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ORIGINAL ARTICLE

Design, Synthesis, and Assessment of Clarithromycin Mesoporous Silica Nanoparticles Encapsulating for Enhanced Topical Drug Administration

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ABSTRACT
The objective of research work was to the development and evaluation of clarithromycin loaded mesoporous silica nanoparticles for topical drug delivery. The mesoporous silica nanoparticles of clarithromycin were prepared with tetraethyl ortho silicate and cetyltrimethyl ammonium bromide (as surfactant). The prepared nanoparticles were evaluated using following parameters such as particle size analysis, scanning of electron microscope, Xrd, FTIR and antimicrobial activity. The particle sizes of clarithromycin-loaded mesoporous silica nanoparticles were found to be 218 ± 8 nm (mean ± SD). The in-vitro drug release study of clarithromycin-loaded mesporous silica nanoparticle was conducted, using phosphate buffer 7.4pH and acidic buffer 1.2pH. In-vitro % cumulative drug release of clarithromycin was found to be 98.46 %. Antimicrobial activity of clarithromycin-loaded mesoporous silica nanoparticle was performed against bacteria such as S.aureus, S.mutans, E.coli, P.vulgais and after the screening of antimicrobial activity. The maximum growth inhibition of bacterial zone was shown by clarithromycin-loaded mesoporous silica nanoparticles when compared with the standard formulation. All the results of evaluation methods of mesoporous silica nanoparticle strongly advocate its good feature for delivery of antibacterial drug. The prepared clarithromycin loaded nanoparticles seem to have potential for use as a topical drug delivery.
Keywords: *Mesoporous silica nanoparticles; Rifampin; Drug delivery; Drug-loading;*

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INTRODUCTION

In the present scenario, mesoporous nanoparticles are promising for their well-known drug deliver and targeting purposes, incorporated within amorphous silica matrix [1]. Mesoporous silica nanoparticles (MSNs) are solid materials and containing hundreds of empty channels. According to various literature and reports the mesoporous silica nanoparticles exhibit superior biocompatibility. It has been used in the formulation of different dosage form at various concentrations.

The MSN also offer several unique and advantageous structural properties, such as high surface area (>700 m^2 g − 1), pore volume (> 1 cm^3 g-1), stable mesostructure, tunable pore diameter (2–10 nm), two functional surfaces (exterior particle and interior pore faces), and modify able morphology (controllable particle shape and size) [2, 3].

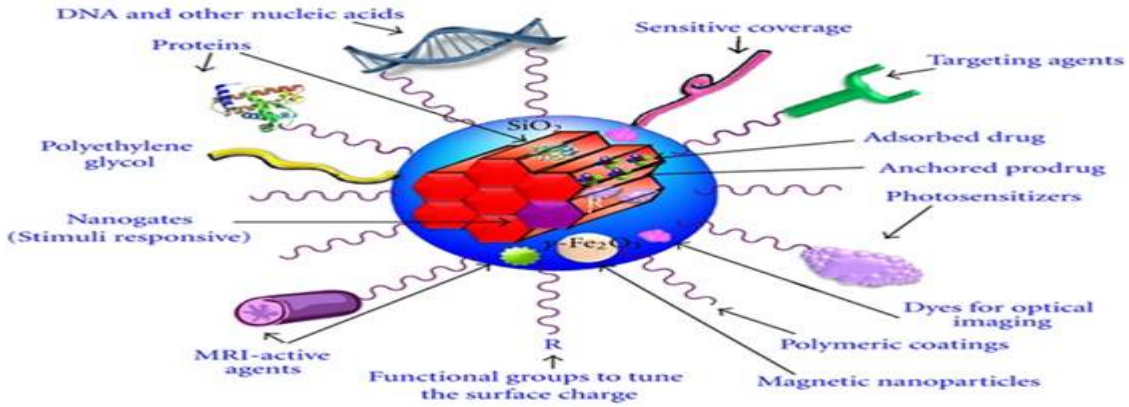


Fig. 1: MSN as Nano-medical Multifunctional Nano-platforms

MSN have tunable nanoscale sizes, different shapes ranging from spheres to rods, uniform cylindrical mesopores, high surface areas, and easily functionalizable surfaces. Owing to these interesting structural features, it has been accepted as valuable delivery vehicles for pharmaceuticals and bioactive molecules (e.g., nucleotides) to desired intracellular sites or as host materials for bioimaging, biocatalytic. The traditional liposome-based drug delivery systems suffer from the low stability in physiological environment, which may result in uncontrollable drug releases. Comparatively, MSNs can release the loaded drug in a sustained manner partially due to their good surface area and high stability [4].

The presence of surface silanol groups facilitates MSN's fictionalization by various groups (hydroxyl, amine, thiol, and carboxyl) which can then conjugate with fluorophores and target ligands for optical imaging of tumour cells *in-vitro* 5-8[5, 6].

Mesoporous silica nanoparticles were independently synthesized in 1990 by researchers in Japan [7, 8]. Clarithromycin is a macrolide drug, orally absorbed, comes under broad spectrum antibiotic. It is usually used in a standard eradication treatment of gastric H. pylori infection and topical infective diseases. It is active against equally gram positive and gram negative microbacteria such as *staphylococcus aureus, E.coli, Klebsiella, Proteus*. Clarithromycin drug is used to treat soft tissue and skin infections. Hence, Clarithrmycin drug was selected in the present research work and our objective was to formulation and evaluation of clarithromycin loaded mesoporous silica nanoparticles for topical drug delivery for the treatment of acne disease. The prepared mesoporous silica nanoparticles were to evaluate by using drug loading efficiency and to screening its antimicrobial activity on selective skin disease causing bacteria [9].

MATERIAL AND METHODS

Materials: Clarithromycin drug were procured from Himedia Labs, India. Cetyl trimethyl ammonium bromide (CTAB) and Tetra ethyl orthosilicate (TEOS) were obtained from Sigma Aldrich, India. Acetone, methanol, ethanol, were purchased from Merck Company, India. All other chemical were analytical grade used.

Preparation of mesoporous silica nanoparticles

Accurately 1g N-Cetyl Trimethyl Ammonium Bromide (CTAB) was dissolved in 480 ml of deionized water. Next Sodium hydroxide (NaOH) 2 mol was mixed into previously prepared solution of CTAB, then after adjusting the solution temperature to 80 °C and TEOS 5 ml was added drop-wise into the surfactant solution. The whole mixture was allowed to stir for 6 hrs to give white precipitates (as prepared thiol-Sphere). The white precipitate was filtered, washed by using ethanol, deionized water and dried in air. To wash-away the surfactant template (CTAB), 1.5 g of as-synthesized thiol-Sphere was refluxed for 24 hrs in a solution of 9 ml of hydrochloric acid and washed by using deionized water. The finally surfactant-remove thiol mesoporous sillica material was placed under high vacuum to remove the remaining solvent in the mesopores [10, 11].

Drug loading method

The mesoporous silica nanoparticle (10 mg/ml) was dispersed into clarithromycin aqueous solution (1 mg/ml). Clarithromycin-loaded mesoporous silica nanoparticles were obtained by centrifugation; then the MSN were washed by using deionized water. The supernatant and the washing liquor were collected, and the residual clarithromycin was evaluated by using the calibration curves of standard clarithromycin solutions obtained by UV-Vis spectroscopy [12, 13].

Loading efficiency (wt %) = $\frac{\text{mass of drug in the MSNs}}{\text{Mass of the drug-loaded MSNs}}$

Characterization of the mesoporous silica nanoparticle

Particle size analysis

The particle size analysis of mesoporous silica nanoparticles were determined by using Zeta Sizer (Malvern Instrument Ltd. UK ZS-90). The mesoporous silica nanoparticles was taken in cuvette and put on the sample holder. The images of mesoporous silica nanoparticles were obtained [14, 15].

Scanning electron microscopy

SEM study was done by using FEI Nova Nano SEM (450, Netherland). In this technique, firstly ready the sample and its tablets were prepared. The pellet was carefully placed on a glass cover slip followed by air-drying. The cover slip was used during scanning electron microscopy (SEM) analysis. The images of mesoporous silica nanoparticles were obtained by using scanning electron microscope [16].

LA-XRD of mesoporous silica nanoparticle

The powder character of prepared silica nanoparticle was characterized by using XRD, Rigaku-Japan (Miniflex) with a scanning range of 0 to 100 (2θ). The mesoporous silica nanoparticle of powder diffraction data was collected from transmission or reflection geometry of XRD. The XRD result data were used and calculated. The peaks of mesoporous silica nanoparticle (MSN) were found at the low angle.

Fourier transform-infrared spectroscopy

The FTIR spectra of MSN without drug and clarithromycin-loaded MSNs were obtained by using Prestige-21, FTIR spectrophotometer, Shimadzu Corp, Japan. 1 mg of each sample was finely grounded with KBr (Merck) into a fine powder separately in motor pestle and poured into the sample holder and scanned over a wave number of 4000-650 cm^{-1}.

Drug loading efficiency

Drug loading efficiency was determined, using centrifuge method. The prepared formulation of drug mixture centrifuge at 20000 rpm and collect supernatant layer, Supernatant layer was observed in UV spectrophotometrically at 666.0 nm meter. The clarithromycin-loading efficiency was calculated, using the following formula:

$$\%\ \text{loading efficiency} = \text{weight of drug loaded msn} - \text{weight of free drug}$$

***In-vitro* release study**

In-vitro release study of clarithromycin-loaded MSN was carried out by using phosphate (7.4pH) and 1.2pH HCl acid buffer as the recipient media at 37± 0.5°C using dialysis membrane packet in dissolution apparatus. Aliquots (1 ml) were withdrawn at pre-determined time intervals (1, 2, 3, 4, 5, 6, 7, 8 and 24hrs.) and after withdrawal of aliquots the recipient medium was replenished with the same volume of buffer solution (1 ml). The concentration of drug was determined by UV-Visible spectrophotometry . The *in-vitro* drug release studies data was obtained. It was fitted to various release kinetic models such as zero order, first order, and Higuchi and Korsemeyer Peppas models in order to determine the release mechanism from the MSN [17-19].

Data interpretation

The results of *in-vitro* release studies were subjected to the following kinetic models: Zero order (% cumulative of drug release v/s time), First order (log cumulative per cent of drug remaining v/s time), Higuchi square root law (cumulative per cent of drug release v/s square root of time) and Korsemeyer Peppas model (log of cumulative per cent of drug release v/s log time)

The release data was plotted according to the following equation:

Zero order: $M = M0 - K0t$

First order: $\log C = \text{Log } C0 - Kt/2.303$

Higuchi square root law: $Q = Ktn$

Korsemeyer's Peppas model: $Mt/M\infty = Ktn$

Where M, C and Q are the amount of drug release at time t, M0 & C0 is the total amount of drug. K0, K & k are corresponding rate constants. In case of Korsemeyer's Peppas model, "Mt/M∞" is the fractional drug release at time, "K" is the rate constant and "n" is the release exponent. The value of "n" is calculated from Korsemeyer's Peppas equation. It is used to interpret different mechanisms of drug release.

Antimicrobial activity of clarithromycin loaded mesoporous silica nano particle

The disc diffusion method was used to analysis the antibacterial activity of clarithromycin loaded MSN by using gram-positive (*Staphylococcus aureus*) bacteria and gram negative (*Escherichia coli*) bacteria as test microorganisms.

In-vitro antimicrobial activity was measured by using muller hinton agar (MHA) obtained from Himedia. The Muller hinton agar plates were prepared and the plates were free to solidify for 5 min. The 0.1% inoculums suspension was swabbed uniformly, and after the inoculums was allowed to dry for 10 min. The 50 µl concentration of test sample (prepared MSN) were loaded on 0.5 cm sterile discs. The drug loaded disc was placed on the surface of the medium and after the compound was allowed to diffuse for 10 min. The prepared plates were kept for incubate at 37 °C for 24 hrs. After the end of incubation period, the inhibition zones were formed around the disc. The zone of inhibition in mm was measured by zonal scale [20, 21].

RESULTS

The synthesis of mesoporous silica nanoparticle using sol-gel method was confirmed by the formation of white colour formation after the addition of TEOS. The synthesis of MSNs is performed at low concentration of CTAB to make assembly of mesophase by interaction between the cationic surfactant and developing anionic oligomer orthosilic acid.

Charecterization of the mesoporous silica nanoparticle

Particle size analysis

The particle size of MSN was determined by Zeta-sizer (Malvern). The size of MSN was found to be 218 ± 8 nm (mean ± SD). The particle size analysis report of zeta sizer is shown in below in Fig. 2.

			Size (r.nm):	% Number	Width (r.nm):
Z-Average (r.nm):	218.8	Peak 1:	246.0	8.1	81.22
PdI:	0.491	Peak 2:	65.64	91.9	18.14
Intercept:	0.932	Peak 3:	0.000	0.0	0.000
Result quality :	Good				

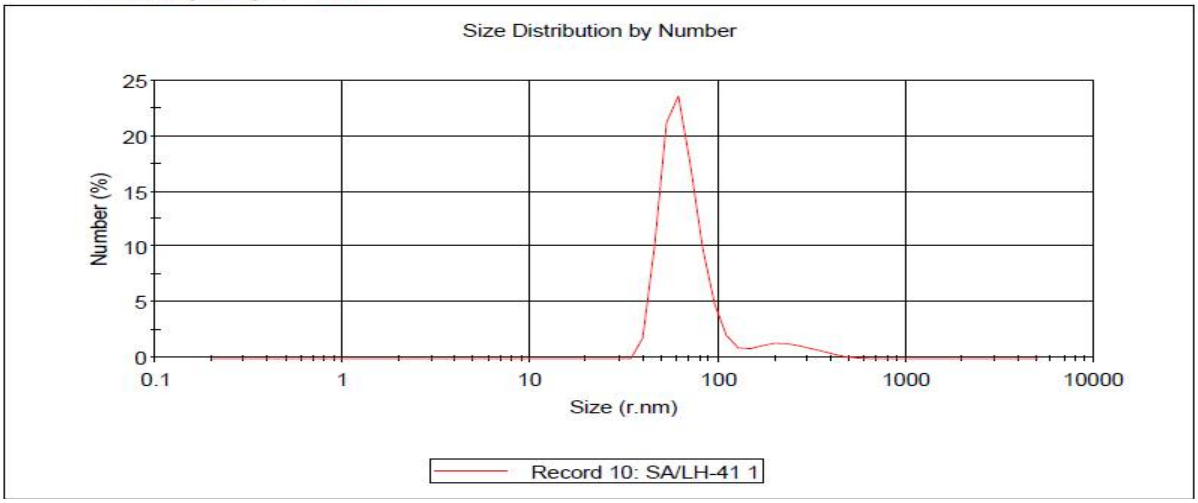


Fig. 2: Microscopic image of MSN by zeta potential

Scanning electron microscopy

Figure 3 and 4 exhibits the SEM showing surface morphology of clarithromycin-loaded MSN. SEM micrographs displayed that MSN formed are predominantly spherical and entire clarithromycin crystals was not seen.

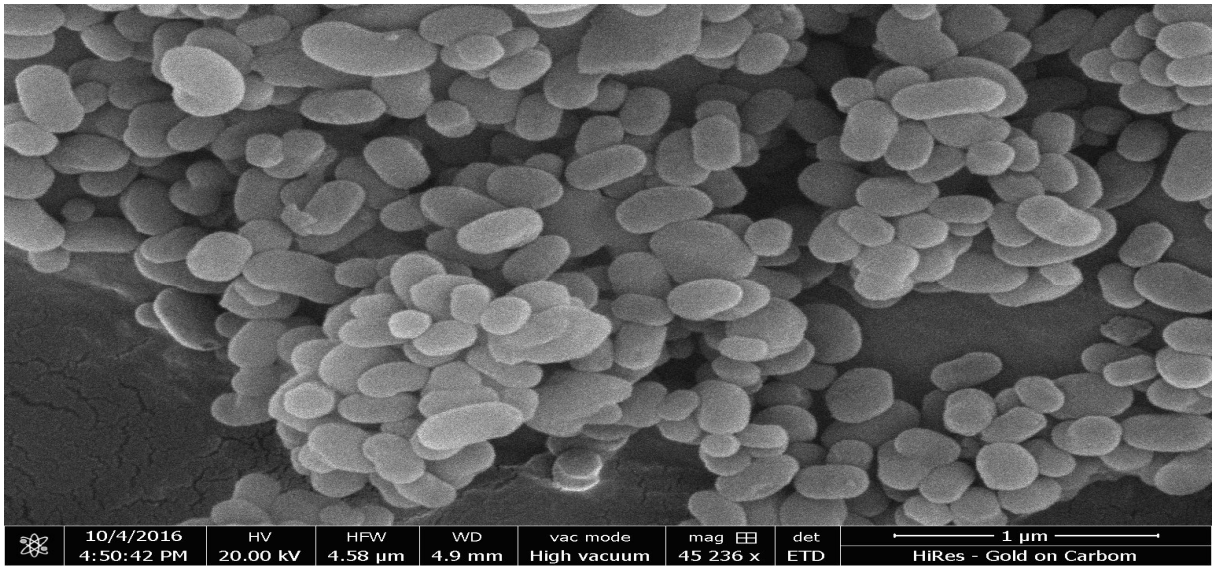


Fig. 3: Microscopic image of MSNs at 1µm

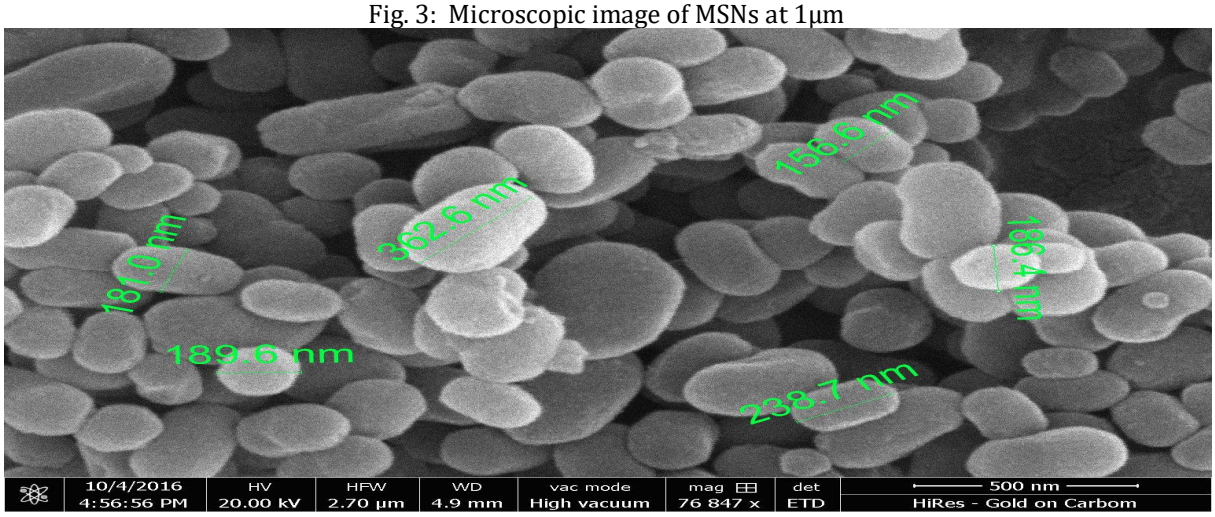


Fig. 4: Microscopic image of MSNs at 500nm

LA-XRD of mesoporous silica nanoparticle

The crystallography was study by using Low angle X-ray diffraction, Rigaku - Japan (Miniflex) at 2θ scanning range 0 to 5. The result of clarithromycin-loaded sample of MSNs was found, sharp peak on the 2.059^0 angle, Peak on 2.059^0 angles define the MCM-41 type of mesoporous silica nanoparticle (MSN). The result is shown in Fig. 5.

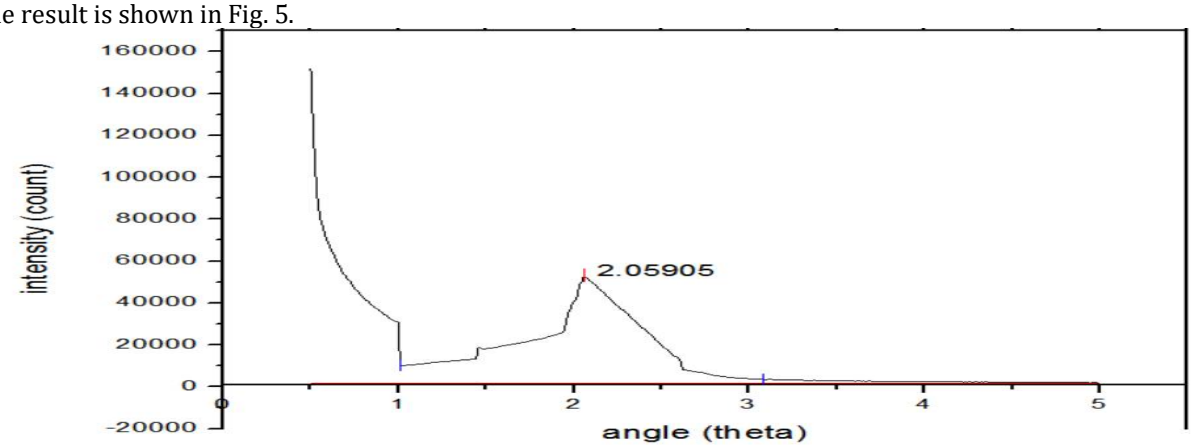


Fig. 5: LA XRD of mesoporous silica nanoparticle (MSN)

Fourier Transform-Infrared Spectroscopy:

FTIR analysis of clarithromycin-loaded MSN was carried out. The FTIR scanning process was performed and interpreted. The data are shown in the following Fig. 6, 7, table 1and 2. The peak of 1224.80 cm^{-1} represented the presence of Si-o-Si and peak 3213 cm^{-1} show presence of Si-OH group which are responsible for silica nanoparticle formation. Peak 1236.46 cm^{-1}, 3483.44 cm^{-1} the presence of Si-O-Si group, SiOH which show the silica nanoparticle and peak 1456.57 cm^{-1}show the presence of N-CH_3 group which is important functional group of clarithromycin. Ketone, O-C-O- streaming and Alkane stretching found at1691.57, 1172.72 and 2970.38 cm^{-1}. Following interpretation show the no interaction happened between silica nanoparticle and clarithromycin drug. The result is shown in Table 3 and Fig. 8.

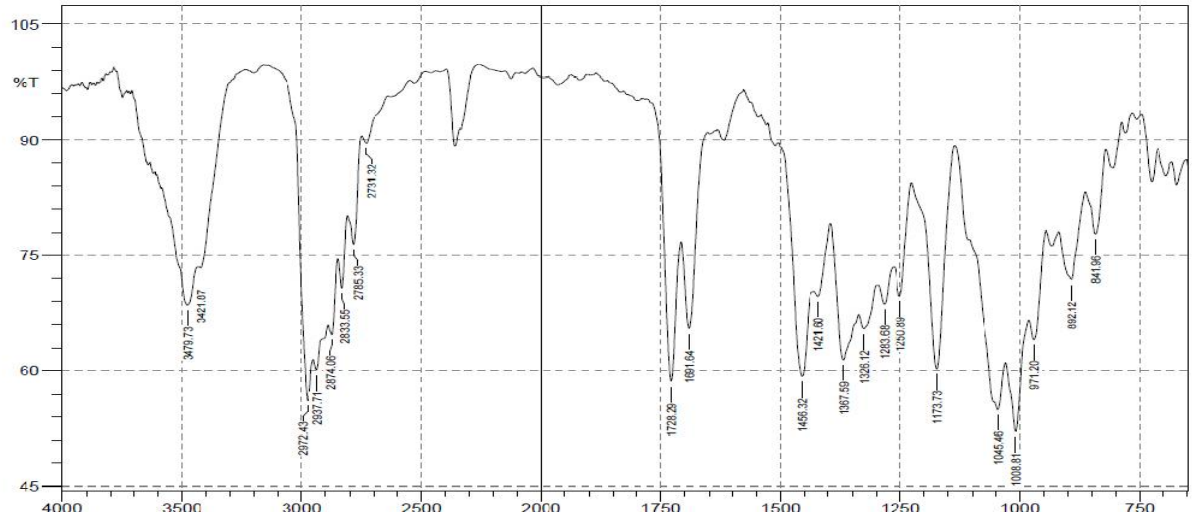


Fig. 6: FT-IR of clarithromycin

Table 1: Characteristic IR absorption bands of clarithromycin

Reported IR Absorption band, cm^{-1}	Sample IR absorption cm^{-1}	Inferences
1690	1691.64	Ketone carbonyl
1730	1728.29	Lactone carbonyl
1420	1421.60	N-CH_3
2780-3000	2972.43	Alkane stretching
3450	3479.73	H-Bond between OH group
1000-1200	1173.73	-C-O-C stretching
1340-1400	1367.5	CH_2 group

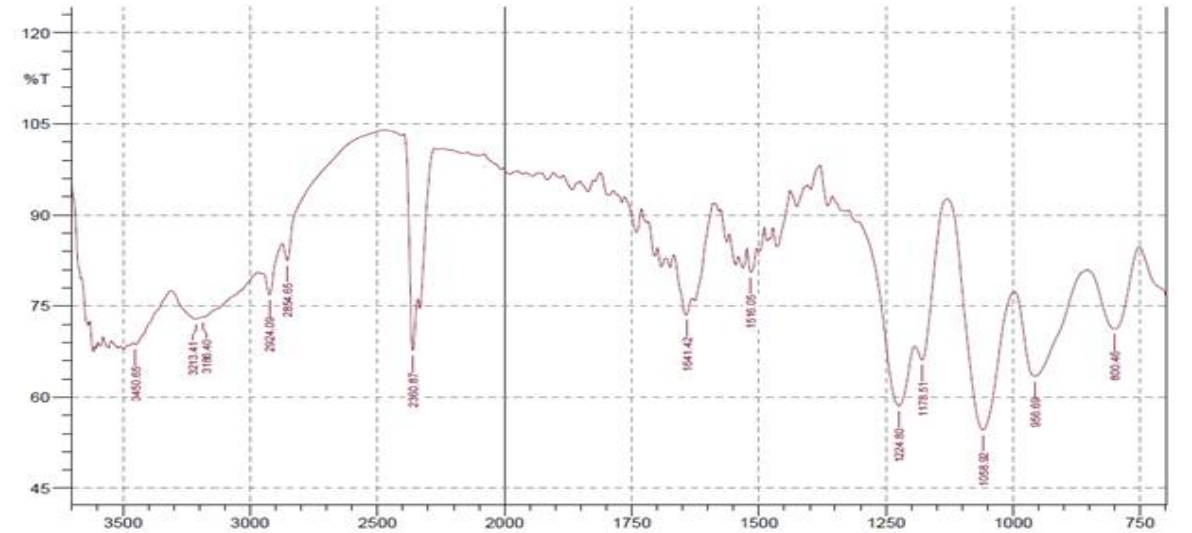


Fig. 7: FT-IR of mesoporous silica nanoparticle

Table 2: Characteristic IR absorption bands of mesoporous silica nanoparticle

Reported I.R. Absorption band cm^{-1}	Sample IR absorption cm^{-1}	INFERENCES
1200-1400	1224.80	Si-O-Si group
3200-3400	3213	Si-OH

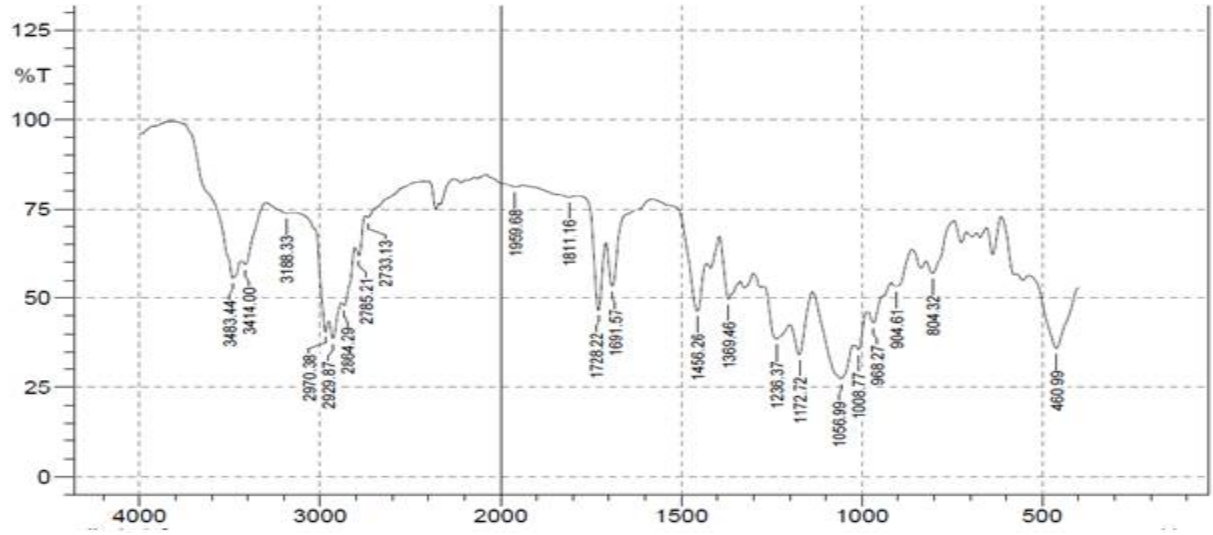


Fig. 8: FT-IR of drug loaded mesoporous silica nanoparticle

Table 3: Characteristic IR absorption bands of mesoporous silica nanoparticle

I.R.Absorption band cm^{-1} Reported	Sample IR absorption cm^{-1}	Inferences
1200-1400	1236.46	Si-O-Si
3200-3400	3483.44	SiOH
1420	1456.57	$N\text{-}CH_3$
1000-1200	1172.72	O-C-O stretching
1690	1691.57	Ketone group
2780-5000	2970.38	Alkane stretching

Loading efficiency:

The loading efficiency of clarithromycin-loaded MSN was calculated in PBS (pH 7.4) at 666.0 nm using UV/Visible spectrophotometer. The drug loading efficiency was found to be 96 %.

***In-vitro* release studies:**

In-vitro drug release study of clarithromycin-loaded MSN was performed and determined; using PBS pH 7.4 and HCl buffer pH 1.2 over a period of 24 hrs. The release of drug (clarithromycin) from MSN was checked in PBS 7.4 and HCl buffer1.2pH. The release rate of drug was found in pH 7.4, 98.46% and 89.24 % respectively. The correlation coefficient values of different release kinetic models were compared for PBS 7.4 and HCl buffer 1.2. The data is presented in the following Table 4:

Table 4: Comparison of correlation values of different release kinetic models

Correlation coefficient		
Kinetic models	**PBS 7.4 pH**	**HCl buffer 1.2pH**
Zero order plot	0.5142	0.6535
First order plot	0.8542	0.7735
Higuchi plot	**0.7699**	**0.8737**
Korsemeyer Peppas model	0.3584	0.314

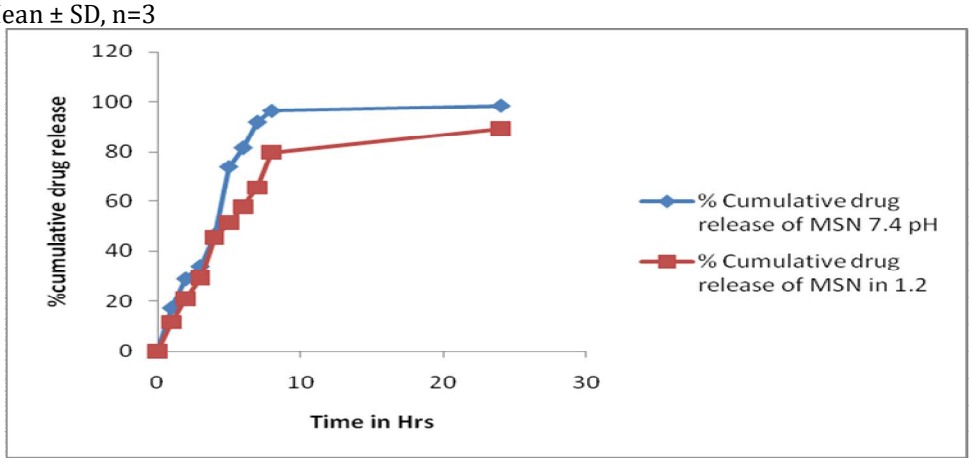
From the above data, it can be concluded that drug loaded MSN follow the Higuchi equation because its r^2 value are close to unity. This explains that the drug release mechanism follows Higuchi model, in which

the drug release occurs as a result of diffusion from the mesoporous silica nanoparticle. The results are shown in Table 5 and Figure 9:

Table 5: % Cumulative drug release

S.NO	Time	% Cumulative drug release of MSN 7.4 pH	% Cumulative drug release of MSN in 1.2
1	0	0	0
2	1	17.34±.14	11.62±.70
3	2	28.97±.90	20.95±.11
4	3	34.03±.37	29.4±.63
5	4	46.56±.30	45.32±.41
6	5	73.98±.61	51.54±.57
7	6	81.71±.43	57.78±.80
8	7	91.94±.71	65.44±.17
9	8	96.43±.24	79.86±.20
10	24	98.46±.12	89.24±.43

Mean ± SD, n=3



Mean ± SD, n=3

Fig. 9: % Cumulative drug release

Data treatment:

To determine the mechanism of the drug release from the drug loaded formulations, the *in-vitro* release data were treated using the following mathematical models. The model based fitted graphs are shown in Figure 10, 11, 12 and 13. The release data were plotted according to the following equations:

- Zero order : $M = M_0 - K_0 t$
- First order : $\text{Log } C = \text{Log } C_0 - Kt/2.303$
- Higuchi square root law: $Q = Kt^n$
- KorsemeyerPeppas model: $M_t/M_\infty = kt^n$

Fig. 10: Zero order release graph of Clarithromycin/Mesoporous silica nanoparticle in PBS7.4 pH and HCl buffer 1.2 Ph

Fig. 11: First order release graph Clarithromycin/Mesoporous silica nanoparticle in PBS7.4 pH and HCl buffer 1.2 pH

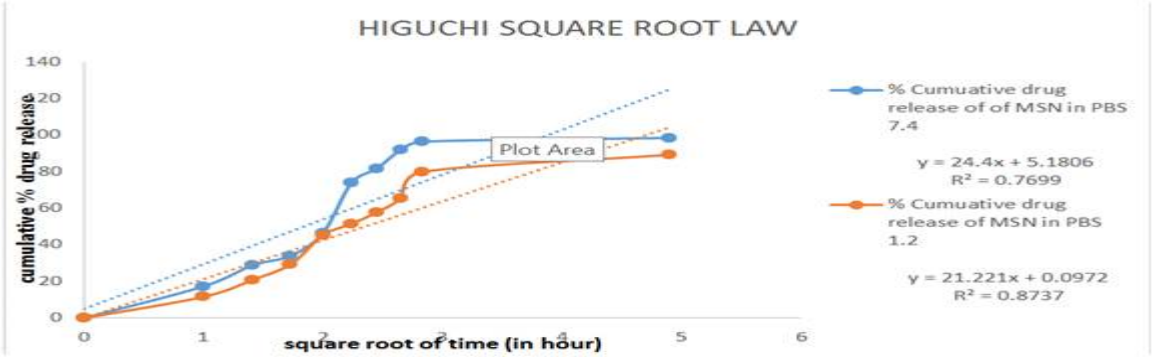


Fig. 12: Higuchi diffusion release graph Clarithromycin/Mesoporous silica nanoparticle in PBS7.4 pH and HCl buffer 1.2 pH

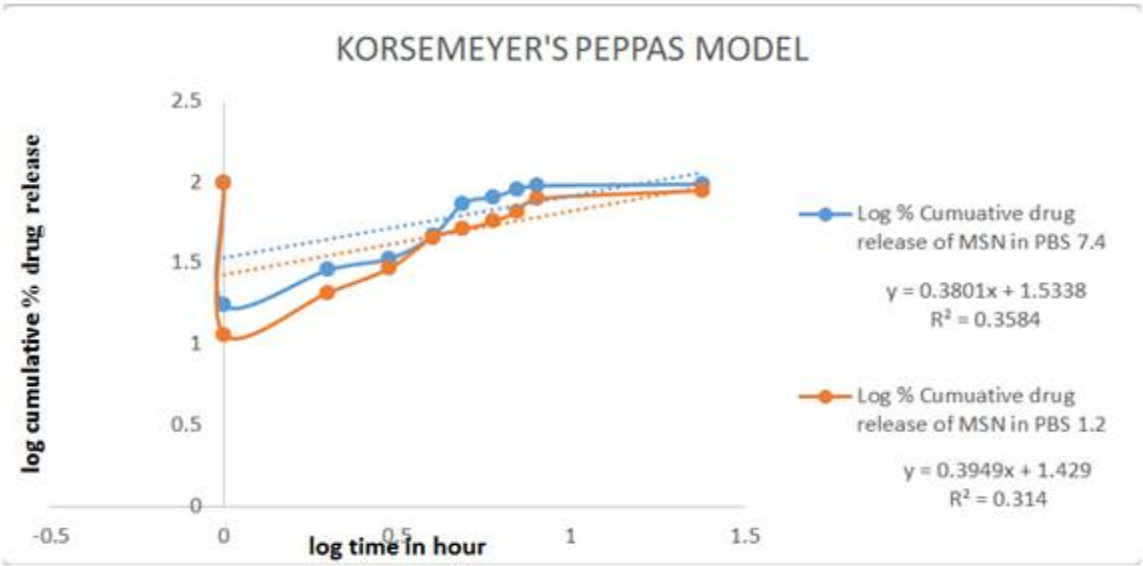


Fig. 13: Korsemeyer's Peppas release graph of Clarithromycin/Mesoporous silica nanoparticle in PBS7.4 pH and HCl buffer 1.2 pH

Antimicrobial activity of clarithromycin loaded mesoporous silica nano particle

Antimicrobial activity of clarithromycin loaded mesoporous silica nanoparticle was performed against bacteria *S.aureus, S.mutans, E.coli* and *P.vulgais*. The zone of bacterial inhibition was found to be much better in mesoporous silica nanoparticles when compared with the standard formulation. In bacteria *E.coli* zone of inhibition showed the good results.

The antimicrobial results are shown in below Table 6, 7 and Fig. 14 and 15:

Zone of inhibition

Table 6: zone of inhibition

S.No.	Bacteria	Zone of inhibition (mm)	
		Standard drug sample	Drug loaded mesoporous silica nanoparticle
1	*S.aureus*	12	21
2	*S.mutans*	23	24
3	*E.coli*	10	15
4	*P.vulgais*	24	25

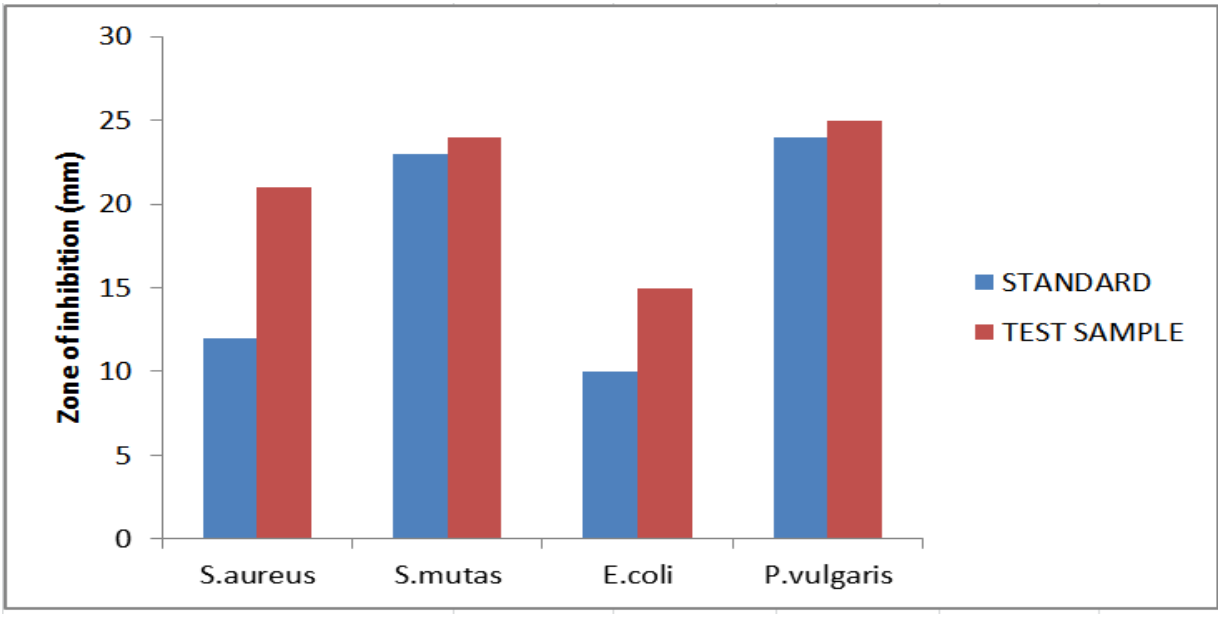


Fig. 14: zone of inhibition

Minimum effective concentration study

Table 7: minimum effective concentrations

S.No.	Bacteria	MIC (µ/ml)	
		Standard drug sample	Drug loaded mesoporous silica nanoparticle
1	*S.aureus*	0.113	0.16
2	*S.mutans*	0115	0.121
3	*E.coli*	0.245	0.247
4	*P.vulgais*	0.348	0.289

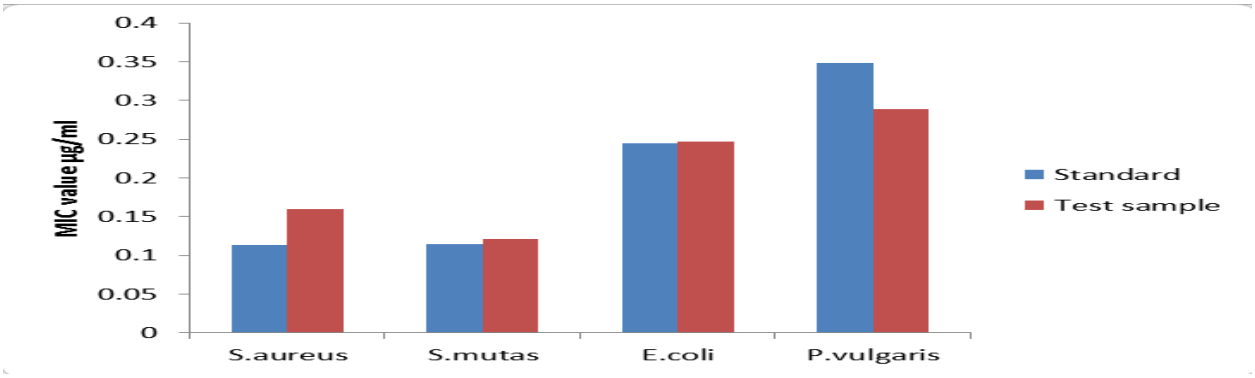


Fig. 15: minimum effective concentrations

DISCUSSION

In summary mesoporous silica nanoparticle (MSN) with the controlled particle size (198nm) were prepared by using the soft-gel method [21-23]. The particle size was analyzed by using zeta sizer and scanning electron microscope as shown in fig. 3 and 4. The average particle size was founds to be diameter 187.67 and length 300.65. The MSN was containing TEOS (Tetraorthosilicate), TEOS was used as silica precursor and CTAB (cetyl triammonium bromide) is used as the surfactant [24]. Clarithromycin was loaded in a ratio of 1: 2where one part of system and 2 part of drug was taken. It was treated by NaOH in the presence of CTAB in suitable concentration, as the solid nano-spheres were successfully converted into homogeneous hollow spheres obtained. The MSN showed high loading capacity in which 96% of drug was found to be entrapped in the nanoparticle. The LA-Xrd analysis report of the prepared MSN indicated the peak of MCM-41type silica nanoparticle on 2.059o between the ranges of 1o to 5o of 2Θ. The intense peak at $\theta=2059^{0}$ indicates the MSN peak which represents the crystalline nature, owing to the smaller particle size and incomplete inner structure of the nanoparticles. The FTIR spectra of the MSN indicated the peak at 1224.80 cm^{-1} and that represented the Si-O-Si group, which is responsible for formation of the MSN. The presence of these wide peaks confirms the loading of drug into the MSN, where oxygen atom plays the role of a bridge between two silicon sites. The % cumulative drug release study of the clarithromycin-loaded MSN was performed, using Phosphate buffer 7.4pH and acidic buffer 1.2pH. Clarithromycin from MSN were found to be released in sustained manner, approx. The drug release studies were performed for 24 hrs. The release rate of clarithromycin-loaded MSN was found to be 89.24%.

The antimicrobial activity of clarithromycin-loaded MSN was performed against bacteria *S.aureus, S.mutans,E.coli* and *P.vulgais*. Zone of inhibition was found to be much better in MSN when compared with the standard marketed formulation. In bacteria E.coli zone of inhibition showed the good results [25-27]. All above discuss all properties of MSN strongly advocate its good feature for topical delivery of antibacterial drug.

CONCLUSION

To summarize, in this study, we have successfully formulated of clarithromycin-loaded MSN for the treatment of skin diseases. The use of cationic surfactant such as Cetyl Trimethyl Ammonium Bromide (CTAB) is critical to the formation of hollow MSN structure. The antibacterial activity of MSN and clarithromycin-loaded MSN was carried out by using standard clarithromycin. The antibacterial studies results suggest that the MSN dosage form can be used as potential drug dosage form to treat various skin diseases.

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AUTHORS' CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTEREST

No conflicts of interest related with this work.

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