSC thermogram of silymarin shown in figure 5. suggested that it might be absorbs moisture from air, which shows deep endotherm at about 82^{0}C.The peak was observed at 147.16^{0}C which corresponds to melting point of silybin, an active constituent of silymarin complex. The weak endothermic peak at 262^0 C, which corresponds to melting point of taxifolin and silychristin which is active constituent of silymarin. In SLM-MSN, the melting endotherm was observed at 86.91^0 C and 147^0 C which reveals the existence of drug in MSNs. The complete disappearance of endothermic peak at 235^{0}C as compared to SLM; Thus it confirms that the presence of SLM in amorphous state in MSNs. In surface functionalized silymarin loaded MSNs, the melting endotherm was observed at 82^{0}C which was due to the silymarin absorbs moisture from air. The absence of a drug melting peak of SLM in CH-SLM-MSN provides strong evidence for the drug's full inclusion in the carrier[18].

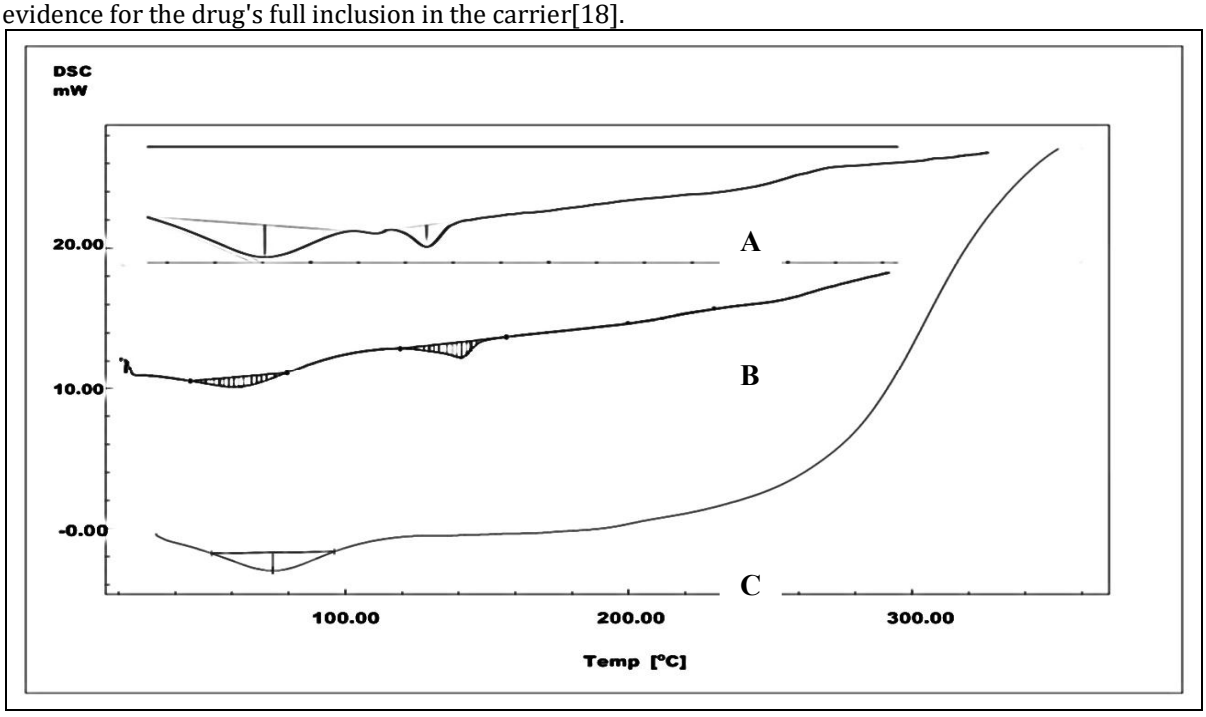


Figure 5: DSC of A) SLM B) SLM-MSN C) SLM-CH-MSN

SEM images of blank MSNs, silymarin loaded MSNs and Amino functionalized silymarin loaded MSN shown on figure 6A, it was observed that the porous and uneven nature of blank MSNs. In figure 6B, the porous, uneven nature and shows aggregation of silymarin loaded MSNs. In figure 6C, after surface functionalization it was observed that the porous nature MSNs shows no aggregation.

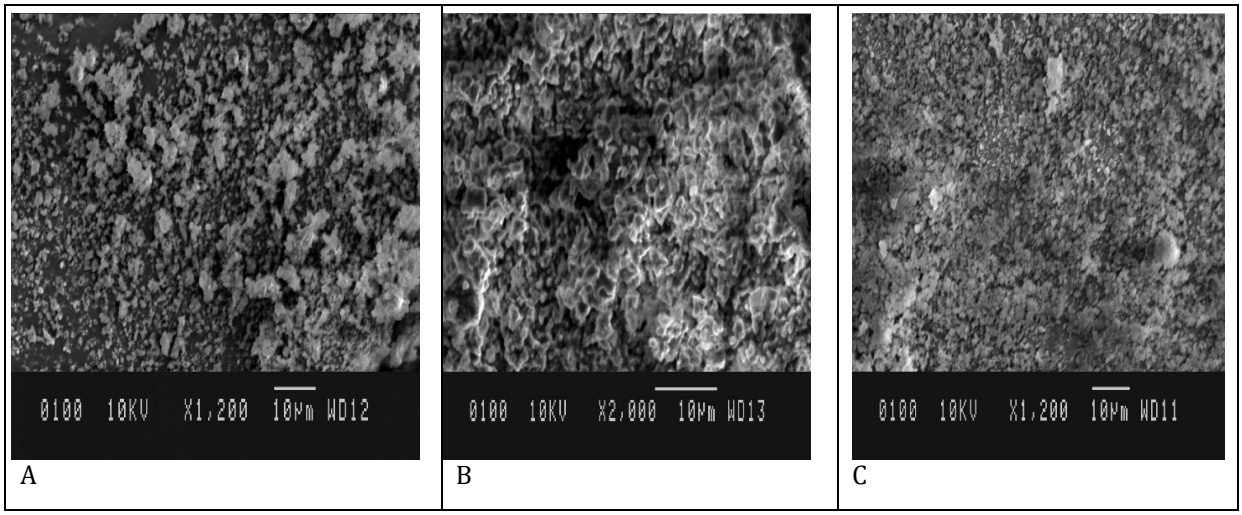


Figure 6: SEM for A) Blank MSN B) SLM-MSN C) SLM-CH-MSN

Nitrogen adsorption/desorption isotherm, Particle size and Zeta potential

Assuming pores are filled with liquid adsorbate, the amount of vapour adsorbed at a temperature near unity is used to compute the pore volume. The pore volume is used to assess the average pore size. Nitrogen adsorption and desorption isotherms of blank, silymarin loaded MSNs, surface functionalized silymarin loaded MSNs particles are shown in figure 7. Nitrogen adsorption desorption isotherm of the blank MSNs showed a type IV isotherm, associated with mesoporous materials. The initial loop indicates the mono-multilayer adsorption and the second loop indicates desorption. These adsorption isotherms confirm the porous nature of the Mesoporous silica nanoparticles. It was observed that surface area as well as pore volume of the blank MSNs was more as compare to the silymarin loaded MSNs and surface functionalized silymarin loaded MSNs. The blank nanoparticle has a smaller pore size than silymarin-loaded MSNs. The decrease in surface area and pore volume might be attributed to silymarin and Chitosan adsorption on blank MSN surfaces. Data on surface morphology are provided in Table 1.

Table 1: Surface area and porosity information for Blank MSN, SLM-MSN, CH-SLM-MSN

Sr. No.	Formulation	Surface area m^2/g	Pore volume (cc/g)
1	Blank MSN	491.460	0.668
2	SLM-MSN	100.028	0.527
3	CH-Blank MSN	247.870	0.140
4	CH-SLM-MSN	62.315	0.094

The zeta potential of blank MSNs is -23.9, the negative value is due to -Si-O-H group present on surface of MSNs. The zeta potential of SLM-MSN is -19.1 because of surface hydroxyl groups (-OH) is present in silymarin. The zeta potential of surface functionalized silymarin loaded MSNs are -33.6 due to and $-NH_2$ groups present in chitosan. This value of zeta potential suggested that the MSNs have good stability by the virtue of electrostatic repulsion. Particle size of blank MSN, SLM-MSN and surface functionalized silymarin loaded MSNs was determined by using Horiba. According to Figure 8 the particle size of SLM-MSN, SLM-CH-MSN is detected at 265.0 nm, nm, 273.5 nm respectively. As predicted, functionalization resulted in an increase in particle size due to the addition of bulky groups to the surface.

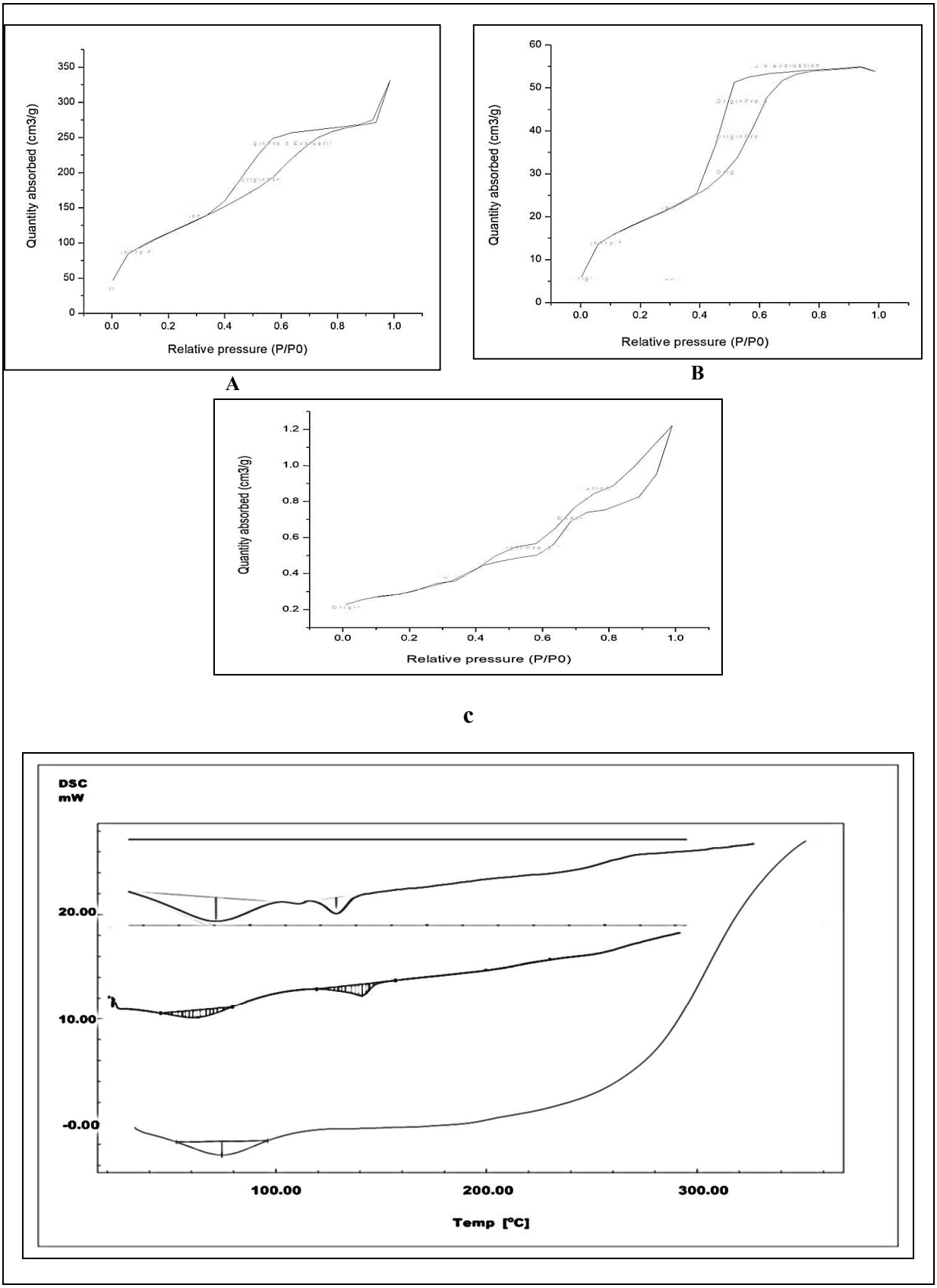


Figure 7: N_2 Adsorption desorption A) Blank MSN B) SLM-MSN C) SLM-CH-MSN

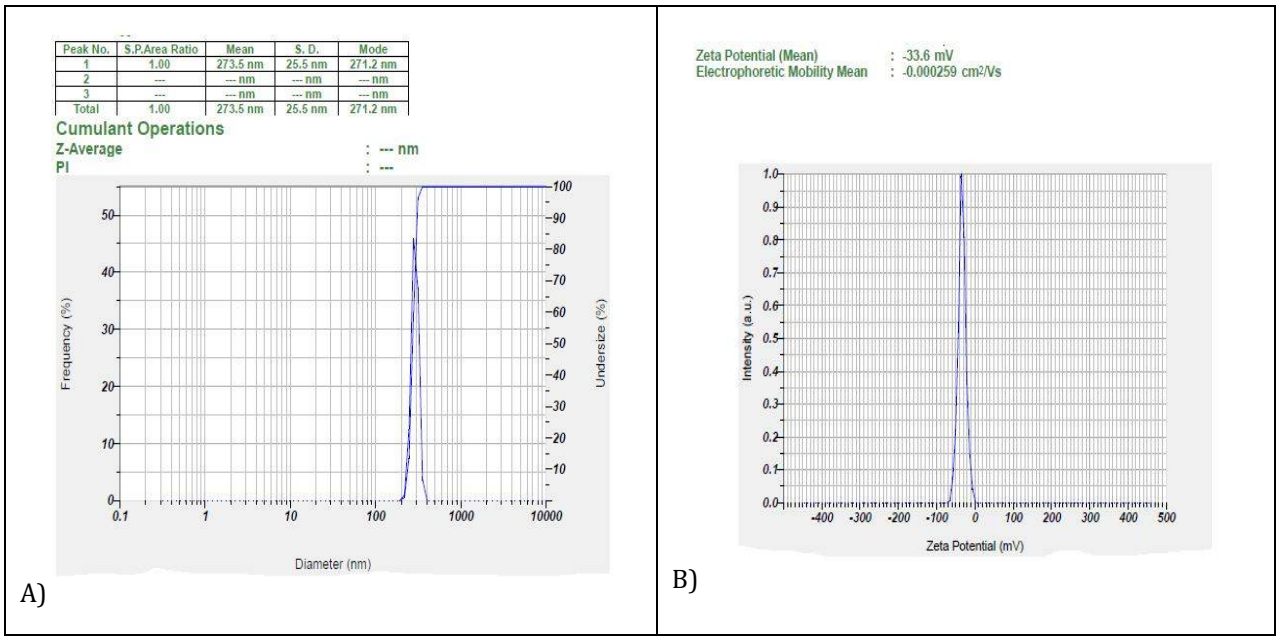


Figure 8: A) Zeta potential of CH-SLM-MSNs B) Particle size of APTES Functionalized Silymarin Loaded MSN

%DL and %EE

By using various concentration of APTES the Amino functionalized MSN were prepared and investigated for the drug loading, entrapment efficiency. Drug loading and EE% were found for unmodified mesoporous silica nanoparticles were 87.97±1.42% and 68.45±0.74% optimized batch 90.20±0.17% and 97.50±0.62% respectively. For CH functionalized MSN These observation were found more as compared to the unmodified mesoporous silica nanoparticles.

***In vitro* dissolution**

Figure 10 compares the SLM release patterns of non-modified MSN and CH-MSNs in dissolving media their releasing habits were as varied as could be seen. The burst release and total quantity of SLM released from the CH-MSN was noticeably slower than that from the SLM-MSN. The burst release of the SLM from the SLM-CH-MSNs was around 3% in 1 h; while the burst release of the SLM from the MSN was roughly 12% 1 hour, respectively. During the twelve hour period, the cumulative release of the MSN was 92% from the SLM-CH-MSNs whereas it was 79% from the SLM-MSN. In Chitosan functionalized MSN burst release is very less due to attachment between NH2 groups because of surface functionalization by NH2. In vitro dissolution showed the drug release up to 12 hr. also showed the effect of concentration of chitosan on drug release. As the concentration of chitosan increases, medication release decreases as shown in figure 9.

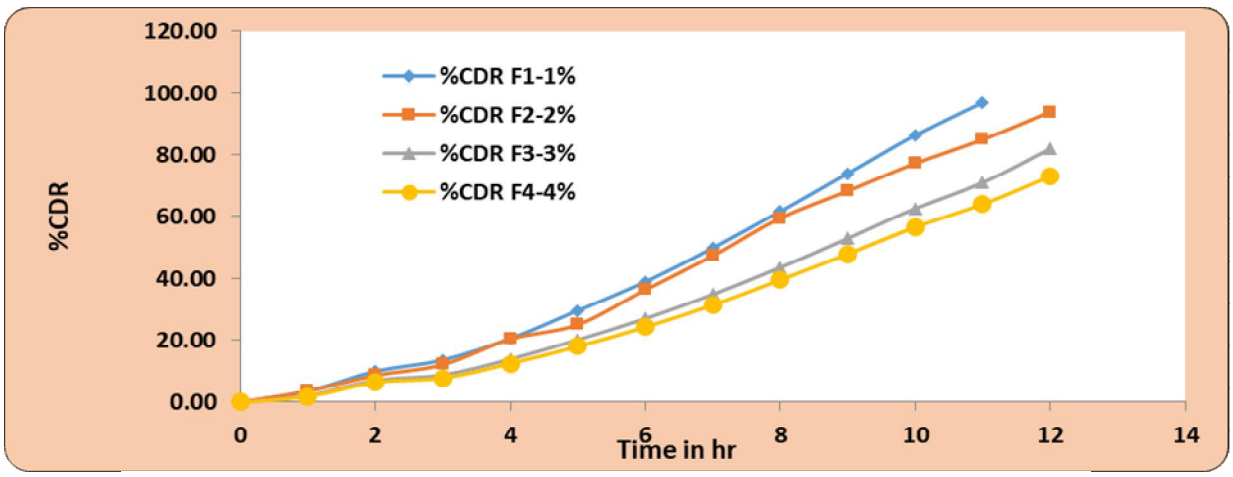


Figure 9: Drug release of CH-SLM-MSNs containing various concentration of chitosan

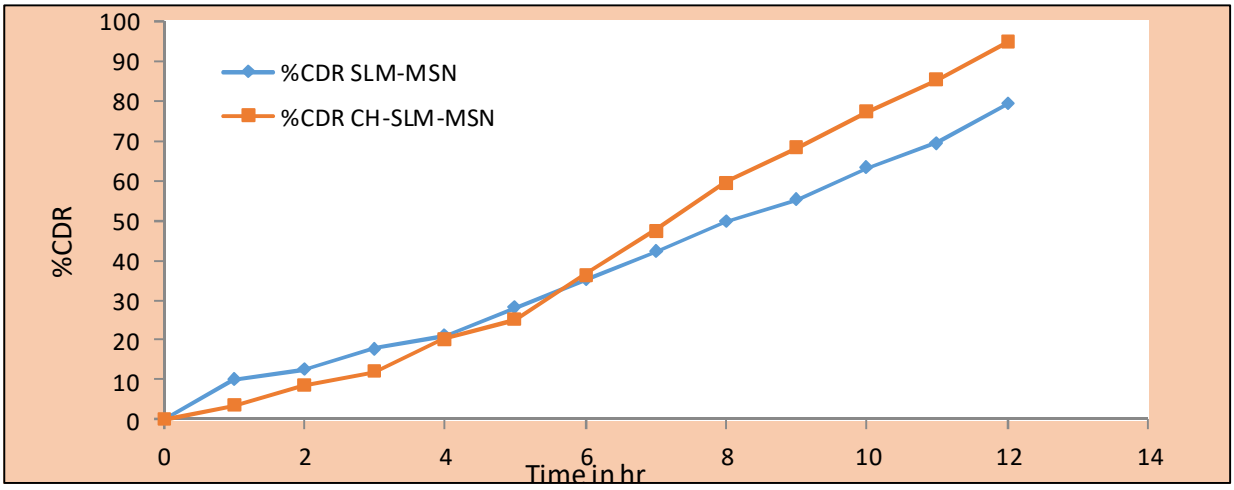


Figure 10: Drug release of SLM-MSN (Unmodified silymarin loaded MSN) and CH-SLM-MSN (Chitosan modified silymarin MSN)

CONCLUSION

In this work, MSNs' exterior surfaces were modified with chitosan. The CH-MSNs were made using the post-grafting technique at room temperature in a non-toxic solvent. The obtained results demonstrated that the encapsulation efficiency and drug-loading content in the CH-MSNs were greater than those in the SLM-MSNs (unmodified MSN). Furthermore, it was discovered that, in contrast to SLM-MSNs, CH-SLM-MSNs exhibited suitable characteristics for delayed drug release carriers, providing enough release over a predetermined time to prevent recurrent administration.

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CONSENT FOR PUBLICATION

Not applicable

COMPETING INTEREST

The author declares that they do not have any competing interests.

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