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**ORIGINAL ARTICLE**

# Controlled Release of Amoxicillin from Bis(2-hydroxyethyl)amine Functionalized SBA-15 as a Mesoporous Sieve Carrier

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**KEYWORDS**

Bis (2- hydroxy ethyl) amine functionalized mesoporous SBA-15; Amoxicillin; Controlled release; Drug delivery

**ABSTRACT:** In this study, Bis (2-hydroxyethyl)amine functionalized mesoporous SBA-15 was synthesized for utilization in amoxicillin drug-delivery. Amoxicillin could absorb on the prepared functionalized SBA-15. A solution of amoxicillin in a suitable solvent was used for this purpose. Amoxicillin molecules release from the matrix into a simulated body fluid (SBF) solution, and phosphate buffers were studied. UV-Vis spectrophotometric method was chosen for amoxicillin determination. Thermogravimetric analysis (TGA), scanning electron microscopy (SEM), nitrogen adsorption–desorption, and powder X-ray diffraction (XRD) technique were applied for characterization of the synthesized materials. The best loading of amoxicillin was done at pH 8.5 after stirring for 30 minutes. The results showed that, at lower pH, releasing of the drug was done faster than it at higher pH. Also, the average release rate of amoxicillin in the body fluid samples that were simulated was about 7 µg $h^{-1}$. A highly slow release pattern was observed. The proposed material can be used for enhancing the medical impact of amoxicillin and carrying amoxicillin.

## INTRODUCTION

Applications of nanomedicines in drug delivery systems are growing fast. For this purpose, a variety of materials designs have been introduced. Most of them are polymers, liposomes, nanoparticles, and organic and inorganic mesoporous materials. Among them, inorganic-mesoporous silicate materials have found a special place because of their properties such as remarkable biocompatibility, low cytotoxicity, modification ability, especially for organic functionalization. Ordered mesoporous silica like SBA-15 [4] and MCM-41[1], LUS-1 [2, 3] have the potential for use in other fields including catalysis [5], preconcentration of metals [6, 7], dye removal [8, 9] and drug delivery [10-12]. However, some especial properties make them suitable for use in nanomedicines. For example, high pore volume and wide surface area allows the high amount of drug loaded; pore distribution with good ordered, helps the reproducibility and homogeneity on the stages of drug adsorption and release; and highly dense silanol groups allows chemical modification of the pore walls for having better control

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over release and loading of drug. Using a proper organic functionalization, the molecules' release can be controlled in an effective way. Also, the use of organic functional groups promotes attractive host-guest interaction, which slows down the drug release.

One work reported using MCM-41 for ibuprofen's controlled release [13–15], and SBA-15 for controlling release in different drugs [16-22]. Some other mesoporous materials had also provided the possibility of controlling the release model of the guest drug [23–28].

Amoxicillin (Figure 1) was discovered in 1958 and used as medication in 1972 [29, 30]. It is on the WHO's List of Essential Medicines [31]. It is one of the antibiotics that is mostly prescribed for the children [32]. Amoxicillin is from penicillins family originates from the fungi called Penicillium fungi. They are utilized for the treatment of bacteria-caused infections and eliminate them. Amoxicillin can fight bacteria and stops their growth of many bacteria through preventing them from forming cell walls. Bronchitis, tonsillitis, pneumonia, and gonorrhea, and the nose, ear, skin, urinary tract, or throat infections can be treated by Amoxicillin. Moreover, Amoxicillin is administered before operations, and dentists use it for preventing infections in the future [33]. According to the medical studies, systemic blood circulation distributes amoxicillin within the body, and just a small amount of the drug achieves the target organ. Furthermore, the drug is released in bursts, and its concentration through the blood varies during a period of time. But, controlled amoxicillin release at the desired rate has numerous advantages over common forms of dosage. In this system, the whole dose of the drug is administered at one time for a respective period of time in a controlled manner, which enhances the compliance of the patient. Also, the drug release rate is constant and its concentration in the blood always remains stable [34] that it improve its efficacy. Other advantages of controlled amoxicillin release are minimizing harmful side effects and protecting from rapid metabolization.

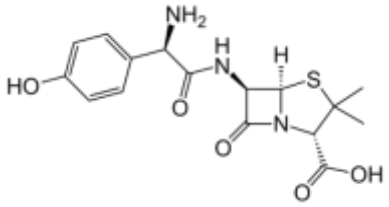



**Figure 1.** Molecular structure of Amoxicillin

This work studies amoxicillin adsorption and release profiles of Bis(2- hydroxyethyl) amine functionalized mesoporous SBA-15, and introduces the adjusted mesoporous SBA-15 as an amoxicillin delivery carrier.

## MATERIALS AND METHODS

### *Reagents*

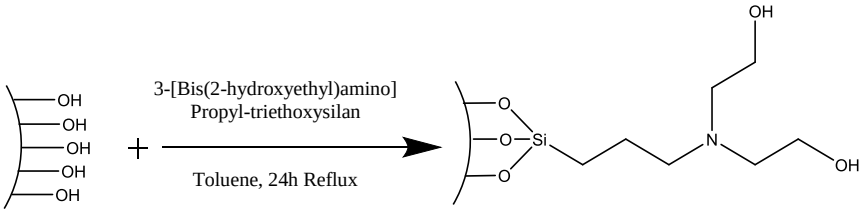
Analytical grade of reagents including poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol) (P123, Aldrich) serving as surfactant, tetraethyl orthosilicate (TEOS, Merck) as the source for silica, 3-[Bis(2-hydroxyethyl)amino]propyl-triethoxysilane solution (~%65 in ethanol, HPTES, Fluka) serving as amine compound were utilized in this work. 2M hydrochloric acid prepared from concentrate hydrochloric acid (Merck), and ethanol (Merck) were consumed in the form they were provided by the suppliers. Double distilled water (DDW) was used in the research. Amoxicillin powder was dissolved in DDW for preparing the amoxicillin stock solution. Then, this stock solution was diluted to prepare the desired concentration of amoxicillin solutions. The following chemicals were dissolved in distilled water for preparing the SBF (1000 mL): $NaHCO_3$ (0.350 g), NaCl (7.996 g), KCl (0.224 g), $MgCl_2.6H_2O$ (0.305 g), $K_2HPO_4.3H_2O$ (0.228 g), 1 M HCl (40 ml), $Na_2SO_4$ (0.071 g), $CaCl_2$ (0.278 g), $NH_2C(CH_2OH)_3$ (6.057 g). The used glassware were soaked in dilute nitric acid for about 12 hours and then washed three times with DDW before use.

***Apparatus***

BELSORP-miniII at -196 °C was applied for the analysis of $N_2$ sorption. SBA-15 was degassed for two hours at 300 °C, and AEF-SBA-15 was degassed for four hours at 100 °C. Brunauer-Emmett-Teller (BET) method was utilized in order to obtain total pore volume, Specific surface area, and pore diameter in the samples. Thus, BELSORP analysis software was used. Scanning Electron Microscopy (SEM) images by LEO 1455VP was used for studying the morphology of the pure AEF-SBA-15 and SBA-15. Thermogravimetric analysis (TGA) of pure AEF-SBA-15 and SBA-15 was performed on TA TGA Q50 in the temperature ranging from ambient temperature to 800 °C. 20 °C/min was used as the ramp rate. pH was controlled or adjusted by Metrohm pH-meter model 713. Varian UV/Vis spectrophotometer (Cary-100) was used for the detection of drug concentration in solutions.

***Synthesis of Bis (2- hydroxyethyl) amine functionalized mesoporous SBA-15***

The synthesis of the SBA-15 mesoporous silica structure was done using template method based on reference [35]. Also, for the modification of prepared material with amine groups, 3-[Bis(2-hydroxyethyl)amino]propyl-triethoxysilane was used. Where, 1 g of the SBA-15 was dispersed with ultrasonic irradiation in 35 mL dried toluene and 1 mL mentioned organosilane was added in a drop wise manner to the suspension, formerly, the mix was refluxed one night under $N_2$ atmosphere. After that, the amine modified SBA-15 filtered and rinsed with ethanol (Figure 2).




SBA-15

**Figure 2.** Modification of SBA-15 with 3-[Bis(2-hydroxyethyl)amino]propyl-triethoxysilane

***Loading and release study***

The loading of amoxicillin was achieved by soaking 0.1 g of the SBA-15 modified with 3-[Bis(2-hydroxyethyl)amino]propyl-triethoxysilane powder in 100 mL of saturated amoxicillin solution and mixed for 30 minutes at room temperature. The produced solid was filtered, washed, and then it was dried at ambient temperature. After drug loading, the sample was weighed about 50 mg and put into 50 mL simulated body fluid (SBF) or phosphate buffers at pH= 5, 7 and 8. The releasing of amoxicillin, at time intervals, was measure by UV-Vis spectrophotometer.

**RESULTS AND DISCUSSION**

***Characterization of Bis (2- hydroxyethyl) amine functionalized SBA-15***

The characteristics and morphology of the adsorbents were specified using SEM, low angle XRD, TGA, and $N_2$ absorption desorption isotherms (Figure 3) It is worth mentioning, the obtained analysis was studied by Hashemi et al. [36].

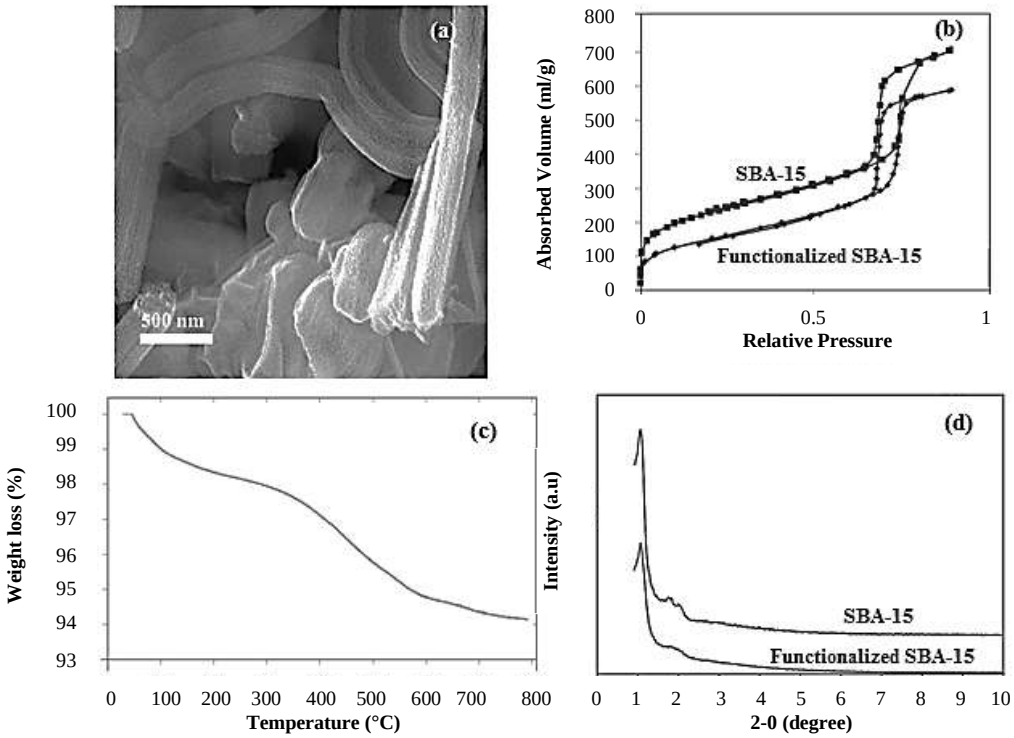



**Figure 3.** SEM image of Bis (2- hydroxyethyl) amine functionalized SBA-15, b) $N_2$ adsorption and desorption isotherms of SBA-15 and Bis (2-hydroxyethyl) amine functionalized SBA-15 measured at - 196 °C, c) TGA curve of Bis (2- hydroxyethyl) amine functionalized SBA-15, d) XRD patterns of SBA-15 and Bis (2- hydroxyethyl) amine functionalized SBA-15.

The scanning electron microscopy image of the modified mesoporous structure showed lengthy rod-like morphology and was showed in Figure 3a and it was clear, the length and width of channels are approximately 1 μm and 100 nm. These results indicated that the SBA-15 structure was maintained after surface modification.

Figure 3b demonstrates the sorption isotherms of SBA-15 before and after functionalization. It is observed that desorption and adsorption branches of functionalized and pure materials are similar, which can confirm the complete accessibility of the mesopores after functionalization. This reveals that no pore blocking takes place, which makes the possibility of facile access for guest species or chemical reagents. Table 1 gives total pore volumes, the specific surface areas, and mean pore diameters. No excessive water was consumed in the current work, and then it can be concluded that functionalization was carried out on silanol capping methodology and a small reduction of pore diameter of Bis (2- hydroxyethyl) amine functionalized SBA-15 rather than SBA-15 possibly show this method of functionalization.

**Table 1.** Specific surface area ($S_{BET}$), total pore volume ($V_p$), and pore diameter (D) for SBA-15 and Bis (2- hydroxyethyl) amine functionalized SBA-15 gotten by BET method

| | $S_{BET}(m^2.g^{-1})$ | $V_p(cm^3.g^{-1})$ | D(nm) |
|---|---|---|---|
| **SBA-15** | 790 | 1.2862 | 7.06 |
| **Bis (2-hydroxyethyl)amine functionalized SBA-15** | 520 | 0.9104 | 7.02 |

The TGA curve of Bis(2-hydroxyethyl) amine functionalized SBA-15 is presented in Figure 3c. Four zones can be observed in TGA curve: 1) up to 130 °C weight loss points out elimination of physically adsorbed water, 2) minor loss of weight between 130-250 °C indicates organic content of HPTES that is stable thermally, 3) major loss of weight (~%3.5) between 250 - 600 °C is due to elimination of organic content of HPTES, 4) small

loss of weight between 600 - 800 °C, is because of the dehydroxylation of silicate networks or removal of residual ethoxy groups.

Figure 3d indicates the low angle XRD patterns of Bis (2-hydroxyethyl) amine functionalized SBA-15 and SBA-15. There is a single intensive reflection at 2θ angle around 1° for the samples as observed in the case for typical SBA-15 materials and the (100) reflection is usually assigned to the long-range periodic. For the SBA-15 material, two additional peaks of higher ordering (110) and (200) reflections can also be seen that is related to a two-dimensional hexagonal (p6mm) structure. Nevertheless, the fact that peak (100) intensity reduces following immobilizations confirms that the coupling agents reduce the peak intensity of diffraction. This is maybe because of the different scattering contrast of the walls and the pores, and to the unstable covering of organic groups on the nano channels.

***Assay of the loading of the Amoxicillin on Bis (2-hydroxyethyl) amine functionalized SBA-15***

This work introduces a method that Bis (2-hydroxyethyl)amine functionalized SBA-15 carries amoxicillin. This can be based on an interaction between amoxicillin and the modified SBA-15 through hydrogen bonding between the silanol groups of the SBA-15 and the functional group amine of amoxicillin. Also, the carboxylic group in amoxicillin interacts with the silanol groups and amino groups of the functionalized SBA-15, allowing the drug to be held within the pores of modified SBA-15 and be released in the body.

The loading of amoxicillin on functionalized SBA-15 was achieved by soaking of 10 mg of the SBA-15 modified with 3-[Bis(2-hydroxyethyl)amino]propyl-triethoxysilane in 20 mL of 3 mg $L^{-1}$ amoxicillin solution and stirred for 30 minutes at ambient temperature. The amount of amoxicillin was obtained by spectrophotometry method. The results revealed that the in all solutions, the concentration of amoxicillin decreases after contact with modified SBA-15, and it can confirm that amoxicillin is integrated into the SBA-15 molecular sieves.

In addition, sorption isotherms before and after loading of amoxicillin on Bis (2- hydroxyethyl) amine functionalized SBA-15 were compared. The specific surface areas, total pore volumes, and mean pore diameters of loaded-AEF-SBA-15 were 381($m^2$ $g^{-1}$), 0.71 ($cm^3$ $g^{-1}$), and 6.1 (nm), respectively. Decrease of these parameters for functionalized SBA-15 loaded with amoxicillin rather than functionalized SBA-15 unloaded can be concluded that drug enters to pores of functionalized SBA-15.

***The impact of the pH on the releasing and loading of amoxicillin***

The loading of amoxicillin on Bis (2- hydroxyethyl) amine functionalized SBA-15 was investigated in different pHs. The pH of amoxicillin solutions were adjusted in the pH range of 3.0-8.5 (using 1 mol $L^{-1}$ of either nitric acid or sodium hydroxide solution) and the loading of amoxicillin was achieved by soaking of 10 mg of the SBA-15 modified with 3-[Bis(2-hydroxyethyl)amino]propyl-triethoxysilane in 20 mL of 3 mg $L^{-1}$ amoxicillin solution, and stirred for 30 minutes at ambient temperature. The contents of amoxicillin were obtained by spectrophotometry method. The percent of amoxicillin adsorbed on modified SBA-15 were 15%, 25%, 37% and 48% at pH 3, 5, 7 and 8.5 respectively. The results show that at lower pH values, the adsorption amount of amoxicillin on the Bis (2-hydroxyethyl) amine functionalized SBA-15 has been decreased. At lower pH values, amino group of the functionalized SBA-15 and amoxicillin can be protonated and therefore, the interaction between the amoxicillin and the adjusted SBA-15 is weaker than it at high pH. Similar results have been reported by Vallet- Regi et al. They investigated the antibiotic amoxicillin with a calcined SBA-15 material, and discovered that the amount of drug integrated in the porous matrix considerably depends on the pH. When the pH of the solution was increased to seven, the adsorption of amoxicillin was significantly improved, reaching 24 wt% under optimal conditions [17]. In addition, as reported by Sevimli and Yılmaz, pure SBA-15, SBA-15–Pr–SH, SBA-15–Pr–$NH_2$ and capped SBA-15 (with triethoxy methyl silane) are identified as carriers for

delivery of amoxicillin. The findings indicated that the amounts of loaded amoxicillin are marginally differ according to the functional group's nature and the interaction between the carrier and drug. SBA-15–Pr–SH adsorbed amoxicillin with maximally (27.5%) while the SBA-15–Pr–NH2 adsorbed less amount of amoxicillin (18.3%) [33].

The release profile of amoxicillin (percent amoxicillin released over time) was monitored in a stirred solution of phosphate buffers with various pH. The release profiles in the three different pH of 5, 7 and 8 were shown in Figure 4. A faster release rate at pH=5 (lower pH), suggesting a weaker amino-carboxylic interaction because of protonation of amino group of the functionalized SBA-15. Prokopowicz et al. have reported similar results. They indicated that the rehydroxylated SBA-15 has a pH-dependent and prolonged drug release profile. A slower drug release was observed in simulated body fluid (pH = 7.4) in comparison with phosphate buffer (pH = 5.0). It is mainly due to stronger electrostatic interactions and simultaneous deposition of phosphate and calcium ions onto the surface of the silica [18]. Doadrio et al. provided a comparison between calcined SBA-15 and the SBA-15 functionalized with long alkyl chains like octadecyltrimethoxysilane and octyltrimethoxysilane in delivery patterns. The macrolide antibiotic erythromycin was used for charging the samples, and the release assays were performed in vitro. It was indicated that the increase in the population of hydrophobic–$CH_2$ moieties in the host reduced the release rate [23]. In addition, Li et al. confirmed the possibility of controlling the ibuprofen (IBU) delivery rate occluded in two multifunctional amine mesoporous silica spheres. They showed pH-responsive control for drug release. They were revealed that amine functionalized mesoporous silica spheres have a faster release rate at low pH (pH 4.5) than it at pH=7.45 [28].

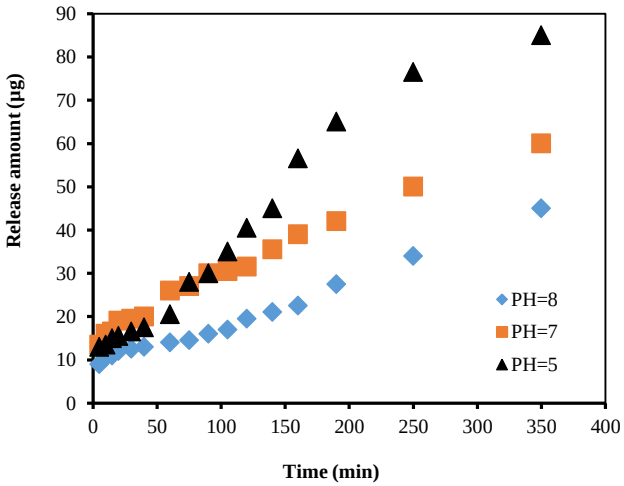



**Figure 4.** Amoxicillin release profile in phosphate buffers

***Release of amoxicillin in SBF***

The release profile of amoxicillin in simulated body fluid was monitored with putting 50 mg Bis(2-hydroxyethyl) amine functionalized SBA-15 into 50 mL simulated body fluid (SBF). The releasing of amoxicillin, at time intervals, was measure by UV-Vis spectrophotometer at λ= 265 nm. The results were indicated in Figure 5. As it is obvious, the procedure was done in a very slow release pattern and has a rather constant rate (about 7 µg $h^{-1}$) over the subsequent hours.

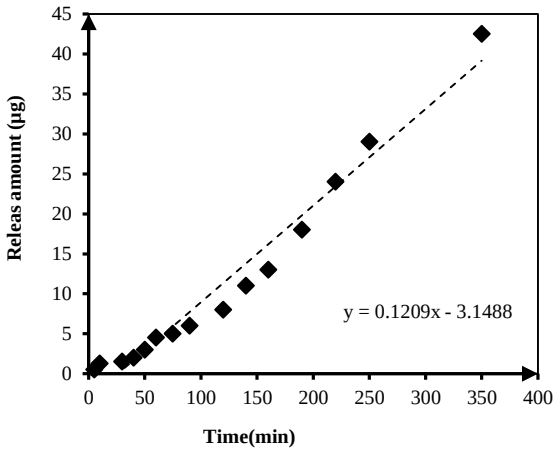



**Figure 5.** Amoxicillin release profile in a simulated body fluid.

## CONCLUSIONS

This work proposes an approach for the carry of amoxicillin by Bis (2- hydroxyethyl) amine functionalized SBA-15 molecular sieve for improving the medical impact of amoxicillin. This is based on the interaction between the carboxylic group in amoxicillin and silanol and amino groups of the functionalized SBA-15. Also, hydrogen bonding between the silanol groups of the SBA-15 and the amine groups of amoxicillin can be formed. The results were shown that loading amount and release rate of drug depends on pH value. The Bis(2-hydroxyethyl) amine functionalized SBA-15 is able to encapsulate the drug molecules through its ordered mesopores. Due to the slow release process, the Bis (2- hydroxyethyl) amine functionalized SBA-15 fits to be applied for controlled release of amoxicillin.

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