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RICE HULK ASH AS AN ALTERNATIVE SOURCE OF SILICA FOR THE PRODUCTION OF MEDICINE RELEASE SYSTEMS – A REVIEW AND NEW PERSPECTIVES

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Abstract: Rice husk ash (CCA) is a residue generated from burning the husk, obtained after processing rice, for energy generation, and may contain around 80 – 98% w/w amorphous silica depending on the conditions of burn. Obtaining silica can be carried out through different processes, however, as it is extracted from industrial waste, with a renewable raw material source, it makes the process economically and ecologically viable. Amorphous silica has been applied in several areas of science and technology, however, due to its physical-chemical characteristics, biocompatibility and chemical inertness, work has been carried out using silica as vehicles for transporting medicines. Release systems aim to control the rate and time of release as well as the location of where the drug must act, thus increasing the efficiency and safety of therapeutic treatment, with the reduction of dosage and side effects, respectively. The systems are prepared by loading bioactive molecules into the system and are analyzed using various analytical techniques. In this review, a survey of publications focused on the production and characterization of silica particles was carried out with the aim of obtaining support for medicines. After analyzing fifteen articles, it was concluded that medicines have the ability to be adsorbed on amorphous materials or in dispersions. Colloidal solutions containing silica, more precisely airgel, are the most widely used medium, as they present requirements for an efficient drug release system, such as low density, high porosity and large specific area, resulting in high adsorption capacity and release control. of the drug, as well as greater efficiency in the interaction between the biological fluid and the polymeric matrix. Ibuprofen was used as a model drug to carry out studies on the loading and release efficiency of the devices. The studies were carried out exclusively on a laboratory scale.

Keywords: Rice husk ash. Silica. Medication delivery system. Colloidal solutions. Airgel.

INTRODUCTION

Every year, the food industry is faced with an abundant amount of waste, requiring a high cost to dispose of these materials due to the environmental problems they can cause. Rice husk ash (CCA) is a residue generated from burning the husk, obtained after processing rice, for energy generation, and may contain around 80 – 98% w/w amorphous silica depending on the conditions of burning (Mostafa,2018).

One of the requirements for using biogenic silica as a drug transport vehicle is high purity, which can reach 99.7% by mass (Hossein Beidaghy Dizaji, 2019). Before the extraction process, it is necessary to characterize the raw material as the possibility of the presence of metals leads to a decrease in the purity and quality of the extracted silica. Once their presence is confirmed, acid treatment can be carried out to remove these metals (Chen, 2017).

Silica production can be carried out through different processes, however, when extracted from industrial waste, with a renewable raw material source, the process becomes more economically and ecologically interesting. The silica extraction process, carried out through alkaline leaching, has as product an alkaline sodium silicate solution and as a by-product a carbonaceous material that can later be used to generate activated carbon. (Patel, 2017)

Obtaining the sodium silicate solution can lead to several applications depending on the silica module generated. One of these applications is in the formation of airgel or sol-gel, for the formation of drug delivery systems. Such colloidal dispersions have high adsorption capacity due to their properties such as low density, high porosity and large specific area providing an efficient drug

release system (Zheng, 2020). However, it is necessary to analyze the structure of the dispersions to determine the affinity of the drugs with the airgel, which will influence the adsorption and desorption of the medicine in the body. Furthermore, attention must be paid to the stability of the system, as the degradation of the colloid makes it toxic and may result in adverse reactions due to the high concentration of silicon in the body. (Suresh, 2017). Figure 1 shows the areas in which airgel can be applied, as well as its characteristics.

Asieh et al (2021) reported the modification of the airgel structure with carboxylic acid, indicating an improvement in drug loading in the new system, and greater ability to adjust drug dissolution. Chemical properties such as pH, ionic strength, temperature and presence of surfactants in the medium in which the system is being prepared directly influence the dissolution of medications and hydration of the airgel (García-González, 2021). The objective of the present work is to demonstrate the feasibility of using rice husk ash as a source of biogenic silica for the preparation of drug transport systems through a critical analysis of the work that has been developed over time, in addition to carrying out a critical discussion for future contributions.

MATERIALS AND METHODS

Research carried out in the Scopus database with the keywords "Rice Husk Ash" and "Drug Delivery" applied in the title and abstract, in the period between 2012-2022, resulted in the selection of fifteen articles focused on the use of CCA as a source of amorphous silica for the formation of drug delivery systems. Through reading, we sought to verify the methodologies used in the silica extraction process and preparation of colloidal solutions, as well as the loading and releasing processes of medicines and characterization of the systems obtained.

RESULTS

SILICA EXTRACTION AND AIRGEL PREPARATION PROCESSES

The silica extraction process can be carried out through heat treatment and chemical treatment. The disadvantage of carrying out heat treatment lies in the costs of the process due to the need to use a large amount of energy for a prolonged period of time and to obtain low quality silica. (Patel, 2017)

Via chemical treatment, the most widespread process today is alkaline leaching, resulting in an alkaline sodium silicate solution. In this process, a sodium hydroxide (NaOH) solution is added to the ash in a reflux system with constant stirring for a period of at least 1h and with a reaction temperature of around 100 °C (Patel, 2017). The preparation of airgel is commonly carried out using the sol-gel method at low temperatures. (Prabha, 2021)

Patel et al (2017) reported a methodology based on pre-treatment using different acids with varying concentrations. The alkaline extraction process was carried out with NaOH with concentrations of 2.0; 2.5 and 3.0 N.

Suresh et. Al (2015) used the usual methodologies to produce the silicate solution. However, in the process of preparing the silica microparticle airgel, they used the combined technique of preparing the sol-gel with emulsification. First, a solution containing mineral oil (kerosene) and a mixture of two commercial surfactants, Spanä80 and TweenÒ80, was generated. The sodium silicate solution was added dropwise while stirring. The second step consisted of adding a 1N HCl solution until a pH of 7.0 was reached. The process was kept under stirring for a period of 1h and left to rest for 1h for the formation and decantation of particles. The formed gel was treated at different concentrations and periods of time with an ethanol/water

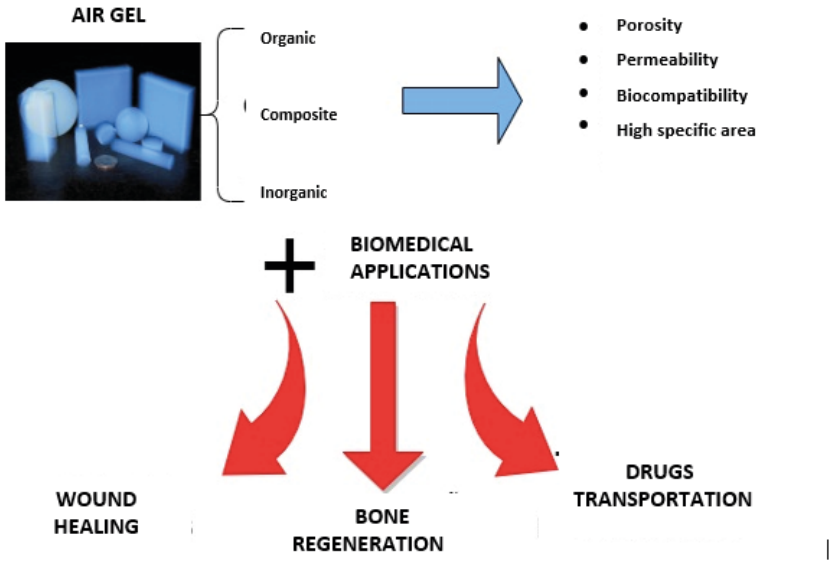

Figure 1- Airgel Applications (Adapted from Longpo Zheng, 2020)

solution to remove water molecules from the particles and subsequently dried using supercritical carbon dioxide so that the pores did not collapse and the crystalline network was not disturbed, allowing, thus preserving the original structure of the silica particles in the gel. Subsequently, the same technique was reproduced, however, with the use of ammonium hydroxide in the second stage. Figure 2 represents the stages of the airgel formation process.

Suttiruengwong et al. (2018) prepared hydrophilic and hydrophobic silica, using excess glycerol as a silica extracting agent, which was mixed at 200ºC for a period of 2h. After removing the glycerol, hydrolysis was carried out with deionized water over different periods of time, followed by washing with distilled water and drying. The modification of silica to obtain its hydrophobic form was carried out in a water/ethanol solution using the reagent trimethylmethoxysilane (TMMS).

The use of a structure directing agent, PluronicÒ123, in conjunction with a micelle expander, 1,3,5-trimethylbenzene (TMB) was also reported in the preparation of the airgel (Iqbal, 2018). The reagents were mixed with the silicate solution until complete homogenization and then the pH was adjusted with HCl. The temperature was kept constant and the medium was stirred for 20h. The solution was heated to 100ºC and left to rest for 48h. Finally, centrifugation and calcination were performed. In the release study, the system formed was mixed with surfactants and kept at 37ºC for one week. At certain time intervals, the supernatant formed was diluted in acetonitrile to prepare the mobile phase, passing through the filtration process and enabling analysis by HPLC.

Differentiating themselves from conventional methodologies, Liang at al (2020) carried out an extraction process using a mixture of alkaline solutions and subsequent use of a solution of 2-acrylamido-2-methylpropane sulfonic acid (AMPS), as a dispersion and precipitation agent. In this process, the alkaline solution containing 20% sodium carbonate was added to the husk and rice ash and kept under stirring for 2.5h at a temperature of 95ºC. After the reaction time had elapsed, the solution was filtered and the

AMPS solution was added to the filtrate, with an optimal concentration of 25% by mass, at a flow rate of 0.05 mL/s at 40ºC. The solution was left to rest for 3h until the formation of the gel, which underwent pH adjustment by washing with deionized water and subsequently filtered to recover the AMPS solution. Figure 3 shows the block diagram of the airgel formation process proposed by Liang and collaborators.

Other chemical methods to obtain silica were carried out using toluene/ethanol, NaClO2, organic acids and ionic liquids, as well as the use of microwaves to produce the gel. (Patel, 2017)

MEDICATION LOADING AND RELEASE

The drug impregnation processes in airgel can be carried out using four strategies that are differentiated by the loading steps. Each strategy is recommended by the characteristics and interaction of the drug-airgel system. Firstly, we add the medicine directly to the colloidal solution. Second, due to the solubility of the drug in the solvent, the bioactive molecule is added to the already formed airgel followed by removal of the solvent. The third methodology is carried out with the addition of the drug during the drying process. Finally, there is the use of supercritical CO2. (García-González, 2021) Figure 4 shows the steps for impregnating biologically active molecules using different strategies.

The release mechanism follows the steps of dissolving the drug and transporting the molecule from the system to the environment. The mechanisms are affected by the hydration of the system, hydrophilic or hydrophobic, molecule-airgel interaction and mass transfer from the drug release system to the dissolution medium. (García-González et al, 2021)

The dissolution of ibuprofen using CO2 under supercritical conditions showed good results. In this process, the gas was preheated and pressurized before feeding into an autoclave, already fed with the reagents, which was kept under agitation for 48h to ensure that equilibrium was obtained. The amount of adsorbed material was determined both by mass difference, before and after loading, and by UV-VIS spectrometry. (Suttiruengwong, 2018) The release of ibuprofen in this process was carried out in an acidic medium containing concentrated HCl at a temperature of 37ºC, under stirring. The analysis was carried out, after filtering the medium, by UV-Vis spectrophotometry.

Suresh et al. (2015) loaded ibuprofen into the airgel through pressurization with CO2 for 24h to reach adsorption equilibrium. The release kinetics were carried out in an acidic medium and the drug was dissolved with the addition of sodium dodecyl sulfate. Aliquots of the supernatant formed were removed and analyzed by UV-Vis spectroscopy, at predetermined times.

Iqbal et al. (2018) loaded a-mangostin, a natural metabolite from the class of polyphenols, xanthones, diluted in ethanol and mixed in the airgel. The mixture was stirred at 35ºC and dried at 100ºC for 24h.

ANALYSIS AND DISCUSSION

The silica extraction process via the chemical route was carried out in all of the aforementioned processes, however, the reagents used were modified, demonstrating the feasibility of extracting silica in different ways and under similar operating conditions. Through alkaline leaching, it was possible to obtain a silicate solution with approximately 90% by mass of silica using NaOH at a concentration of 2.5N (Patel, 2017).

With the use of glycerol followed by hydrolysis, the characteristics of the pore changed with an increase in reaction time of up to 48h. Trimethylmethoxysilane (TMMS) caused the solution to change from hydrophilic

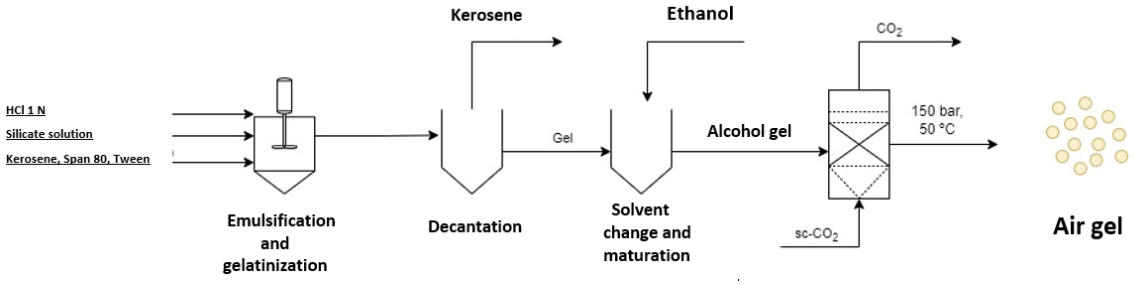

Figure 2- Preparation of airgel with silica microparticles (Adapted from Suresh, 2015).

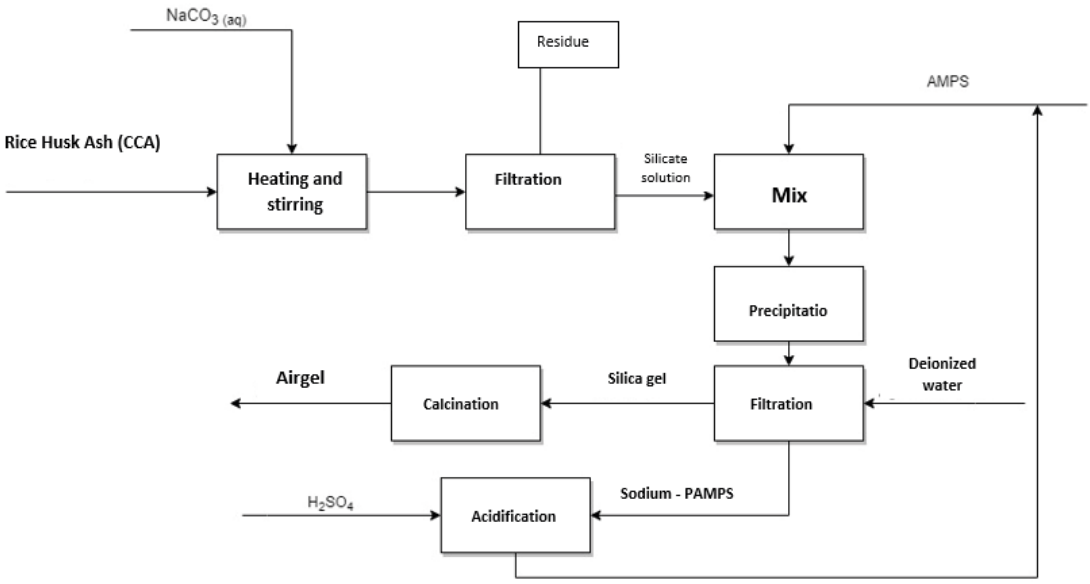

Figure 3- Block diagram of the silica extraction process (adapted from Liang, 2020)

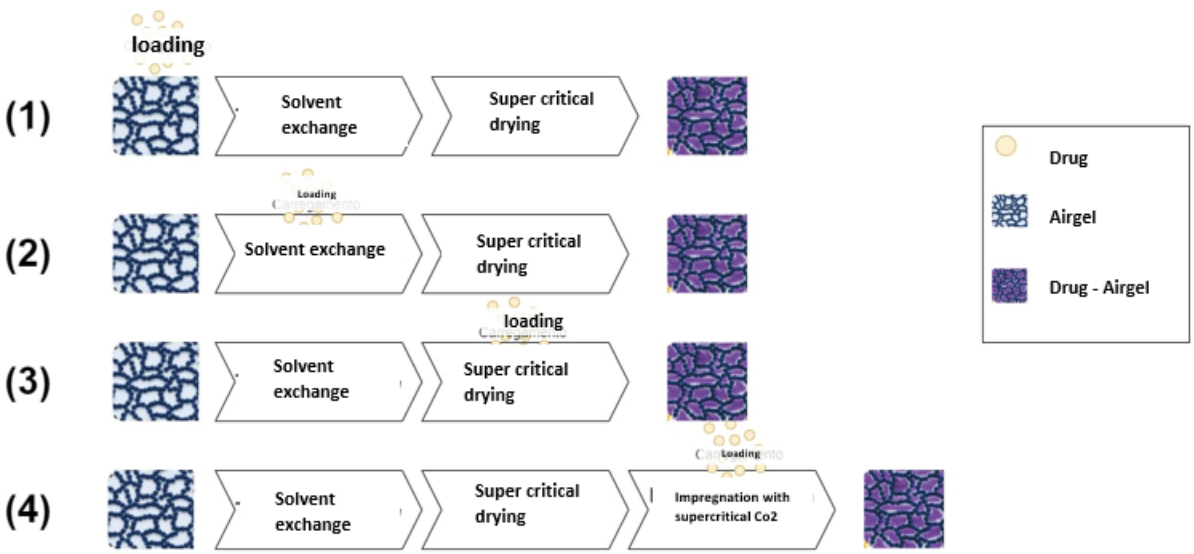

Figure 4- Drug loading methodologies in drug delivery systems (adapted from García-González, 2021)

to hydrophobic (Suttiruengwong, 2018).

The presence of an aromatic ring and a hydrophobic carbon chain favors adsorption on the surface, and its reaction kinetics were characterized as first order. The modification on the surface of the gel treated with TMMS caused the adsorption power to decrease. The release of the drug in the acidic environment was small compared to the untreated gel, which demonstrated greater stability due to its hydrophobic nature. (Suttiruengwong, 2018) Despite the small amount of ibuprofen adsorbed by the TMMS-modified gel, its release mechanism was slow, which favors control.

Iqbal et al (2018) confirmed airgel loading by the coexistence of silica and a-mangostin bands in Fourier Transform Infrared Spectroscopy (FTIR) analysis. Thermogravimetric Analysis (TGA) allowed us to verify that the airgel was capable of immobilizing the drug. When carrying out the test in vitro, in the first 15 min, there was a peak release of the molecule of approximately 47% of the total loaded with release stabilization over time.

The presence of large pores allowed 80% of the loaded ibuprofen to be released in the first 15 min due to the high diffusivity of ibuprofen and rapid penetration of the medium. (Suresh, 2015)

Gel formation was carried out using different methodologies. The production of colloid using AMPS demonstrated advantages over usual processes when compared to the purity of the silica obtained, specific area and uniformity of the particles (Liang, 2020).

The concentration of silica in the airgel influences the biocompatibility of the drug transport system. More efficient systems are formed with a concentration of 0.16% silica in the airgel. The efficiency measurement was carried out in vitro using simulated body fluid, tris-hydroxymethyl-aminomethane, and human fibroblast cells (Sani, 2017).

CONCLUSIONS

In the work carried out, the colloidal solutions obtained with CCA as a source of silica showed promising results, indicating that CCA has the potential for producing medicine distribution vehicles. New extraction agents and new reaction conditions have been studied in order to obtain a more economical silica extraction route with shorter reaction times.

The crystalline structure and pore characteristics are influenced by the way the colloidal solution is prepared. And, as the crystalline structure determines the affinity of the gel for the molecule, ideal conditions of temperature, degree of agitation and reaction time, dispersing agents and other reagents for generating the drug release system must be sought.

Differentiating themselves from the work already carried out, and seeking greater efficiency and control of therapeutic treatment, studies must, in addition to the formation of systems, delve into thermodynamic and kinetic studies, modeling the adsorption and desorption mechanisms for each class of molecule, and determining the synthesis parameters.

The presence of the silinol group in the airgel allows drugs that contain groups capable of hydrogen bonding to be chemically adsorbed, followed by physisorption in multiple layers. The presence of these multiple layers causes the drug to quickly detach, which favors therapeutic treatment in which rapid action of the medication is required.

The use of different drugs to study drug release systems is restricted, with little variability in studies. Ibuprofen was the molecule found as a model in most of the studies found in the literature. Other molecules of the same class must be studied so that thermodynamic and kinetic models can be extrapolated to the entire class. The same

must be expanded to other drug classes.

For in vitro analyses, temperature and acidity conditions must be sought close to the location where the medicine must act. Furthermore, the study will enable the systems to be applied in transdermal, transpulmonary treatments with local, oral and nasal administration.

Finally, further studies will allow the tests to be scaled up until they reach the standards necessary to be applied on an industrial scale.

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