Synthesis and chemical characterization of new silica polyethylene glycol hybrid nanocomposite materials for controlled drug delivery

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A series of inorganic organic hybrid nanocomposite materials, containing indomethacin (IND) as a model drug, were synthesized using an inorganic precursor (tetraethoxysilane, TEOS) and an organic precursor (polyethylene glycol, PEG 400) through sol-gel chemistry. The various synthesized hybrids differed in PEG weight percentage (0, 6, 12, 24, and 50 % wt). On an equal PEG percentage, different amounts of the non-steroidal anti-inflammatory drug were loaded (5, 10, and 15 % wt). The bonding characteristics of the various composites were investigated via FT-IR spectroscopy, which suggests the formation of H-bonds between hybrids components. X-ray diffraction (XRD), used for the investigation of their atomic organization, and scanning electron microscopy (SEM) analysis confirmed the amorphous and nanocomposite structure of synthesized materials, which appeared morphologically homogeneous. The in vitro bioactivity evaluation was carried out by analyzing the apatite layers produced on the hybrid materials using SBF as incubation medium. The apatite formation was analyzed using SEM coupled to energy-dispersive electron X-ray spectroscopy. The in vitro release of indomethacin from the new drug-loaded bioactive materials was investigated by HPLC-UV-ESI MS/MS analysis. Data obtained allowed us to state that the drug release was markedly affected by the PEG percentage in investigated hybrid materials.

Key words: Sol-gel – Organic/inorganic hybrid – Bioactivity – Drug delivery – Kinetic release.

Sol-gel hybrid organic-inorganic nanocomposites have received much attention for many years because of their practical importance in a variety of fields [1-4]. They are biphasic materials where the two components are interpenetrate on nanometer level [5]. The properties of these materials are not only the sum of the individual contributions of both phases, but derive from a great synergic effect and the nature of the bonds present between them has an impact on the properties of the materials.

The hybrid organic-inorganic materials have remarkable features that make them suitable for a wide range of biomedical applications [6-8], e.g. as biosensors [9], scaffold for tissue engineering [10-12], biocompatible coating for metallic implants [13]. Drug delivery is also one of the most promising applications of these biomaterials [14-21]. Drug delivery systems represent an important field to achieve both a high drug loading and a controlled release. Controlled release drug delivery systems are being developed to address many of the difficulties associated with traditional methods of administration providing several potential advantages. First, drug release rates can be tailored to the needs of a specific application; for example, providing a constant rate of delivery or pulsatile release. Second, controlled release systems provide protection of drugs that are otherwise rapidly destroyed by the body. Furthermore, controlled release systems can increase patient comfort and compliance by replacing frequent (e.g., daily) doses with infrequent (once per month or less) administration. Finally, controlled release systems are able to reduce the adverse effects of a drug decreasing its systemic amount [22].

There are several strategies by which controlled release dosage forms may be formulated involving the use of polymers or ceramics. The combination of both these materials to obtain composite and hybrid materials is an attractive approach to develop new products with enhanced benefits with respect to their constituents. In this context, sol-gel processing is a powerful tool that readily yields both inorganic and hybrid organic-inorganic materials.

In this paper the synthesis of silica/polyethylene glycol (SiO_2/PEG) hybrid materials containing indomethacin (IND) as controlled drug delivery systems has been reported. Silica intrinsic advantages, such as its chemical resistance, its thermal and electrical stability as well as important biocompatibility and environmental-friendliness, previously allow to suggest its use as pharmaceutical carrier systems for controlled drug release [23-26]. The biological properties and the release ability of sol-gel glass systems together with the capability of same polymers, i.e. poly(ε-caprolactone), poly(ether-imide), to modulate their release kinetic was already evaluated elsewhere [15-17, 27, 28]. Herein, the choice of PEG as a molecule which allows to increase the dosing interval of biologicals has been largely driven by its lack of toxicity and its immune-modulatory properties [29]. Indomethacin, a common nonsteroidal anti-inflammatory pharmaceutical, was used as a model drug. Different inorganic organic hybrid materials were synthesized by adding to silica inorganic phase, PEG in different weight percentages (0, 6, 12, 24, and 50 % wt). In all the hybrid materials prepared, indomethacin was loaded at weight variable percentages (5, 10, and 15 % wt). The new biomaterials were spectrometrically characterized: FT-IR analysis proved the existence of hydrogen bonds between the organic and the inorganic phases.

As it is known that due to the resulting properties of chemical homogeneity, purity [30, 31], low-temperature preparation and easy shaping, the sol-gel process has been proposed and applied to prepare various components in advanced ceramics for dental and/or orthopaedic use [15, 32], we applied scanning electron microscopy (SEM) for phase homogeneity screening and we evaluated the bioactivity by means of the apatite deposition on surfaces [33] after their soaking in a simulated body fluid (SBF). Moreover, the *in vitro* release of indomethacin from the new drug-loaded bioactive hybrid materials was also investigated and the influence of the PEG and drug amount on release kinetic was studied.

I. MATERIALS AND METHODS

1. Sol-gel synthesis

The silica/PEG hybrids materials were synthesized adding to an inorganic silica matrix different weight percentages of polyethylene

Table I - Sample compositions.

Inorganic matrix	PEG (%)	Indomethacin (%)
SiO_2	0	5 10 15
	6	5 10 15
	12	5 10 15
	24	5 10 15
	50	5 10 15

glycol and indomethacin. Silica solution was synthesized by using tetraethyl orthosilicate (TEOS; $Si(OC_2H_5)_4$, Sigma-Aldrich), HNO_3 (≥ 65 %, Sigma-Aldrich), ethanol 99.8 % (Sigma-Aldrich), and distilled water in the molar ratio TEOS:HNO_3:EtOH:H_2O = 1:1:7.5:1. Polyethylene glycol (MW = 400, Sigma-Aldrich) was dissolved in ethanol and added to silica solution under stirring. When SiO_2/PEG hybrids were preparing, ethanol solutions of indomethacin (5, 10, and 15 % wt, Sigma-Aldrich) were added (*Table I*) and maintained under stirring. After the addition of each reactant, the solution was stirred up to the point where homogeneous and transparent sols were obtained. After gelation, gels were air-dried at 50 °C for 24 h to remove the residual. The obtained hybrid appears orange, transparent and glassy, as shown in *Figure 1*. The flow-chart in *Figure 2* describes schematically the sol-gel synthesis.

2. Chemical characterization

Fourier transform infrared spectroscopy (FT-IR) is a measurement technique in which spectra are collected based on the measurement of the radiative source coherence, using time-domain or space-domain measurements of the electromagnetic radiation. This technique uses Fourier transform, a mathematical transformation employed to transform signals between time domain and frequency domain, to turn the raw data into spectrum [34, 35].

FT-IR spectra were recorded with a Prestige 21 spectrometer (Shimadzu, Kyoto, Japan) in the 400-4000 cm^{-1} region, with a 2 cm^{-1} resolution (45 scans), equipped with a DTGS KBr (Deuterated tryglycine sulphate with potassium bromide windows) detector. The hybrids were pulverized and disks of KBr at sample concentration 1.0 % were prepared for the analysis. FT-IR spectra were elaborated by IR solution software (Shimadzu).

The atomic organization of hybrid materials was investigated by X-ray diffraction (XRD) using a Philips diffractometer. Samples were scanned from $2\Theta = 5°$ to 60° using CuKα radiation.

Scanning electron microscopy (SEM, Quanta 200, FEI, The Netherlands) technique was used to study the hybrids morphology. The samples were fixed on stubs with colloidal graphite and metalized with Au.

3. Study of *in vitro* bioactivity

In order to test the bioactivity of the new hybrids materials, they were soaked in a simulated body fluid (SBF) with ionic concentration nearly equal to that of the blood plasma [33]. The temperature was maintained at 37 °C and the ratio between the surface of exposed sample and SBF volume solution was respected, as reported in literature [33]. The ability to form an apatite layer, after 21 days of incubation,

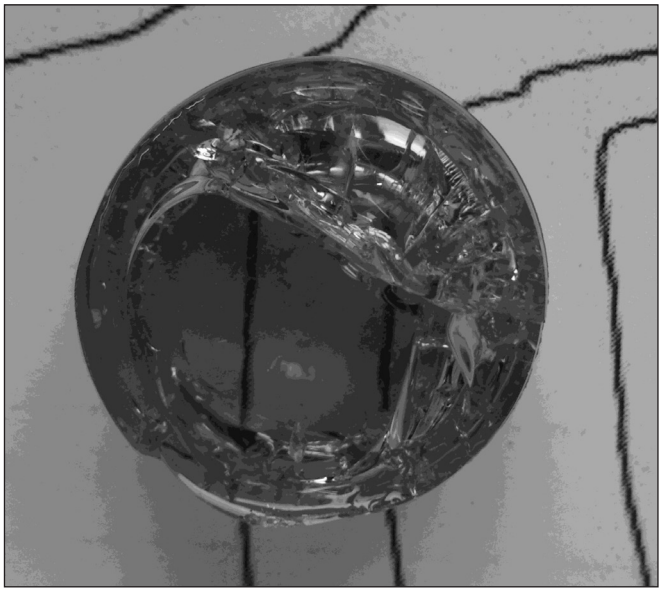

Figure 1 - Bulk of SiO_2/PEG/IND. Only one case is shown as all systems show same aspect.

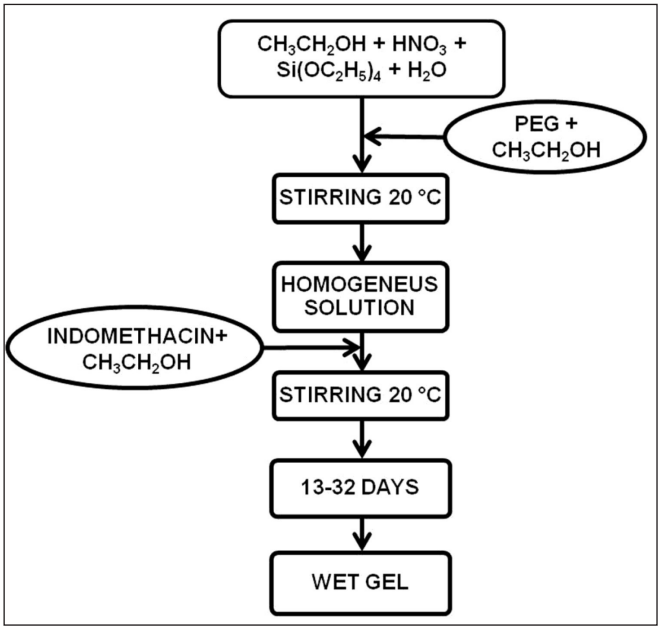

Figure 2 - Flow chart of SiO_2/PEG/IND gel synthesis.

was analyzed by scanning electron microscopy (SEM) with energy dispersion X-ray spectroscopy (EDX).

4. Study of drug release *in vitro*

To study indomethacin release, optimized discs with a diameter of 13 mm and a thickness of 2 mm were obtained by pressing 200 mg of fine (< 125 μm) gel powder into the cylindrical holder of a Specac hydraulic press.

As our goal is the formulation of new dental and/or orthopaedic implant systems, since the pH of saliva lies between 6.4-7.8 and the pH value of the bone tissue environment varies in the range 7.35 to 7.45, the discs were soaked in 3.5 ml Dulbecco's Phosphate Buffer Saline (DPBS), at 37 °C, under stirring. Drug release was monitored through HPLC UV-Vis ESI MS analysis.

Chromatographic analyses were carried out on an Agilent 1100 HPLC system (Agilent Technologies Inc., Santa Clara, CA, United States), equipped with a quaternary pump, a microvacuum degasser,