Nanocarriers for Cancer Therapy

Viviana Vergaro[*], Zhiguo Zheng[**], Xingcai Zhang[**], Yuri M. Lvov[**], Giovanna Giovinazzo[***], Angelo Santino[***], Roberto Cingolani[*], Ross Rinaldi[*] and Stefano Leporatti[*]
[*]NNL-Nanoscience Institute of CNR,Via Arnesano 73100 Lecce, Italy , stefano.leporatti@unisalento.it
[**]Institute for Micromanufacturing, Louisiana Tech University, 911 Hergot Ave, Ruston, LA 71272, USA, ylvov@coes.latech.edu
[***]Institute of Sciences of Food Production C.N.R. Section of Lecce, via Monteroni, 73100, Lecce, Italy, angelo.santino@ispa.cnr.it

ABSTRACT

The desired features of pharmaceutical drug delivery for intravenous administration are their small size, biodegradability, high content of a drug in a final preparation, prolonged circulation in the blood, and the ability to target required areas. These features are usually not met in a single multifunctional carrier. For these reasons we have compared efficacy of different type of carriers having complementary properties for pharmaceutical delivery in cancer therapy. Drug nano-colloids encapsulated by combination of layer by layer (LbL) techniques and ultrasonication (1), phytochemical encapsulated-artificial oleosomes (2) and drug-loaded clay nanotubes (3) have been used for uptake by cancer cells.

Keywords: Nanocolloids, Olesomes, Nanotubes, Confocal Microscopy.

INTRODUCTION

The requested features of pharmaceutical drug delivery (such as biodegradability or targeting) for intravenous administration are reasonably well met by liposomes, microcapsules, and nanoparticles for water-soluble drugs. The development of nanoparticulate drugs displaying all of these properties for poorly soluble pharmaceuticals still represents a challenge. Low solubility in water, however, tends to be an intrinsic property of many drugs, including some powerful anti-cancer agents. Intravenous administration of relatively large aggregates of an insoluble drug may result in embolisation of these particles into small blood capillaries and may cause unwanted effects like tissue ischemia. Hence, it does not allow for achieving therapeutically significant concentrations. Many promising drug candidates never enter further development processes because of solubility problems. On multiple occasions micelles can serve as drug delivery systems for poorly soluble pharmaceuticals. However, there are problems, which include low loading efficacy of the drug into the micelles; problems with controlling the release rate of the drug, and with micelle stability.

RESULTS AND DISCUSSION

In a novel approach to form stable nanocolloids (Figure 1) of these drugs with high content of the active drug and controllable release rate, using a sonicated layer-by-layer (LbL) polyelectrolyte coating technology is suggested. This is development of traditional LbL microencapsulation based on alternate adsorption of oppositely charged components (linear polyelectrolytes, proteins, and nanoparticles). To achieve nanosize cores, aqueous suspensions of poorly soluble drugs are subjected to the powerful ultrasonic treatment [1-2]. Keeping the nanoparticles formed under the sonication to prevent their fast re-aggregation, they have been stabilized in a solution by sequential addition of polycations and polyanions and assembling ultra-thin polyelectrolyte shells on them. LbL assembly allows preparation of multilayer shells with thickness of 5 to 50 nm and necessary composition. In this process, nano-architectural approach designing shells of different components, including ones serving as diffusion barrier and outermost layers containing targeting agents, was realized. After depositing the first polycation layer on the surface of a drug nanoparticle, an oppositely charged polyanion is added. This results in the formation of a stable inter-polyelectrolyte complex shell around each drug nanoparticle [2].

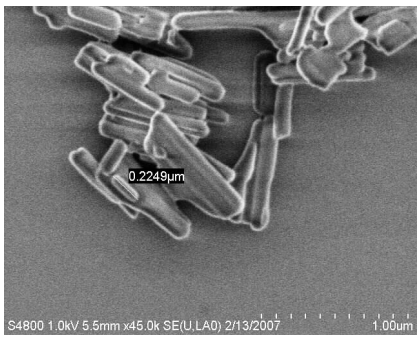

Figure 1: SEM image (Hitachi-2006) of LbL encapsulated drug nanoparticles (Paclitaxel 20 min sonication + LbL coating).

A second high cytocompatible nanocarriers we in vestigated were halloysite nanotubes [3-4]. Such cylindrical hollow aluminosilicate tubes (Figure 2) could encapsulate efficiently anti-neoplastic drugs by pumping cycles. They showed slow release (several hours) and high stability (several weeks).

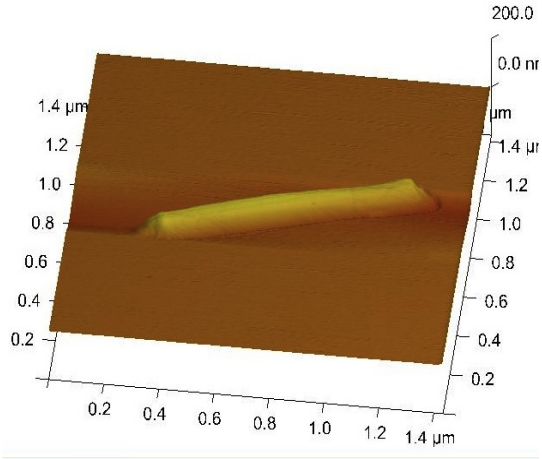

Figure 2: Three dimensional Scanning Force Microscopy image of a halloysite nanotube.

Halloysite nanotubes were readily uptaken by cancer cells and showed very low cytotoxicity, beeing an ideal candidate for drug delivery into human cancer tissues [5].

A third systems as challenging natural carrier for cancer therapy were oleosomes or plaint oil bodies (OBs). [6] They are specialised organelles ubiquitously detected in plant oil seeds, which serve as lipid storage compartments. OBs consist of a hydrophobic core of TAGs, surrounded by a monolayer of phospholipids (PLs) embedded with some specific proteins with a size ranging from 0.5 to 2 µm.

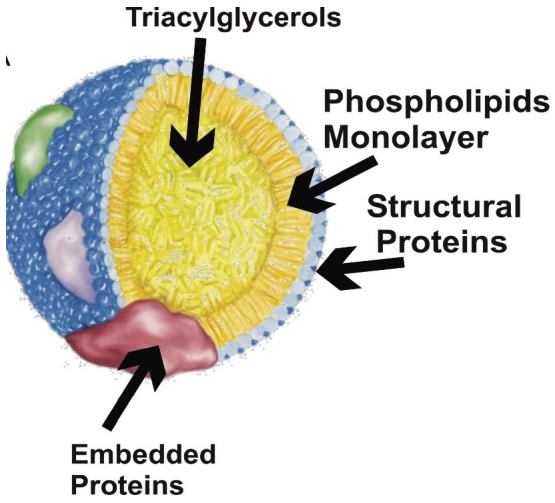

Figure 3: Schematic representation of a plant oil body

An easy method to reconstitute natural OBs starting from their constituents and to encapsulate lipophilic molecules, i.e. the fluorescent fluorescein isothiocyanate (FITC) and carboxyfluorescein (CF), into reconstituted OBs. This methods allowed us to produce OBs 4-10 fold smaller (50-200 nm) than the native one and to obtain a good recovery (about 40 %) of both the fluorescent compounds used in the present work [7].

We verified the uptake of FITC-loaded OBs into the MCF-7 breast cancer cell line (see Figure 4). Therefore OBs could be envisaged as novel carriers to deliver hydrophobic drugs and bioactive compounds.

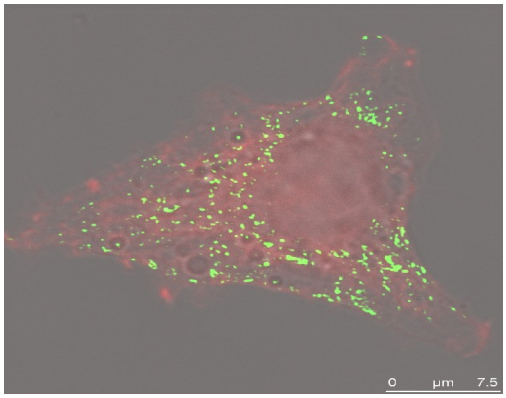

Figure 4: Scanning Confocal image of FITC- encapsulated OBs uptaken by a breast cancer cell (phalloidin-TRITC cytoplasm staining).

CONCLUSIONS

Three different type of nanocarriers as possible drug-*nanovehicle* for cancer therapy were studied in this work.

1) Stable nanocolloids of insoluble drugs with very high drug content were prepared through the application of the sonicated LbL technology, i.e. combination of ultrasonication and alternate adsorption of oppositely charged polyelectrolytes, resulting in coated nanoparticles with the content of the drug far exceeding other known systems. Drug release rate from such nanoparticles can be controlled by assembling organized multilayer shells with required wall composition, density and thickness.

2) Halloysite nanotubes (HNTs) structure and cytocompatibility were investgated. HNTs showed very low cytotoxicity and high uptake efficiency by cancer cells.

3) Plant oil bodies as novel carriers for lipophilic delivery were characterised. Confocal results demonstrated that OBs are readily taken up by neoplastic cells and can be exploited as potential nanocarriers for loading and targeting natural bioactive compounds or anti-cancer drugs.

REFERENCES

[1] A. Agarwal. Y. Lvov, R. Sawant, V. Torchilin *J. Controlled Release*, 128, 255, 2008

[2] A. Agarwal, Y. Lvov, V. Torchilin, *Pharma Focus Asia*, iss.7, 36-40, 2008.

[3] N. Veerabadran, R. Price, Y. Lvov, *Nano J.*, 2, 215-222, 2007.

[4] Y. Lvov, D. Shchukin, H. Mohwald, R. Price, *ACS Nano*, 2, 814-820, 2008.

[5] V. Vergaro, E. Abdullayev, A. Zeitoun, R. Cingolani, R. Rinaldi, Y. Lvov, and S. Leporatti *Biomacromolecules* 11, 820-826, 2010.

[6] N.J.Roberts, R.W. Scott, J.T.C Tzen *Open Biotechnol. J.* 2, 13-21, 2008.

[7] S. Bonsegna et. al. *J. Colloid. Int. Sci.* to be submitted, 2010.