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# A chitosan/silica hybrid 3D scaffold for simultaneous entrapment of two different hydrophilic substances

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ABSTRACT

We report the preparation of a hybrid chitosan/silica three-dimensional (3D) scaffold loaded simultaneously with two model hydrophilic substances, ibuprofen sodium salt and erioglaucine disodium salt. The first substance is entrapped *in situ* during the preparation of chitosan submillimetric beads by ionotropic gelation with sodium triphosphate, while the latter is post-loaded during the scaffold formation. Controlled release experiments carried out under neutral conditions demonstrate that the presence of nanostructured silica within the polymer matrix retards the release of both hydrophilic substances and increases the structure stability of the scaffold. Release profiles can be fitted to a two-component model with a diffusion-controlled term (Korsmeyer-Peppas model), which dominates the release of the post-loaded substance, and a second swelling/erosion term, which becomes relevant for the *in situ* entrapped drug.

## 1. Introduction

Natural polymers are good candidates for drug carriers due to their excellent biocompatibility and biodegradability [1–3]. The incorporation of a drug into a biopolymer matrix enhances its protection against degradation and can control the release [4,5]. In addition, the ability to form hydrogels makes biopolymers ideal candidates for encapsulation of therapeutic molecules [6]. In particular, chitosan, a linear polyaminosaccharide obtained by alkaline deacetylation of chitin, is a very attractive biomaterial in this context [7–9]. In the last years, it has been widely applied in tissue engineering and bone repair [10–12].

On the other hand, organic/inorganic hybrid structures are able to protect the encapsulated payloads from the surrounding environment and allow their release in a controlled manner [11,13–16]. In this sense, silica nanoparticles in suspension can be formed by sol–gel process in the presence of polysaccharides, yielding the formation of a hybrid polymer structure with potential use in the delivery of therapeutic agents [17–24].

In this work, a loaded hybrid chitosan/silica three-dimensional scaffold was prepared by ionotropic gelation, which minimizes the use of toxic organic solvents or chemical cross-linking agents. Its efficiency for entrapping two different hydrophilic molecules was investigated. Chitosan was used as the main polymer component, and silica was used as a structuring additive. Finally, release experiments were carried out in phosphate buffer (pH = 7.4) at 37 °C by using erioglaucine and ibuprofen sodium salts as hydrophilic substances.

## 2. Experimental procedure

Chitosan and chitosan/silica macroscaffolds were prepared in a two-step process based on an ionotropic gelation method, schematically represented in Fig. 1. Sodium triphosphate (STP) was used as an ionic cross-linker. In the first step, analogously to a previously reported strategy [25], chitosan and chitosan/silica submillimetric beads were prepared by extrusion of a 3 wt% chitosan aqueous suspension ($M_v$ = 50,000–190,000 Da, 75–85 % deacetylated), acidified with acetic acid (overall concentration: 2 wt%), into an aqueous STP solution (2.34 wt %). For silica-containing particles, tetraethyl orthosilicate (TEOS) was added to an analogous chitosan solution (overall TEOS concentration: 3.6 wt%), containing hydrochloric acid (1.0 wt%) in addition to acetic acid. The first hydrophilic payload, ibuprofen sodium salt, was dissolved in this suspension (10 wt%). In the second step, the wet beads were placed in a circular Teflon mold (Ø 20 × 9 mm) and gathered and adhered with another chitosan solution that contains the second hydrophilic substance (erioglaucine disodium salt, 1 wt%). Erioglaucine is entrapped via a post-loading mechanism during the formation of the

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scaffold. Samples without the payloads were prepared as references. The different compositions of the scaffolds prepared in this work are summarized in Table 1. Further details about the experiments are given in the Supplementary Information.

## 3. Results and discussion

The morphology of the prepared chitosan scaffolds was compared to the hybrid chitosan/silica ones by optical microscopy and scanning electron microscopy (SEM). The corresponding micrographs are shown in Fig. 2a–d. The pure chitosan scaffold (sample **SF1**) presents a regular structure with a smooth surface, while chitosan/silica hybrid samples (sample **SF2**) show a certain roughness, attributed to the presence of silica nanostructures, embedded within the chitosan matrix during the formation process. The average size of the beads is 800 ± 50 μm, as statistically measured from SEM micrographs. TEOS is added to the chitosan solution in the pre-formation step of the beads, leading to a sol–gel process under acidic conditions. The alkoxide groups of TEOS are hydrolyzed to silanol, which condense to form nanostructured $SiO_2$. Silica is entrapped in the polymer matrix during cross-linking, being responsible for the observed roughness of the hybrid structures. The comparison of measurements by thermogravimetric analysis (TGA) of samples with and without silica indicates a silica amount of *ca.* 10 % (see Supplementary Information).

**Table 1**
Formulation of the prepared scaffolds.

| Sample | System | Polymer:STP:TEOS weight ratios | *In situ* loaded drug | Post-loaded drug |
|---|---|---|---|---|
| **SF1** | Chitosan | 3:12:0 | — | — |
| **SF2** | Chitosan/ silica | 3:12:4 | — | — |
| **SF3** | Chitosan | 3:12:0 | Ibuprofen | Erioglaucine |
| **SF4** | Chitosan/ silica | 3:12:4 | Ibuprofen | Erioglaucine |

The swelling behavior of the prepared scaffolds, presented in Fig. 2e–f, was evaluated in both neutral (pH = 7.4) and acidic (pH = 3) buffers at different times. For samples without silica, the swelling percentage is higher in acidic than in neutral medium, which is related to the dissolution of chitosan at low pH values. In contrast, as a result of the increased structural stability of the silica-containing samples, the acidity shows little effect on the swelling of silica/chitosan hybrids. The presence of silica retards and even avoids the dissolution of the chitosan network, limiting the swelling of the scaffolds.

As previously reported [25], the entrapment efficiency of hydrophilic substances in systems with silica increases significantly with respect to systems without. Ibuprofen sodium salt was entrapped *in situ* during the precipitation of the hydrogel beads, whereas erioglaucine

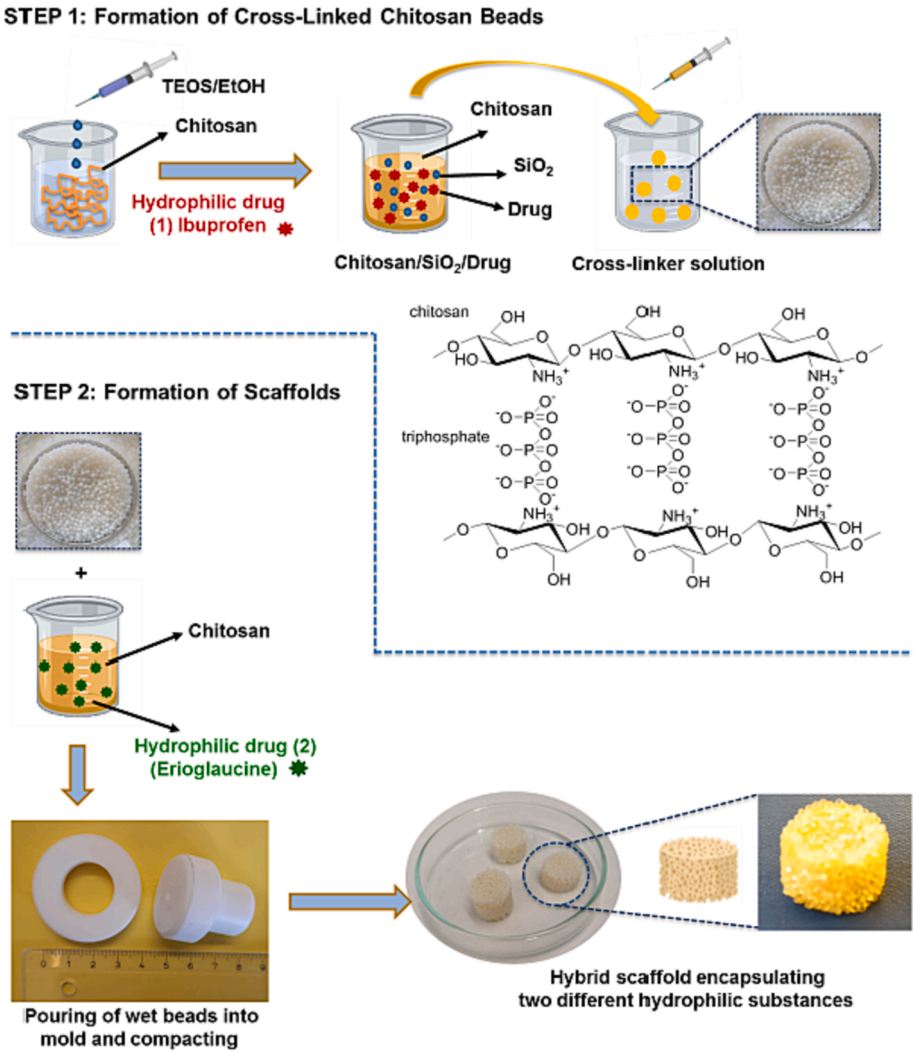


**Fig. 1.** Schematic representation of the formation of chitosan/silica scaffolds in two steps: first, preparation of cross-linked chitosan/silica hydrogels encapsulating a first hydrophilic substance by *in situ* loading, and second, collecting and adhesion process of hydrogel beads to form the hybrid scaffold.

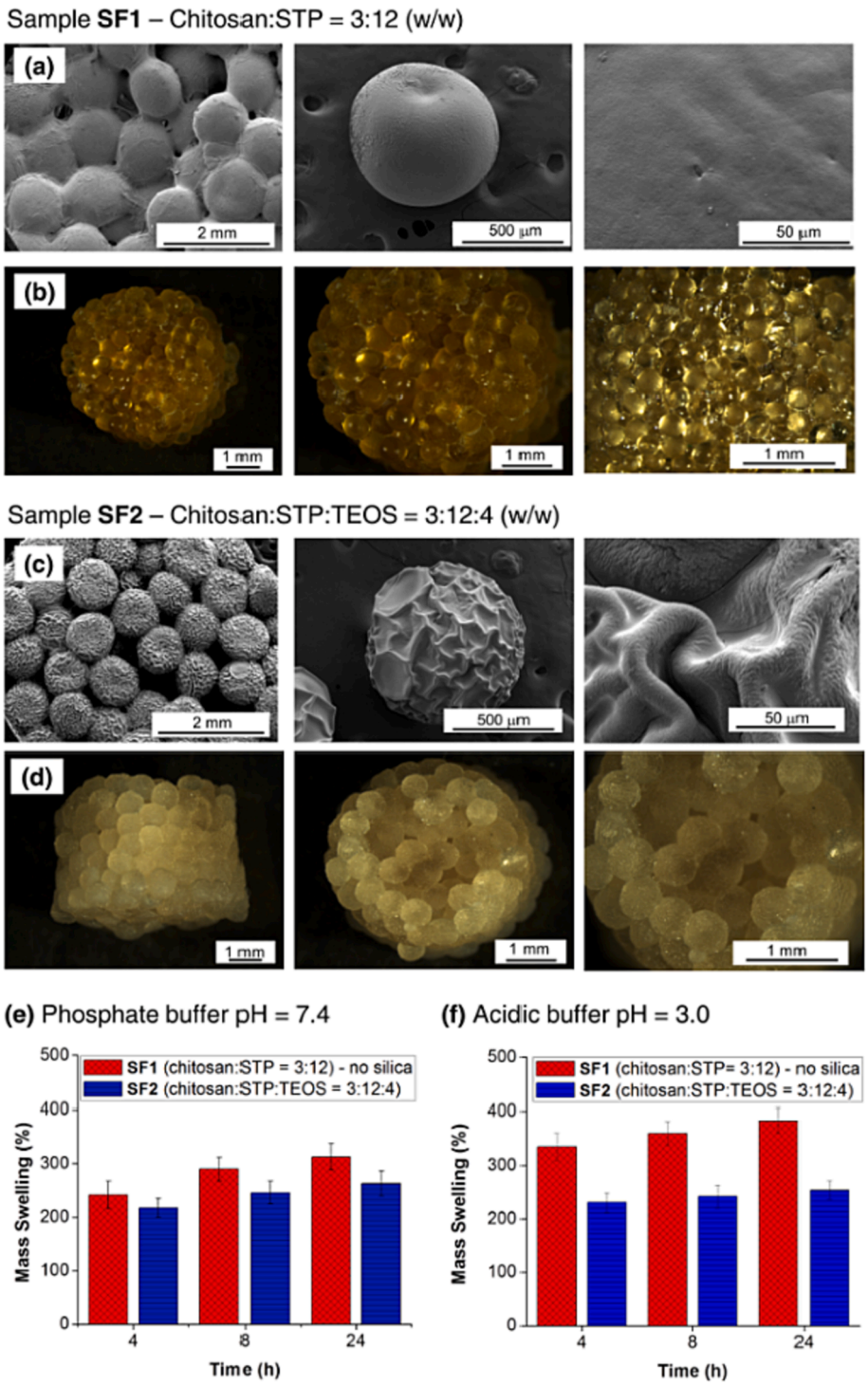


**Fig. 2.** Micrographs of a chitosan and a chitosan/silica scaffold by SEM (a,c) and optical microscopy (b,d), and swelling percentage at different times of chitosan and chitosan/silica scaffold with different polymer:STP:TEOS weight ratio (3:12:0 and 3:12:4, respectively) in two different immersion media: (e) pH = 7.4 and (f) pH = 3.

disodium salt was post-loaded during the formation of the 3D-scaffold. In phosphate buffer, the presence of silica retards the release of both substances with respect to only chitosan samples (Fig. 3). The obtained data of cumulative release as a function of time, $Q(t)$, can be well fitted to a two-term model, previously reported for drug release in mesoporous silica [26,27], which follows the expression.

$$Q(t) = \frac{Q_{\max}}{1 + e^{-k_1(t-t_{\max})}} + k_2 t^n \quad (1)$$

where the first term is a sigmoidal component related to modifications in the scaffold (swelling and/or erosion caused by degradation) and the second term is related to diffusion (analogous to the Korsmeyer–Peppas power law [28]). $Q_{\max}$ is the total release fraction at infinite time, $k_1$is a rate constant, $t_{\max}$ is the time for the maximum rate in the sigmoidal release, $k_2$ is a constant related to the diffusion, and $n$ the diffusional parameter typical of the release mechanism (see fitting parameters in Supplementary Information). The percentage contribution of the second term to the final fitting indicates how much diffusion

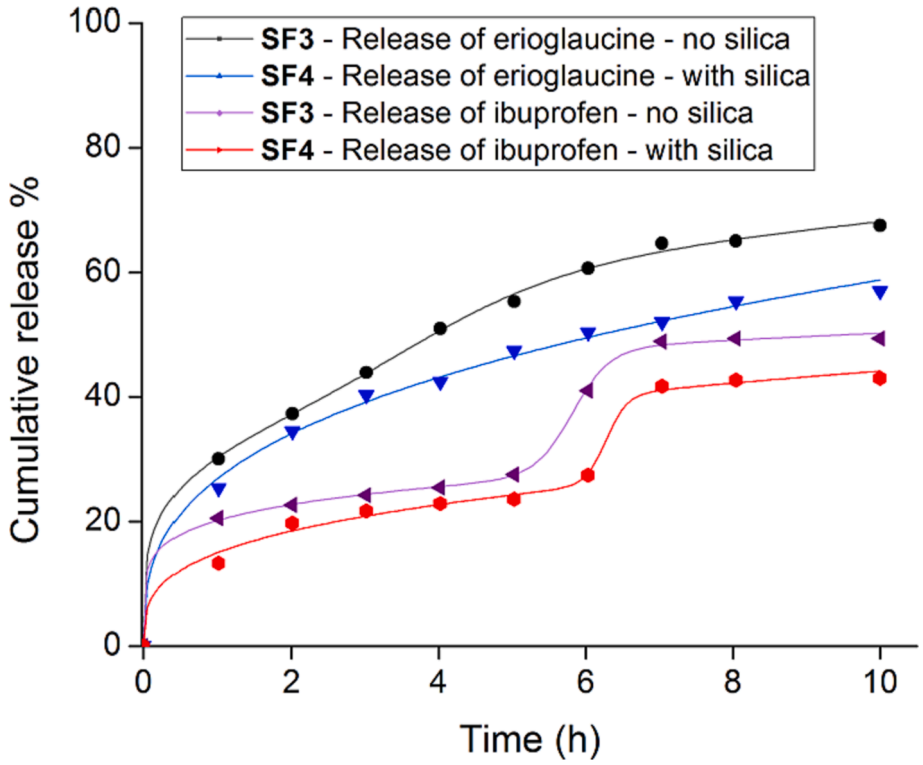


**Fig. 3.** Cumulative release of both ibuprofen and erioglaucine from the chitosan and hybrid chitosan scaffold in phosphate buffer pH = 7.4. Solid lines were calculated from fitting data to Eq.(1).

controls the release. The results demonstrate that the release of erioglaucine occurs mostly by diffusion (diffusive contribution of 75 % for **SF3** 75 % and of 100 % for **SF4**), that is, it follows a Korsmayer–Peppas kinetics. In contrast, ibuprofen releases by a mixed mechanism (diffusive contribution of 58.8 % and 66.7 % for **SF3** and **SF4**, respectively), which is explained by the "double barrier" that the drug needs to pass: a liberation of the beads during the swelling process and a diffusion from the scaffold to the release media. The swelling has an influence in the liberation of the drug loaded during the formation of the particles (ibuprofen), but it does not significantly affect the liberation of the one entrapped outside during the formation of the scaffold (erioglaucine).

## 4. Conclusions

Chitosan was used as a polymer matrix for generating a hybrid polymer/silica scaffold based on submillimetric beads prepared by an ionotropic gelation method. The scaffolds, which are able two encapsulate simultaneously-two hydrophilic substances (i.e., erioglaucine and ibuprofen sodium salts) are prepared by adhesion of the beads within a mold. The incorporation of silica nanostructures in the scaffold increases its structural stability and retards the release behavior in neutral environments. Our results indicate that the release can be fitted to an expression with two terms: a first one related to changes in the scaffold structure by swelling or erosion (the latter caused by possible degradation of the polymer matrix in the release medium), and a second one related to diffusion. The two terms are important for ibuprofen, embedded *in situ* during preparation of the beads, while the release of the post-loaded erioglaucine is mainly controlled by diffusion.

## CRediT authorship contribution statement

**Asmaa Elzayat:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Visualization. **Francisco F. Pérez-Pla:** Methodology, Validation, Formal analysis. **Rafael Muñoz-Espí:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing, Supervision, Project administration.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rafael Muñoz-Espí reports that financial support was provided by Max Planck Society (Germany).

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.matlet.2022.132941.

## References

[1] F. Maestrelli, M. Jug, M. Cirri, I. Kosalec, P. Mura, Carbohydr. Polym. 192 (2018) 176–183.
[2] M.A. Hood, K. Landfester, R. Muñoz-Espí, Colloids Surf. A 540 (2018) 48–52.
[3] V. Mukwaya, C. Wang, H. Dou, Polym. Int. 68 (3) (2019) 306–319.
[4] J. Park, M. Ye, K. Park, Molecules 10 (2005) 1.
[5] J. Tsung, D.J. Burgess, in: Fundamentals and Applications of Controlled Release Drug Delivery, Springer, US, Boston, 2012, pp. 107–123.
[6] L.A. Caetano, A.J. Almeida, L. Gonçalves, Mar. Drugs 14 (5) (2016) 90.
[7] E. Cevher, Z. Orhan, L. Mülazımoğlu, D. Şensoy, M. Alper, A. Yıldız, Y. Özsoy, Int. J. Pharm. 317 (2) (2006) 127–135.

[8] H. Peniche, C. Peniche, Polym. Int. 60 (6) (2011) 883–889.
[9] M. Fernández-Gutiérrez, O. Bossio, L.G. Gómez-Mascaraque, B. Vázquez-Lasa, J. S. Román, Macromol. Chem. Phys. 216 (12) (2015) 1321–1332.
[10] G. Toskas, C. Cherif, R.-D. Hund, E. Laourine, B. Mahltig, A. Fahmi, C. Heinemann, T. Hanke, Carbohydr. Polym. 94 (2) (2013) 713–722.
[11] C.E. Tanase, M.I. Popa, L. Verestiuc, J. Biomed. Mater. Res. B 100 (3) (2012) 700–708.
[12] D. Meng, L. Dong, Y. Wen, Q. Xie, Mater. Sci. Eng. C 47 (2015) 266–272.
[13] S. De Koker, R. Hoogenboom, B.G. De Geest, Chem. Rev. Soc. 41 (7) (2012) 2867–2884.
[14] J. Gaitzsch, X. Huang, B. Voit, Chem. Rev. 116 (3) (2016) 1053–1093.
[15] S. Behzadi, M. Steinmann, D. Estupiñán, K. Landfester, D. Crespy, J. Controlled, Release 242 (2016) 119–125.
[16] M. Hajir, P. Dolcet, V. Fischer, J. Holzinger, K. Landfester, R. Muñoz-Espí, J. Mater. Chem. 22 (12) (2012) 5622–5628.
[17] Y. Zhang, B.Y.W. Hsu, C. Ren, X. Li, J. Wang, Chem. Rev. Soc. 44 (1) (2015) 315–335.
[18] T.P. Doan-Nguyen, P. Natsathaporn, R. Jenjob, Y. Niyom, S. Ittisanronnachai, A. Flood, D. Crespy, Langmuir 35 (35) (2019) 11389–11396.
[19] J.-L. Blin, M.-J. Stébé, B. Lebeau, Curr. Opin. Colloid Interface Sci. 25 (2016) 75–82.
[20] J. Fan, S. Wang, W. Sun, S. Guo, Y. Kang, J. Du, X. Peng, AlChEJ. 64 (3) (2018) 835–859.
[21] E. Ilhan-Ayisigi, O. Yesil-Celiktas, Eng. Life Sci. 18 (12) (2018) 882–892.
[22] Y. Niyom, T. Phakkeeree, A. Flood, D. Crespy, J. Colloid Interface Sci. 550 (2019) 139–146.
[23] S.K. Pramanik, S. Seneca, M. Peters, L. D'Olieslaeger, G. Reekmans, D. Vanderzande, P. Adriaensens, A. Ethirajan, RSC Adv. 8 (64) (2018) 36869–36878.
[24] Y. Wen, J.K. Oh, Macromol. Rapid Commun. 35 (21) (2014) 1819–1832.
[25] A. Elzayat, E. Tolba, F.F. Pérez-Pla, A. Oraby, R. Muñoz-Espí, Macromol. Chem. Phys. (2021) 2100027.
[26] L. Gao, J. Sun, Y. Li, J. Solid State Chem. 184 (8) (2011) 1909–1914.
[27] P. Burguete, A. Beltrán, C. Guillem, J. Latorre, F. Pérez-Pla, D. Beltrán, P. Amorós, ChemPlusChem 77 (9) (2012) 817–831.
[28] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Int. J. Pharmaceut. 15 (1) (1983) 25–35.