RESEARCH ARTICLE

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Sol–Gel Synthesis, Thermal Characterization, Surface Interactions, and Release Kinetics of Silica/Drug Hybrid System

Michelina Catauro, Ignazio Blanco, Ronald J. Clarke, Marika Fiorentino, Antonio D'Angelo, and Giuseppina Raffaini*

Controlled and local drug delivery systems of anti-inflammatory agents are attracting increasing attention thanks to their possible pharmaceutical and biomedical applications. These systems have extended therapeutic effects and reduced side effects.

The aim of this work is to synthesize a system composed of SiO_2 glass and ketoprofen, an anti-inflammatory drug, by the sol–gel process. Two different percentages (5 and 15 wt%) of drug are entrapped in the silica matrix via the sol–gel method and the dried material are analyzed via Fourier transform infrared spectroscopy (FTIR) and simultaneous Differential Scanning Calorimetery/Thermogravimetric analysis (DSC/TGA). The drug release kinetics of the amorphous bioactive materials are investigated. Molecular Mechanics and Molecular Dynamics simulations are currently in progress to investigate possible interactions between the silica-based surface and the ketoprofen molecules both at low and high concentration for comparison with experimental data.

1. Introduction

In recent years, silica-based materials have been the object of great interest because of their wide range of applications. They have been found to be ideal for the production of biomaterials employed in the regeneration and replacement of damaged tissue. Among the several processes suitable for the production of biomedical materials such as electrospinning and 3D printing processes,[1–3] the sol–gel route represents an ideal method for the synthesis of materials for biomedical applications. Indeed, the entire process through to the formation of the gel matrix requires a low working temperature and it allows the encapsulation of drugs capable of accelerating the healing process. In this regard, the entrapment of ketoprofen in silica glass material can block the inflammatory process and avoid subsequent painful biomaterial implants thanks to its controlled release from the inorganic matrix. As a result, it can also help to avoid early failure of medical device implants caused by adverse reaction.[4]

2. Experimental Section

The sol–gel method was used to synthesize a silica/ketoprofen systems with 5 and 15 wt% of drug (see **Figure 1**). The precursor of the silica matrix, tetraethyl orthosilicate (TEOS; Si $(OC_2H_5)_4$ Sigma-Aldrich, Darmstadt, Germany) was mixed with ethanol (EtOH 99.8%, Sigma-Aldrich, Darmstadt, Germany) and then water was added to the solution under magnetic stirring. The solution appeared clear and transparent. In a second beaker, ketoprofen (Ket ($C_{16}H_{14}O_3$) 98% ChemPUR;) was solubilized in ethanol and was then added to the solution of TEOS drop by drop under constant stirring. The resulting solution still appeared clear and homogeneous. The molar ratios of the silica/ketoprofen systems were: H_2O/TEOS = 0.9; EtOH/TEOS = 2.8 for SiO_2/Ket 5%, and EtOH/TEOS = 5.5 for SiO_2/Ket 15% in accordance with the volume of EtOH used to solubilize Ket. After gelation, the systems were dried at 50 °C for 24 h and then sealed.

FT-IR analysis was performed over the range of 400–4000 cm^{-1} using a Prestige21 Shimadzu FTIR spectrometer equipped with a DTGS KBr (deuterated triglycine sulfate with potassium bromide

M. Catauro, M. Fiorentino, A. D'Angelo
Department of Engineering
University of Campania "Luigi Vanvitelli"
Via Roma 29, Aversa I-813031, Italy
E-mail: michelina.catauro@unicampania.it
I. Blanco
Department of Civil Engineering and Architecture and UdR-Catania
Consorzio INSTM
University of Catania
Viale Andrea Doria 6, Catania 95125, Italy
R. J. Clarke
School of Chemistry
University of Sydney
Eastern Avenue, Sydney, NSW 2006, Australia
G. Raffaini
Dipartimento di Chimica
Materiali ed Ingegneria Chimica "G. Natta" Politecnico di Milano
piazza Leonardo da Vinci 32, Milano 20131, Italy

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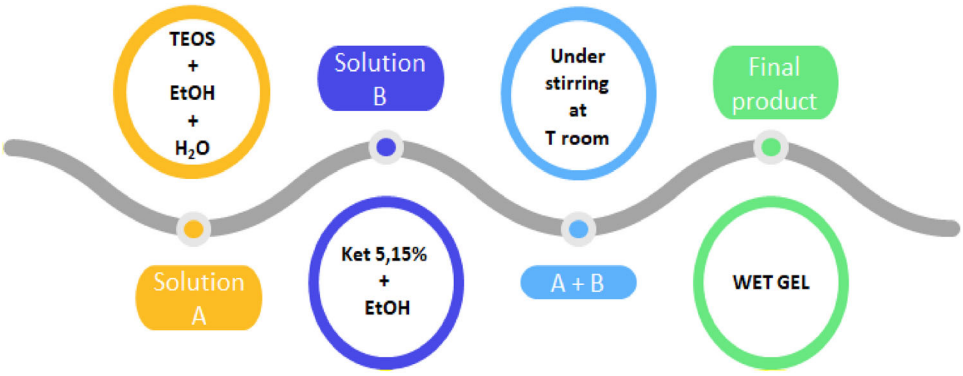

Figure 1. Flow chart of SiO_2/Ket synthesis by the sol–gel route.

windows) detector and a resolution of 2 cm^{-1} (60 scans). The analysis procedure used KBr disks (2 mg of sample and 198 mg of KBr). FT-IR spectra were analyzed by IR solution and Origin 8 software.

The thermal behavior of the systems was investigated using the simultaneous DSC/TGA, discovery SDT650. For this analysis the samples were ground to a powder. About 10 mg were weigh and placed into an alumina crucible. A nitrogen atmosphere was used with a flow rate of 100 mL min^{-1} and a heating rate of 10 °C min^{-1}. The test was run from room temperature up to 1200 °C for the SiO_2/Ket system and up to 800 °C for ketoprofen alone. The results were analyzed with the software TRIOS of TA instruments.

To study the kinetics of ketoprofen release from SiO_2 glass, a powder of each hybrid glass was dissolved in Simulated Body Fluid (SBF) under continuous magnetic stirring. For SBF solution, NaCl, $NaHCO_3$, KCl, $MgCl_2{\cdot}6H_2O$, $CaCl_2$, Na_2SO_4, HEPES (reagent grade chemicals, Sigma-Aldrich) were added to distilled water to obtain ion concentrations equivalent to those in Human Blood Plasma. Drug release measurements were carried out via UV–vis spectroscopy with a Shimadzu UV-1700 Double Beam Scanning UV-VIS Spectrophotometer (Kyoto, Japan). Absorbance values were taken at a wavelength of 259.5 nm, which corresponded to the drug's absorbance maximum. Ketoprofen release was investigated as a function of time from 0 to 360 min to estimate the highest released drug amount. A calibration curve of encapsulated ketoprofen was obtained by plotting the absorbance value at 259.5 nm versus concentration between 0 and 50 mg L^{-1}. Over this concentration range the calibration curve (see **Figure 2**) fits the Beer-Lambert law:

$$A = \varepsilon_{\lambda} Cl \tag{1}$$

where A was absorbance, ϵ was molar absorptivity coefficient, l was pathlength in cm, and C was the concentration in mg L^{-1}.

3. Results

The main FT-IR signals are summarized in **Table 1**. The formation of the hybrid is confirmed by the copresence of characteristic SiO_2 peaks (Si—O—Si asymmetric stretching at 1080 cm^{-1}, Si—OH stretching and OH stretching at 3400–3100 cm^{-1}, Si—O bending at 450 cm^{-1}), [5] and some slightly shifted ketoprofen

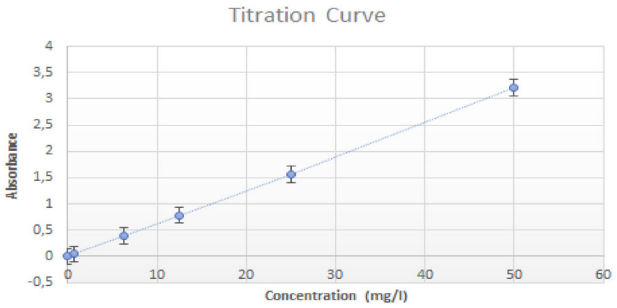

Figure 2. Calibration curve of ketoprofen concentration versus UV absorbance.

Table 1. FT-IR description peak of ketoprofen.[6]

Wavenumber [cm^{-1}]	Interpretation peaks
513, 614, 642, 866, 1068	C—O—H bending
691, 703, 717, 827, 916, 929, 1075	C—H bending
773, 811	C—H wagging
787, 866, 968, 1061, 1068	CH_3 rocking
1003, 1195, 1285	Ring deformation
1068	C—CH_3 stretching
1135	Ring-C-Ring stretching
1228	C—O stretching
1370, 1421	C—C—H deformation
1445, 1480, 1584	C—C stretching
1458, 1480	CH_3 asymmetric deformation
1656, 1697	C = O stretching
2979, 3053	C—H stretching
3295	O—H stretching

peaks.[6–8] Indeed, the peaks at 2979 and 1697 cm^{-1} shift slightly to higher wavenumbers (2985 and 1720 cm^{-1}), while the signal at 1656 cm^{-1} shifts to lower wavenumber (1651 cm^{-1}). Moreover, the presence of a broad and large peak at 3400–3100 cm^{-1} indicates the possibility of hydrogen bonds between SiO_2 and ketoprofen.

TGA curves of ketoprofen, pure SiO_2, SiO_2/Ket (5%), and SiO_2/Ket (15%) hybrids are reported in **Figure 3**A. Ketoprofen shows a weight loss of 99.1% with an end value of 293.9 °C

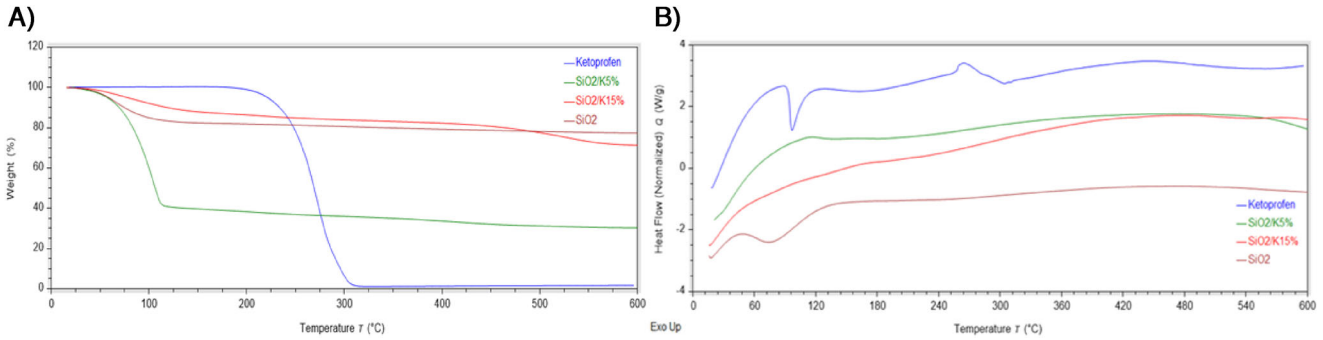

Figure 3. A) Thermogravimetric (TG) curves of pure SiO_2 and SiO_2/Ket hybrid material at 10 °C min^{-1} under a flowing atmosphere of nitrogen. B) DSC curves of pure SiO_2, SiO_2/Ket (5%), SiO_2/Ket (15%), and Ketoprofen, hybrid material at 10 °C min^{-1} under a flowing atmosphere of nitrogen.

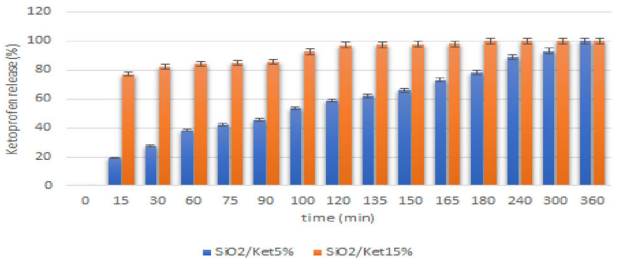

Figure 4. Time dependent-release plot of SiO_2/Ket 5% and SiO_2/Ket 15%.

attributed to its thermal decomposition[9]; this phenomenon is associated with exothermic peaks between 220 and 294 °C in Figure 3B. SiO_2 glass without encapsulated drug shows a first weight loss (17.8%) (Figure 3A) between room temperature and 100 °C, caused by physically absorbed water and organic solvent used for sol–gel synthesis and associated with an endothermic peak in the DSC curves (see Figure 3B). A second loss (6.4%) between 200 and 600 °C is attributed to the elimination of structural.[10]

Similarly, SiO_2/Ket5% and SiO_2/Ket15% show TGA curves with two weight losses, the first one between room temperature and 200 °C and the second one between 200 and 600 °C, with SiO_2/Ket5% having a greater content of water and solvent loss (see Figure 3B). DSC curves of SiO_2/Ket hybrids do not show the sharp endothermic peak present in the ketoprofen thermograph with a peak temperature of 96.8 °C. Drug particles are, therefore, not absorbed on the surface of silica glass.[11,12]

The kinetic release of ketoprofen from SiO_2 glasses is shown in **Figure 4**. SiO_2/Ket15% releases anti-inflammatory drug faster than SiO_2/Ket15% hybrid. Indeed, the former achieved complete drug release within 180 min, while the latter reached the same result within 360 min of release. The time-dependent release plot (see Figure 4) indicates that a greater amount of ketoprofen in the silica matrix causes a faster release in a first phase because some of the drug molecules cannot for hydrogen bonds to the silica matrix because all of the —OH groups are already involved in H bonding.[13]

4. Conclusion

In this paper silica glass materials with 5 and 15 wt% of entrapped ketoprofen were synthesized by the sol–gel technique. FTIR analysis performed on both hybrid materials proves that H-bonds between the drug and the inorganic matrix are established. Thermal analysis of the SiO_2/Ket hybrid material shows that drug is entrapped inside the silica, not just absorbed on its surface. The release kinetics of SiO_2/Ket5% show a slower and more controlled release of drug in comparison to the hybrid with a greater amount of ketoprofen. The SiO_2/Ket15% hybrid already supplies high doses of drug in the first 30 min of the experiment. Using a simulation protocol proposed in previous work,[14–18] Molecular Mechanics and Molecular Dynamics simulations are in progress to determine the possible H-bonds that form between an ideal surface of amorphous SiO_2 and ketoprofen when present at low and high concentrations.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Keywords

drug delivery, hybrids, sol–gel

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