

FORMULATION AND CHARACTERIZATION OF MESOPOROUS SILICA NANOPARTICLES CONTAINING BACLOFEN FOR NEUROPATHIC PAIN MANAGEMENT

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ABSTRACT

Neuropathic pain remains a challenging condition to treat due to limited efficacy and adverse effects of conventional therapies. Baclofen, a GABA-B receptor agonist, is effective in reducing spasticity and neuropathic pain but suffers from poor bioavailability and rapid clearance. In this study, mesoporous silica nanoparticles (MSNs) were formulated via a sol-gel method using varying concentrations of CTAB and TEOS, followed by baclofen loading through solvent immersion. The nanoparticles were characterized for particle size, polydispersity index (PDI), zeta potential, drug loading, and surface morphology. Results demonstrated particle sizes ranging from 251 to 736 nm, with PDI values <0.25, indicating uniformity. Drug loading efficiency ranged between 83.2–90.6%, with higher CTAB concentrations yielding smaller, more uniform particles and improved loading. In vitro release studies revealed sustained drug release, with smaller particles (S3, 251 nm) achieving 89.5% release at 24 h, while larger porous particles (S4, 736 nm) exhibited rapid release (100.8% at 16 h). Overall, formulation S3 emerged as optimal, combining high drug loading, uniform particle distribution, and controlled release. These findings suggest that baclofen-loaded MSNs may serve as a promising nanocarrier system for sustained neuropathic pain management.

KEYWORDS: Baclofen; Neuropathic pain; Mesoporous silica nanoparticles; Sol-gel method; Drug delivery; Controlled release.

INTRODUCTION

Neuropathic pain is a chronic condition resulting from injury or dysfunction of the somatosensory nervous system, often characterized by hyperalgesia and allodynia, and remains difficult to manage with conventional therapies.^[1] Baclofen, a selective γ -aminobutyric acid type B (GABA-B) receptor agonist, has shown efficacy in reducing spasticity and neuropathic pain, but its clinical use is limited by poor bioavailability and rapid clearance.^[2] To overcome these limitations, nanotechnology-based drug delivery systems have been explored to enhance therapeutic efficacy and sustain release.^[3]

Among various nanocarriers, mesoporous silica nanoparticles (MSNs) have emerged as promising platforms due to their high surface area, tunable pore size, chemical stability, and ease of functionalization.^[4] The sol-gel synthesis of MSNs using surfactants such as cetyltrimethylammonium bromide (CTAB) and precursors like tetraethyl orthosilicate (TEOS) allows precise control over particle size, morphology, and

porosity.^[5] These physicochemical properties directly influence drug loading efficiency, release kinetics, and biocompatibility, making MSNs suitable for central nervous system drug delivery.^[6]

Recent advances in MSN design have demonstrated their ability to encapsulate poorly soluble drugs, improve pharmacokinetics, and provide controlled release profiles, thereby reducing systemic toxicity and enhancing patient compliance.^[7] In this context, the formulation and characterization of baclofen-loaded MSNs may offer a novel therapeutic approach for sustained neuropathic pain management.

MATERIAL AND METHODS

Baclofen (>98% purity) was purchased from Yarrow Pharmaceuticals; all other reagents and chemicals were of analytical grade.

Preliminary studies

Organoleptic features, qualitative solubility, melting point, loss on drying, partition coefficient, infra-red

spectral analysis and compatibility studies (spectral) were carried out for the purchased baclofen.^[8,9]

Calibration Curve

The calibration curve of baclofen was constructed by measuring the absorbance of using different concentrations of the drug using methanol at 240 nm. The stock solution was freshly prepared by dissolving 10 mg of baclofen in 10 ml of methanol in a 1 ml volumetric flask and then made up the solution upto the mark using methanol for obtaining the solution of strength 1000 µg/mL (stock I). 1 ml of this solution was diluted to 10 ml with phosphate buffer pH 6.8 to obtain a solution of strength 100 µg/mL (stock II). From this solution with draw 1, 2, 3, 4, 5 & 6 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using phosphate buffer pH 6.8 to get the solutions of 10, 20, 30, 40, 50 & 60 µg/ml. The absorbance of each solution was determined at 240 nm using UV

spectrophotometer. A standard curve was constructed against absorbance and concentration.

Formulation of Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles were prepared by sol-gel method. Briefly, varying molar concentrations of CTAB and TEOS were used while molar ratio of ethanol, water, and ammonium hydroxide was kept constant.^[10] The composition is shown in Table 1. Initially ethanol, water and ammonia solution (NH₄OH) were mixed together to form silica sol. Then CTAB was added with constant stirring for 15 min. Finally, TEOS was added drop by drop under continuous stirring for 2 h at room temperature. The start of the reaction was confirmed by immediate formation of opaque solution. The white powder precipitated was filtered and washed with deionized water. The particles were calcined at 550°C for 3 h to remove the surfactant.^[11]

Table 1: Composition of MSNs.

Code	TEOS (mL)	CTAB (g)	Ammonium hydroxide (mL)	Ethanol (mL)	Water (mL)
S1	1	0.1	1	80	20
S2	1	0.2	1	80	20
S3	1	0.3	1	80	20
S4	0.5	0.1	1	80	20
S5	0.5	0.2	1	80	20
S6	0.5	0.3	1	80	20

Loading of Baclofen on to MSNs

Baclofen was loaded onto mesoporous nanoparticles by solvent immersion method. In this method n-hexane; a nonpolar solvent was used for drug loading because polar solvent may compete for drug molecule for adsorption site. The blank MSNs and baclofen were dispersed in 20 ml hexane. The dispersion was stirred for 4 h, centrifuged and the supernatant was removed. Finally mesoporous silica nanoparticles were collected and dried at room temperature for 24 h.^[12]

Evaluation of MSNs^[13]

Determination of particle size and zeta potential

The particle size and zeta potential of each formulation batch was determined using a laser diffraction particle size analyzer.

Surface morphology

The surface morphology of the prepared nanoparticles was studied using scanning electron microscopy by gold coating of the lyophilized nanoparticle.

Determination of drug loading

Amount of baclofen loaded on mesoporous particles were determined by suspending particles equivalent to 10 mg of baclofen in 100 ml of phosphate buffer (pH 5); stirred continuously on magnetic stirring for 24 h at room temperature. After stirring; the solution was filtered through cellulose acetate membrane (0.22 µm). The

amount of drug in the filtrate was analyzed using UV spectrophotometer at 240 nm.^[14]

In vitro release study

USP type II dissolution apparatus (paddle type) was performed at 50 rpm in 900 mL 0.1N HCl, maintained at 37 ± 0.5°C. 50 mg of nanoparticles were placed in the dissolution vessel for studying the rate and extent and dissolution. 5 mL of the sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding equal volume of fresh dissolution medium. The absorption of the withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve¹⁵. The percentage of drug released at various time intervals was calculated and plotted against time.

RESULTS AND DISCUSSION

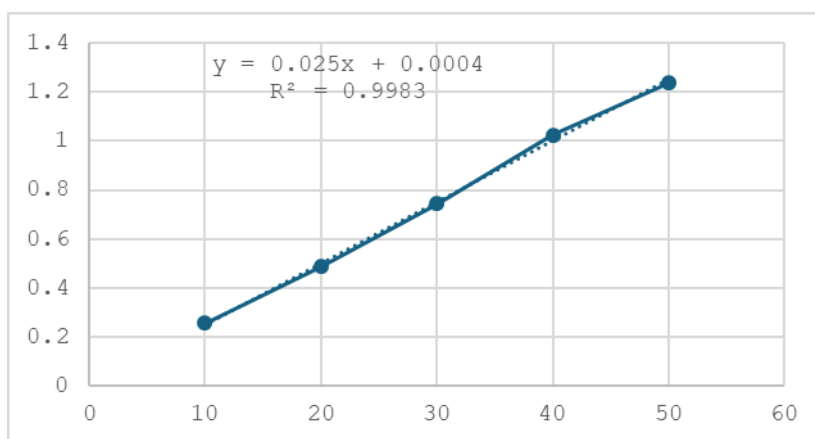
Preliminary Studies

The preliminary preformulation studies are an aid to have the required information of the drug to make it sure that the drug is pure as well as to determine the utility of drug in the type of dosage form that is being developed. The result of the organoleptic, solubility, melting point and partition coefficient studies are presented in table 2.

Table 2: Observations of the preliminary studies of baclofen.

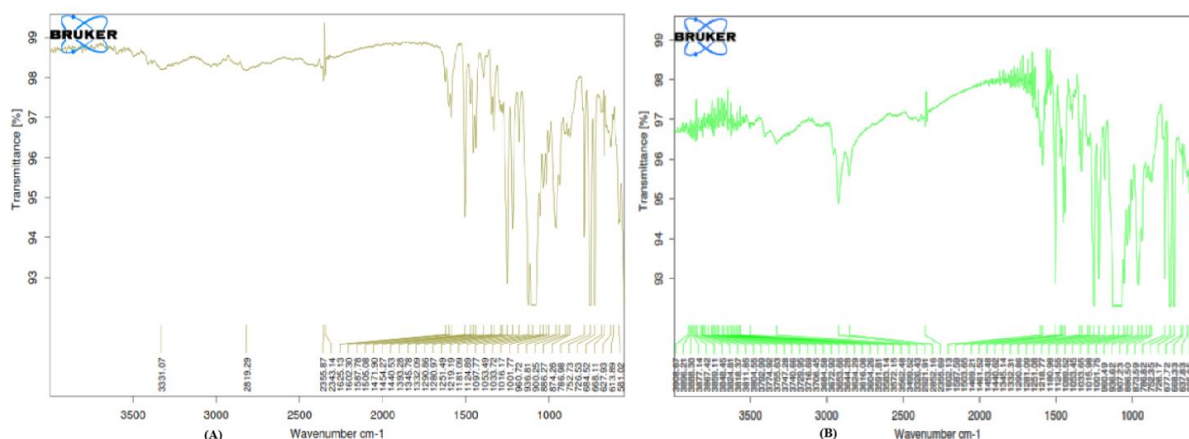
Test	Observation
Color	White
Odor	Odorless
Appearance	Crystalline powder
Melting point	206-208°C
Partition coefficient	3.49
Loss on drying	0.17%w/w
Solubility	Water, methanol, ethanol, acetone

Calibration curve of baclofen was determined by plotting absorbance versus concentration ($\mu\text{g/ml}$) at 240 nm (Figure 1).

**Figure 1: Calibration curve of baclofen by UV spectrophotometry.**

FT-IR spectrum of the sample of baclofen was obtained and examined for the presence of characteristic peaks and matched with that of the reference spectra in databases for confirmation of the identity of the drug. On comparison of the FTIR spectra of the drug and the

mixture it was observed that no peak was deleted and only the intensities of the existing peaks changed which might be due to the coupling of absorption frequencies (Figure 2). This provides evidence of compatibility between the drug and the matrix forming polymers.

**Figure 2: Infrared spectrum of (A) Baclofen (B) Baclofen and excipient mixture.**

Evaluation of MSNs

The MSNs were evaluated for particle size, polydispersity index (PDI), zeta potential, drug loading percentage and surface morphology.

Particle size, polydispersity index and zeta potential

The particle size of the MSNs ranged from 251 to 736 nm with a PDI ranging from 0.218 to 0.141. The zeta potential of the produced MSNs was found to be in the range of -17.1 to -21.4 mV for the various formulations (Table 3).

Drug loading

The drug loading was achieved by surface adsorption method and ranged from 83.2 to 90.6 % across various formulated MSNs (Table 3).

Table 3: P Particle size, PDI and zeta potential of MSNs.

Code	Particle Size (nm)	PDI	Zeta Potential (mV)	Drug loading (%)
S1	521	0.157	-17.1	87.9
S2	378	0.213	-18.3	90.1
S3	251	0.141	-21.4	90.6
S4	736	0.218	-19.3	83.2
S5	544	0.171	-19.7	84.5
S6	397	0.156	-20.6	85.7

Surface Morphology

The surface morphology of the MSNs was visualized using scanning electron microscopy. The particles are irregular to quasi-spherical, not perfectly round, implying non-uniform growth kinetics. The measured sizes (170–395 nm) confirm nanometer-scale

morphology, consistent with moderate polydispersity. Such shapes often result from precipitation or sol–gel processes, where growth is diffusion-controlled rather than template-directed. The surface looks granular and porous, suggesting high surface area beneficial for catalytic or adsorption applications (Figure 3).

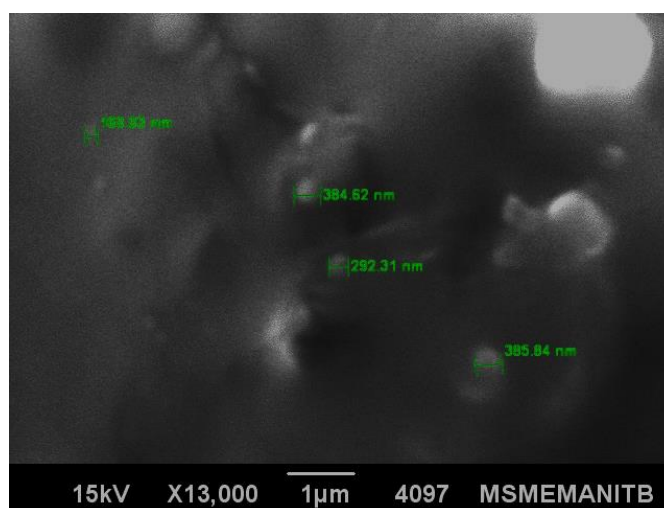


Figure 3: SEM pictograph of S3.

The sol-gel formulations prepared with varying concentrations of TEOS and CTAB demonstrated clear differences in particle size, polydispersity index (PDI), drug loading, and zeta potential. The data reveal that increasing CTAB concentration consistently reduced particle size, with S1 (0.1 g CTAB) showing the largest particles (521 nm) and S3 (0.3 g CTAB) yielding the smallest (251 nm). This reduction in size is attributed to the surfactant's role in stabilizing nuclei and preventing uncontrolled growth. The PDI values across all formulations remained within acceptable limits (<0.25), indicating relatively uniform particle populations, with the lowest PDI observed in S3 (0.141), confirming that higher CTAB concentrations promote better size homogeneity. Drug loading efficiency was highest in smaller, more uniform particles (S2 and S3, >90%), likely due to increased surface area and pore volume, whereas larger particles (S4, 736 nm) exhibited reduced loading (83.2%). Zeta potential values ranged between -17.1 and -21.4 mV, with more negative values observed at higher CTAB concentrations, suggesting improved

electrostatic stabilization. However, since the values remain below the ± 30 mV threshold, long-term colloidal stability may require additional surface modification. Overall, S3 (TEOS 1 mL, CTAB 0.3 g) emerged as the optimal formulation, combining the smallest particle size, lowest PDI, highest drug loading, and most negative zeta potential, thereby offering the best balance of physicochemical properties for drug delivery applications.

In vitro drug release

Formulations with higher CTAB concentrations (S3, S6) and lower particle sizes exhibited faster drug release compared to their counterparts. For example, S3 (251 nm, PDI 0.141) reached 89.5% release at 24 h, while S1 (521 nm, PDI 0.157) released only 87.4%. This supports the principle that smaller, more uniform particles provide greater surface area and shorter diffusion pathways, enhancing release kinetics. Similarly, S6 (397 nm, -20.6 mV) achieved 98.9% release, outperforming S5 (544 nm, -19.7 mV) at 96.3%.

The TEOS concentration also influenced release. Lower TEOS (0.5 mL, S4-S6) produced larger but more porous particles, leading to faster release profiles. S4 (736 nm, 83.2% drug loading) showed the highest release (100.8% at 16 h), likely due to weaker matrix density and higher porosity, which facilitated diffusion. In contrast, higher TEOS (1 mL, S1-S3) yielded denser matrices with slower release, though still achieving 87-89% at 24 h (Figure 4).

Drug loading efficiency also played a role showing that formulations with higher loading (S2, S3) maintained sustained release, while lower-loading samples (S4, S5) released more rapidly, suggesting that drug distribution within the matrix affects release kinetics.

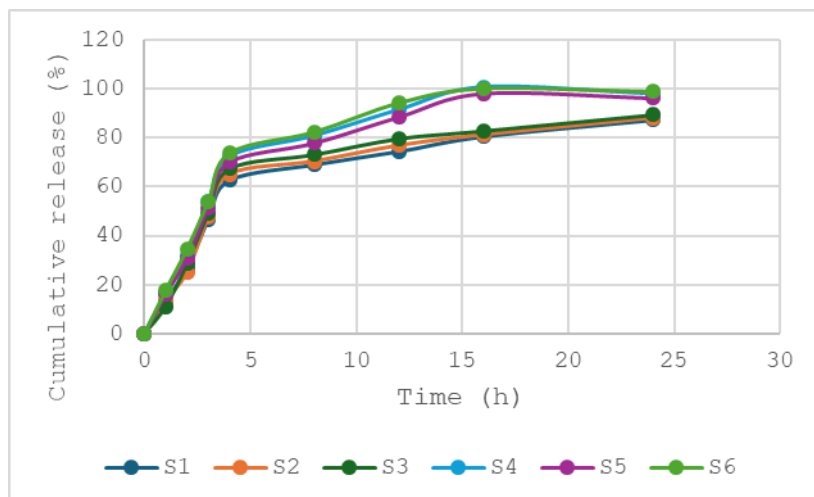


Figure 4: Release profile curve of baclofen from MSNs.

The data indicate that CTAB concentration is the dominant factor controlling particle size, uniformity, and release rate, while TEOS concentration modulates matrix density and porosity. Among the formulations, S3 offers the best balance of small particle size, high drug loading, uniformity, and controlled release.

CONCLUSION

The present study successfully formulated and characterized baclofen-loaded mesoporous silica nanoparticles using a sol-gel approach. Variation in CTAB and TEOS concentrations significantly influenced particle size, drug loading, and release kinetics. Smaller, uniform particles demonstrated enhanced drug loading and sustained release, while larger porous particles facilitated rapid release. Among the tested formulations, S3 (TEOS 1 mL, CTAB 0.3 g) exhibited the most favorable physicochemical properties, including smallest particle size, lowest PDI, highest drug loading, and controlled release profile. These results highlight the potential of MSNs as an effective nanocarrier system for improving baclofen delivery in neuropathic pain management, offering enhanced therapeutic efficacy and patient compliance. Future studies should focus on in vivo evaluation and surface functionalization to improve long-term stability and targeted delivery.

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