

Drug Confinement and Delivery in Ceramic Implants

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Abstract: Ordered silica-based mesoporous materials could be specially designed and chemically modified for the adsorption of drugs that would be locally released. The drug adsorption and release kinetics are controlled by several factors such as pore size, volume, architecture and chemistry of the silica walls.

Key Words: Bioceramics, bone tissue regeneration, drug-delivery, mesoporous materials.

INTRODUCTION

The drug release from bioceramic matrices has a double scope. One is aimed to locate organic molecules on biomaterials the application of which is to reconstruct or regenerate living tissues together dealing with infections or inflammations, consequence of surgical implantation. The second one consists on the more traditional systems of introducing drugs for oral use. Considering the first approach, the main interest is the introduction of drugs, peptides, proteins or bone growth factors in ceramic materials that will be employed for the production of implants.

The ceramics with medical applications is an interesting research and development field for obtaining biomaterials useful for the implant production and/or fixation [1-4]. With biomaterials, and more specifically with bioceramics, many parts of human body can be replaced or repaired [1,5]. Independently of the type of the ceramic used and the way of implantation, the introduction of an implant in a living body always causes inflammation phenomena and, frequently, infection processes. These problems can be overridden by using local drug delivery systems to confine pharmaceuticals, as antibiotics, anti-inflammatory, anti-carcinogens, etc. [6-8]. The possibility of introducing certain drugs into the ceramic matrices employed for bone and teeth repair is, undoubtedly, an added value to be taken into account.

The utilization of the conventional high temperature procedures to conform ceramics in the desired form is a very common strategy. The degradation temperature of pharmaceutical compounds is normally around 100°C, which is very low compared to the high temperature needed for the pieces to be compacted, that is around 1000°C. Consequently, this is the main problem to include pharmaceuticals in these conventional ceramic implants. So the scientific community is currently demanding new procedures for incorporating drugs into implantable biomaterials.

The possibility of ceramic implants to work as drug delivery systems is an added value in addition to all the ceramic properties. For this purpose, firstly, drug molecules have to be confined into the empty pores of the ceramic

matrix (drug-loading) and then the drug is released in a controlled fashion (drug-delivery). In this way, the first step consists on designing the ceramic with high porosity and tailored pore number, size, shape, distribution and connectivity. This design is carried out depending on the drug to be confined and subsequently released on the chemical nature of the wall to achieve a greater control of the chemical interaction between the silica and drug. With this aim, the size of guest drug molecules included into the bioceramic matrix has to be considered. In general, the size of drug molecules falls within the nanometer scale and consequently, every porous material showing pore sizes higher than one nanometer is expected to host these drug molecules.

ORDERED MESOPOROUS MATERIALS VS CONVENTIONAL CERAMICS

Conventional ceramics have been used as host materials for a variety of drugs against inflammation after material implantation. Imaginative drug loading strategies have been developed to avoid high temperature treatments that would decompose the loaded drugs [9,10]. Using such procedures, controlled drug loading and delivery have been achieved through room temperature routes. Therefore, ceramic pieces that could act as drug delivery systems have been produced to be used as implants to regenerate bone tissues. When gentamicin was confined in bioactive sol-gel glasses, which were implanted into rabbit femur, the maximum gentamicin levels were observed in the proximal bone. Other vital organs were almost gentamicin-free, which confirmed the local delivery of the drug where the implant was fixed (Fig. (1)) [9,10].

In some cases, high homogeneity can be reached, but traditional ceramic synthesis procedures usually lead to heterogeneous drug loading because the ceramic porosity is not specially designed. For the sake of obtaining a better efficiency in the drug loading and release and reproducible results, the used matrices should have homogeneous porous systems.

If drugs have to be placed into pores, a material with a homogeneous ordered pore distribution should be specially designed. In such material, the drug adsorption and subsequent delivery will be more regular and reproducible than that coming from a disordered pore distribution. A step forward to this type of systems is the transition from non-

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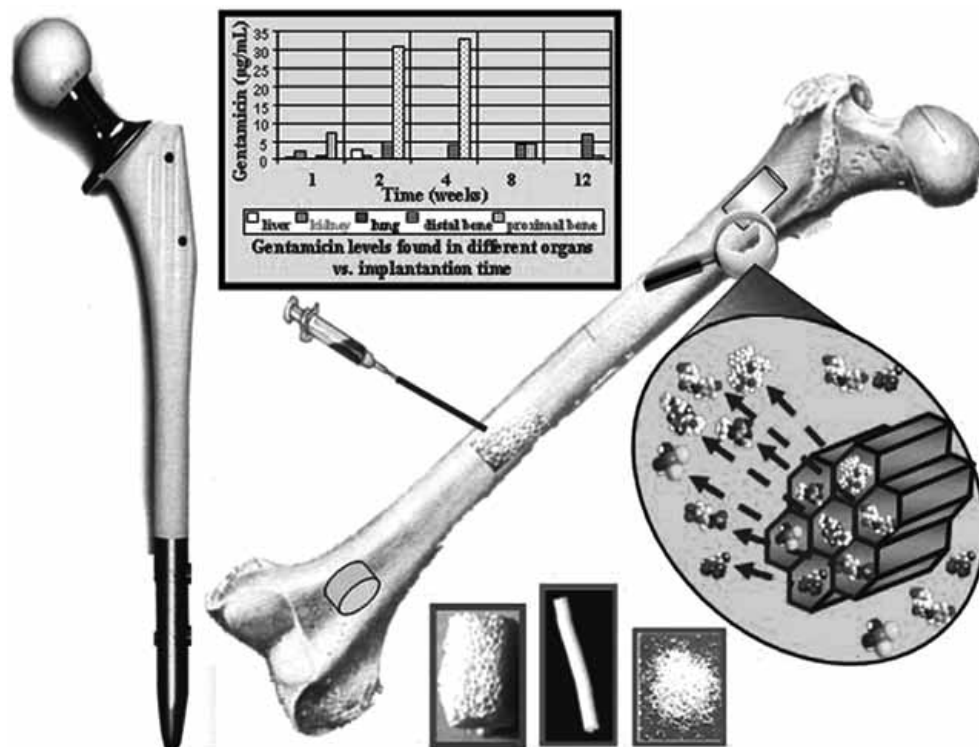


Fig. (1). Examples of ceramics used for drug release in implants for bone repairing and reconstruction. The table in the upper part shows data of gentamicin confined in a bioactive glass implant [10].

designed materials (conventional ceramics) to specially designed porous matrices (ordered mesoporous materials).

In 1992, a research team from Mobil Oil Company synthesised a new family of materials, the so-called M41S that presents ordered pore distributions, with homogeneous sizes (D_p) ranging between 2 nm and 10 nm [11,12]. These materials present a very high pore volume (V_p), *ca.* 1 cm³/g, and a surface area (S_{BET}) between 500 m²/g and 1000 m²/g. All these properties make these materials as potential candidates to adsorb a large amount of molecules such as drugs and then release them during long periods of time in an appropriate medium [8]. The possibility of using silica-based mesoporous materials to confine drugs and then release them in a controlled manner and their bioactive behaviour are two outstanding properties of these materials. The combination of these two particular properties opens the gates for using this type of ceramics in the biomedical research area [3,13]. Thus, these materials would be able to act as cellular scaffolds where proteins, peptides or growth factors can be easily incorporated and subsequently released to the surrounding environment promoting cell proliferation and differentiation. Since 2001, around 100 publications have been reported on this application field.

From the starting M41S family, novel mesoporous systems have been developed by modifying the synthesis methods. These new mesoporous materials normally show homogeneous and ordered mesopore architecture with different structures, from simply hexagonal planar (MCM-41, SBA-15) [14,15] to more complicated 3-dimensional frameworks with interconnected porosities (MCM-48, SBA-16) [16,17].

Although cubic structures have been used for the adsorption and release of drugs [18], the 2-dimensional hexagonal planar matrices seem to show more effective and reproducible results, since the diffusion paths are promoted for the drug molecules. The drug loading produces a remarkable reduction of the pore size and volume that can be observed in the N₂ adsorption isotherms in Fig. (2) where ibuprofen was loaded onto MCM-41 mesoporous materials [8].

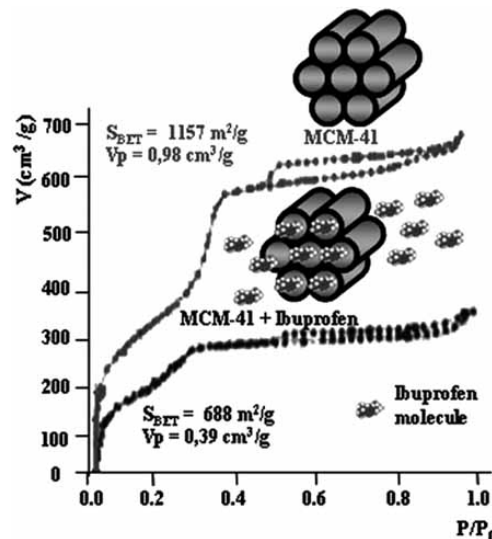


Fig. (2). Ibuprofen confinement in MCM-41 mesoporous matrices (S_{BET} is the specific surface area calculated using the BET method [19]. V_p is the total pore volume measured at P/P_0 0.998).

DRUG CONFINEMENT AND DELIVERY IN ORDERED MESOPOROUS MATRICES

Once the mesoporous matrix has been selected attending to the characteristics of the drug and the application, the drug loading is performed by direct impregnation methods. The mesoporous matrix is placed either as powder particles with regular sizes or as compacted pieces into the solution of the drug with a given concentration. In this impregnation procedure several factors have to be considered like the solution pH, temperature, drug solubility and polarity and generally its chemical nature. The release process is then carried out placing the drug-loaded mesoporous matrices into a solution and monitoring the drug concentration along the test time. In particular, a good election is a simulated body fluid, [20] which is related to the human blood plasma or even a physiological serum for facilitating the detection procedure (Fig. (3)).

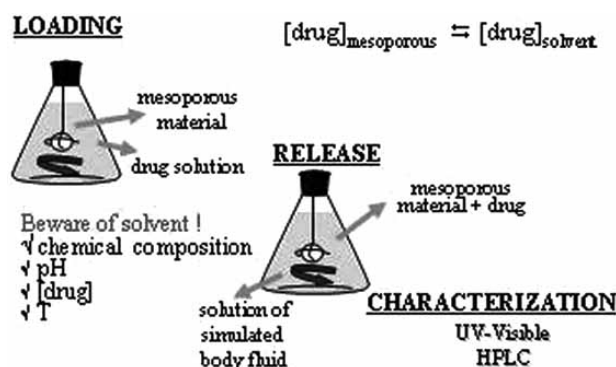


Fig. (3). Experimental methods for the loading and release of drugs from ordered mesoporous matrices.

The selection of the loading solvent will have an effect on the amount of loaded drug. Thus when polar drug molecules such as amoxicillin [21] or gentamicin [22] are targeted, a polar solvent like water have to be used to enhance the concentration of drug into the pores. Sodium alendronate [23,24] is a water-soluble salt, so an aqueous saline solution buffered at pH 4.8 was used to load this drug into mesoporous matrices. On the other hand, when a non-polar drug is aimed like ibuprofen, the chosen solvent also needs to be non-polar like hexane. Intermediate cases can also be found like erythromycin [25] that has to be loaded using acetonitrile. In any case, all these parameters should be always fixed before the drug adsorption and release (Fig. (4)).

The drug loading into the mesoporous matrices is controlled by the chemical nature of the pore walls. The inorganic network of silica-based ordered mesoporous materials is plenty of silanol groups (Si-OH) that would interact with the functional groups of the drug. Depending on the strength of this attracting interaction, the drug retention will be modulated. Thus, ibuprofen that has a carboxylic acid group would form hydrogen bonds with the silanol groups and consequently drug molecules would be retained into the mesopores [8].

Silanol groups on the pore walls are also susceptible of undergoing a chemical modification with a large variety of

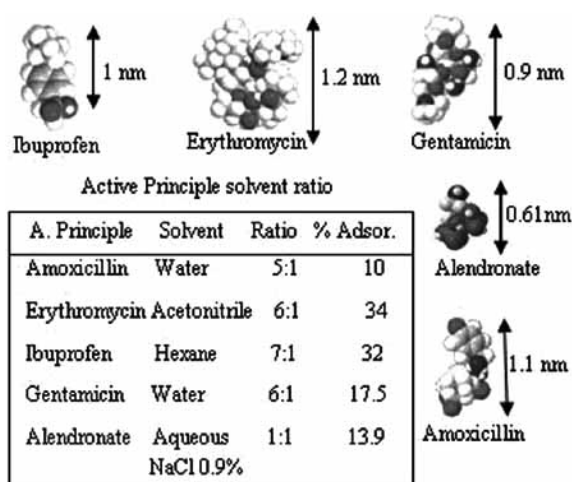


Fig. (4). Conditions employed with several drugs for their anchoring on mesoporous matrices.

organic groups through a functionalisation process. Indeed, the pore-wall modification would be performed depending on the functional groups of the drug molecules to be adsorbed. Thus sodium alendronate, a drug employed for osteoporosis treatments, has two phosphonate groups that would undergo stronger attracting interactions with amine groups than with silanols [23]. Therefore, if the pore wall surface is covered by amine groups, there would be a larger alendronate loading than in unmodified materials. In the case of hexagonally-ordered SBA-15, the alendronate loading was increased from 8% in unmodified matrices ($D_p = 9.0$ nm) up to 22% for amine-grafted materials ($D_p = 7.5$ nm). The same trend was observed for MCM-41 ($D_p = 3.8$ nm), ranging from 14% (unmodified) upto 37% (amine modified, $D_p = 2.7$ nm) [23], as it can be observed in Fig. (5). A similar effect on the ibuprofen loading and delivery kinetics was observed when amine-modifying the silica walls of MCM-41 [26,27].

A greater alendronate adsorption was achieved when amine modification was carried out on MCM-41 and SBA-15 mesoporous matrices. The chemical design of the pore walls is always aimed to increase the loading degree, though in some cases the pore size reduction due to functionalization decreases it. Nevertheless, the functionalisation process also affects the release kinetics of the adsorbed drugs, effectively reducing the delivery rate in the same testing conditions. For unmodified SBA-15 matrices, the release of adsorbed alendronate is completed after 10 days of assay, while for amino-functionalised SBA-15 matrices *ca.* 70% of the total drug loading is released within the same time (Fig. (5)). Similar behaviour was observed for MCM-41 materials where amino-grafted matrices developed a slower delivery rate of the total amount of adsorbed alendronate [23].

CONCLUSIONS

Silica-based ordered mesoporous materials with designed porosity have been used as drug delivery systems in homogeneous and reproducible performances. The drug loading

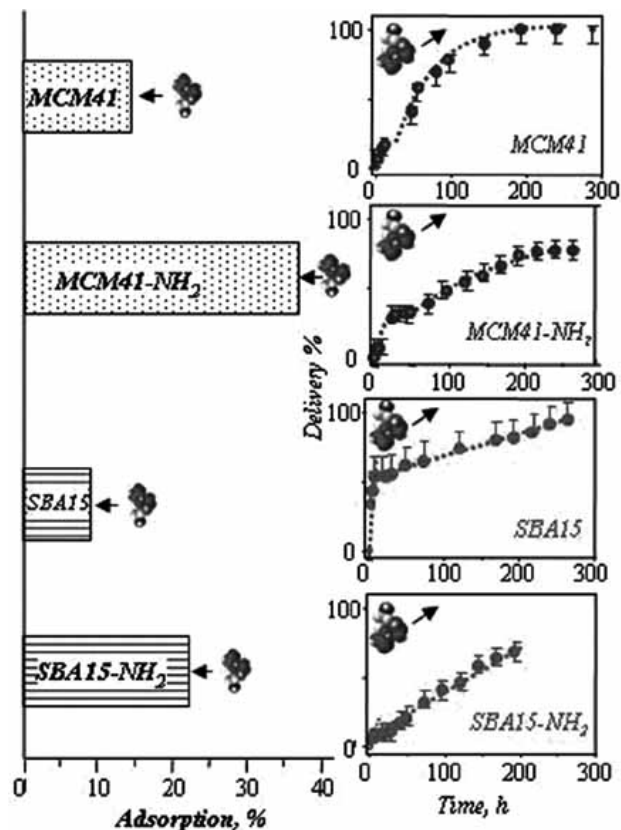


Fig. (5). Adsorption and release of alendronate from hexagonally ordered mesoporous matrices with different pore sizes. Comparison between unfunctionalised matrices and amino-grafted matrices.

and delivery conditions have been established depending on the drug chemistry. All these procedures enhance the drug adsorption and control release in the physiological conditions. The chemical nature of the silica pore walls has been modified to modulate the confinement and delivery kinetics of the drug.

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