Compressed Fluid Based Technologies for the Preparation of Drug Delivery Systems

Elizondo E[1], Ventosa N[1], Sala S[1], González D[2], Blanco-Príeto M.J[2], Veciana J[1]**

[1] Molecular Nanoscience and Organic Materials Department. Institut de Ciència de Materials de Barcelona (CSIC)-CIBER-BBN, Campus de la UAB s/n 08193-Bellaterra (Barcelona), SPAIN. Phone: 34 93 580 18 53, Fax: 34 93 580 57 29
[2]Department of Pharmacy and Pharmaceutical Technology , University of Navarra, Irunlarrea s/n, Pamplona 31080, Spain
contact e-mail: vecianaj@icmab.es, ventosa@icmab.es

From an esthetic perspective, it is attractive to build all desirable pharmacological features of a drug- such as solubility, stability, permeability to biological membranes, and targeting to particular tissues, cells and intracellular compartments- into the drug molecule itself. But it would be simpler and perhaps more powerful to obtain these features by decoupling the biological action of the drug from the other biochemical and physicochemical characteristics that determine these key features of its pharmacology [1]. In agreement with this, the obtaining of new micro- and nanostructured molecular materials, and the understanding of how to manipulate existing materials at nanoscopic level, are playing a crucial role in the fields of drug delivery and clinical diagnostics.

However, in order to be able to commercially exploit the enormous potential of these nanomedicines is necessary the development of efficient and environmental respectful technologies for the manufacturing at industrial scale of these nanostructured materials. Technologies using compressed fluids (CFs) – such as CO_2 – have been proved to be very effective for the straightforward preparation of micro- and nanoparticulated materials, with reproducible supramolecular organization (i.e. crystallinity degree, polymorphic form) [2-7]. Therefore, using compressed solvent media it is often possible to prepare materials with unique physico-chemical characteristics (size, porosity, supramolecular organization, morphology, etc…) unachievable with classical liquid media. Therefore, in this work, we have chosen a CO_2 based process for the preparation of a micro and nanoparticulate material for the treatment of Brucellosis.

Brucellosis is a worldwide zoonosis caused by different species of the genus Brucella. The intracellular location of this pathogen, particularly in macrophages, renders treatment difficult since most antibiotics –such as gentamicin- known to be efficient in vitro, do not actively pass through cellular membranes. The enhancement of intracellular penetration by using biodegradable polymers as drug carriers has already been studied [8,9]. Complementary to other conventional methods, compressed fluid techniques have found many useful and sometimes unique applications in the production and processing of such drug delivery systems [10]. In this work, the gentamicin:polymer microparticles were prepared by the method called Precipitation with a Compressed Antisolvent (PCA). In a PCA process a liquid solution is sprayed though a nozzle into a compressed antisolvent, which rapidly diffuses into the sprayed droplets causing the precipitation of the solute. It was proved that by using this PCA process much higher loading factors of the antibiotic were achieved compared to conventional processes for production of nanoparticles. Five different composites were prepared with different proportions between the antibiotic (an inonic complex of gentamicin sulphate and bis(2-ethylhexyl) sulfosuccinate sodium salt (AOT), *GmAOT*) and the biodegradable polymer (poly(methylvinylether/maleic anhydride), *gantrezAN*): 0.09:1, 0.19:1, 0.37:1, 0.67:1, 1:1 (GmAOT:gantrezAN, w:w) [11].
It was observed that by increasing the amount of antibiotic in the composite, both the morphology and the primary particle size of the resulting nanostructured material changed. In vitro studies were performed in order to check the activity of the composites against the

Brucella. All the compositions have shown the same activity as the one observed for the equivalent quantity of gentamicin sulphate. By achieving this high loading factors reduced doses would be needed and therefore, an easier and faster treatment could be provide to the patients.

References:

[1] J.A Hubbel, Science, **300** (2003) 595.
[2] D.W. Matson, J.L. Fulton, R.C. Petersen, R.D. Smith, Ind. Eng. Chem. Res, **26**, (1987) 2298.
[3] (a) N. Ventosa, S. Sala, J. Veciana, J. Llibre, J. Torres, Cryst. Growth & Design, **1** (2001) 299. (b) N. Ventosa, S. Sala, J. Veciana, J. Supercrit. Fluids, **26 (**2003) 33. (c) M. Gimeno, N. Ventosa, S. Sala, J. Veciana, Cristal Growth & Design, **6** (2006) 23.
[4] M. Cano-Sarabia, N. Ventosa, S. Sala, C. Patino, R. Arranz, J. Veciana, Langmuir, DOI: 10.1021/la7032109
[5] E.Weidner, Z. Knez, Z. Novak, PGSS (Particles from gas saturated solutions) a new process for powder generation, in: G. Brunner, M. Perrut, (Ed.), Proceedings of the third International Symposium on Supercritical Fluids, **3** (1994) 229.
[6] P.M. Gallagher, M.P. Coffey, V.J. Krukonis, N. Klasutis, ACS Symp. Ser., **406** (1989) 334.
[7] J. Bleich, B.W. Müller, W. Wabmus, Int. J. Pharm., **97** (1993) 111.
[8] C. Lecaroz, C. Gamazo, M-J. Blanco-Príeto, J. Nanosci. Nanotechno, **6** (2006) 3296.
[9] E. Briones, C.I. Colino, José M. Lanao, J.Controlled Release, **125** (2007) 210.
[10] P. Pathak, M.J. Meziani, Y.-P. Sun, Expert Opin. Drug. Deliv, **2** (2005) 747.
[11] E. Elizondo, N. Ventosa, S. Sala, J. Veciana, E. Imbuluzqueta, D. Gonzalez, M.J. Blanco-Prieto, C. Gamazo, Patents: P200703314, P200703315. Aplication date: 7th of December of 2007.

Figures:

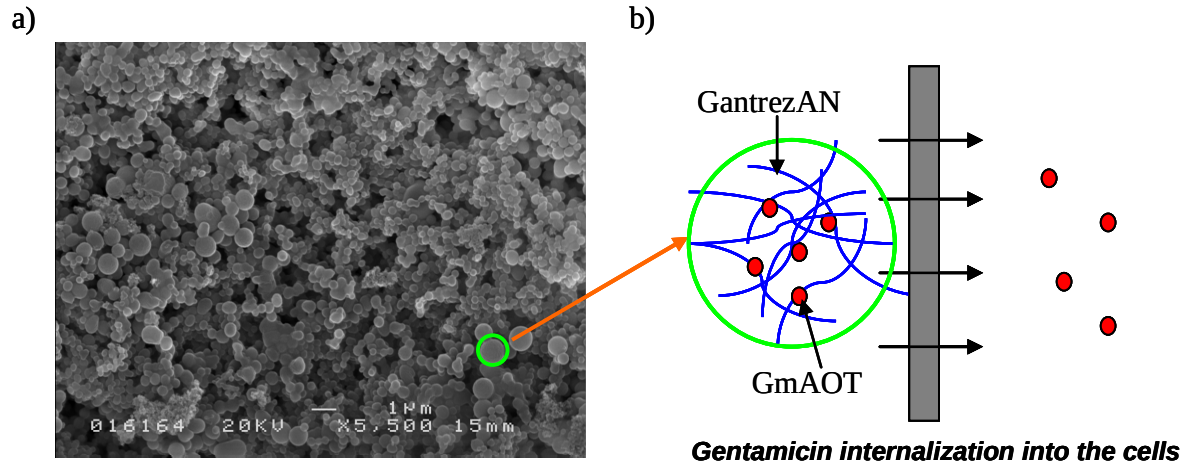

Figure 1. a) SEM image of a GmAOT:GantrezAN composite. b) Squeme of the enhanced permeability of gentamicin through cell membranes by using GantrezAN as a carrier.