Nanostructured materials as drug delivery systems

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Nanotechnology represents a new field of research and includes a wide range of technologies and potential applications. One approach consists on creating new materials which are structured at the nanoscale using sol-gel chemistry. Such materials could be of different pore size or morphology. Nanostructured silicas such as Micelle-Templated Silicas (MTS) materials feature unique textural properties owing to their uniform distribution of mesopores with tunable sizes. Since 2002, we have developed a synthesis strategy to control the particle morphology of MTS at the micro- to millimeter scale. Concerning drug delivery systems, we have evaluated the ability of such mesoporous materials for hosting a non-steroidal anti-inflammatory drug (ibuprofen). Different procedures were evaluated: impregnation of calcined mesoporous materials[1], direct synthesis and drug grafting[2]. We show that it is possible to incorporate ibuprofen in MTS in a range compatible with poorly soluble drugs. The release depends on the way ibuprofen is incorporated. Fast release is observed for the “impregnation” and the “direct synthesis” methods that may indicate that ibuprofen is in a molecular state[3]. We have chosen a second direction that allows in fully investigating the potentialities of sol-gel, self-assembly and spray-drying processes in order to form directly new textured materials acting as DDS with tuneable properties. Spray-drying bears also the advantage of being a scalable process and reducing the number of steps. Furthermore we consider a one-pot synthesis in which organometallic oligomers, drug and surfactant molecules are mixed together in solution. During spray-drying of the solutions, these chemicals interact together, eventually phase-separate inside the droplets and form the final microspheres. Here, we particularly show how a simple tuning of the drug and the surfactant contents can lead to very different drug dispersions at the nanometre scale, and consequently to very different drug release profiles[4]. Finally, we proposed a novel approach to confine drugs in mesoporous silica materials. We first prepared a new ionic liquid ([BMIm][Ibu]) were the drug (Ibuprofenate) is the anion and used this new IL to prepare ionogels. Their silica walls could be functionalized to control the drug release[5].

Another example of nanostructured silica materials as DDS is given by the preparation and release property of hybrid lipid/silica materials. First, we have adapted a typical two-step room-temperature MTS (micelle-templated silica) preparation in which the colloidal solution of amphiphiles is replaced by small unilamellar liposomes[6]. The result is the formation of silica shell nanospheres with non-porous walls and a narrow size distribution. We show that kinetic releases of a hydrophilic fluorescent probes depend on the lipid composition of liposomes. The use of zwitterionic phospholipids (non toxic) as templates requires a modified approach since the liposome structure is sensitive to low pH, high ionic strength. The silica growth is directed by the receptiveness of the quaternary ammonium surface of the phospholipid to the silica. We have also advanced this original report in a number of ways. We have reduced the cluster-like particle aggregation into chain-like aggregates of particles by the use of PEGylated phospholipid. We extended the liposil's shell nature to include hydrophobic modifications. We showed the feasibility of the triggered release of the encapsulated content with two types of remote energy sources[7]. Finally, a new supra-organized hybrid material obtained in “green“ conditions via anionic exchange of self-assembled unilamellar anionic liposomes with the nitrate ions present in the interlayers of layered double hydroxides (LDH), is fully characterized[8]. This material presents original properties linked to the simultaneous presence of a phospholipid bilayer derived from liposomes, still used as vectors for lipophilic drugs, and LDH which protects the bilayer and brings about a pH-sensitivity. The exchange rate is controlled via the added amount of liposomes. TGA, XRD and TEM confirm the organisation of the trapped phospholipids as a bilayer. The presence of the latter allows the material to load lipophilic and neutral drugs which represent the largest fraction of those newly synthesized. Furthermore, in physiological conditions, preliminary tests show a sustained release of phospholipids (1.5% for 7 days and 6% for 14 days) while a fluorescent lipophilic drug-mimic reveals the reorganisation of the phospholipids into liposomes in the release medium. In the field of biocompatible materials these new hybrid particles have a strong potential for the storage and sustained release of neutral or lipophilic drugs.

References

[1] C. Charnay, S. Bégu, C. Tourne-Peteilh, L. Nicole, D.A. Lerner, J-M. Devoisselle., *European Journal of Pharmaceutics and Biopharmaceutics,* (2004) 57, 533-540.
[2] C. Tourné-Péteilh, D. Brunel, S. Bégu, B. Chiche, F. Fajula, D.A. Lerner, J.-M. Devoisselle *New Journal of Chemistry* (2003) 27, 1415 – 1418.
[3] T. Azais, T. Tourné-Péteilh, F. Aussenac, N. Baccile, C. Coelho, J-M Devoisselle, F. Babonneau, *Chemistry of Materials* (2006) 18, 6382-6390.
[4] M. Fatnassi, C. Tourné-Péteilh, T. Cacciaguerra, J-M. Devoisselle, B. Alonso, *New. J. Chem* (2010) 34, 607–610.
L. Viau, C. Tourné-Péteilh, J-M. Devoisselle, A. Vioux. *Chem. Comm.,* 2010, 46, 2, 228-230.
[6] S. Begu, A. Aubert-Pouessel, D.A. Lerner, C. Tourné-Péteilh, J-M Devoisselle. *Journal of Controlled Release* (2007) 118, 1, 1-6.
[7] Y. Steinberg, A. Schroeder, Y. Talmon, J. Schmidt, R.L. Khalfin, Y. Cohen, y, J-M. Devoisselle, S. Bégu, D. Avnir *Langmui*r (2007), 23(24), 12024-12031.
[8] S. Bégu, A. Aubert, R. Polexe, E. Leitmanova, D-A. Lerner, C. Tourné-Peteilh, J-M. Devoisselle, D. Tichit. *Chem. Mater* (2009) *21,* 13, 2679–2687.