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Synthesis, characterization and bioevaluation of drug-collagen hybrid materials for biomedical applications

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ABSTRACT

This work presents a study based on the preparation and characterization of drug-collagen hybrid materials. Materials used for obtaining drug-collagen hybrids were collagen type I (Coll) as matrix and fludarabine (F) and epirubicin (E) as hydrophilic active substances. After incorporation of drugs into Coll in different ratios, the obtained hybrid materials (Coll/F and Coll/E) could be used according to our results as potential drug delivery systems in medicine for the topical (local) treatment of cancerous tissues (*e.g.* the treatment of breast, stomach, lung, colorectal or advanced ovarian cancer).

The materials were characterized considering their composition (by XRD, FT-IR and DTA–TG) and their morphology (by SEM). The delivery of drug was assessed by UV–vis.

The *in vitro* citotoxicity demonstrates an antitumoral activity of the obtained hybrid materials and their potential use for biomedical applications as drug delivery systems in tumoral treatments.

1. Introduction

Drug delivery systems (DDS) with control release are one of the top applications for human health, a new domain in material science with biomedical application. Developing new active molecules and possible treatments like genetic therapy leads to discovering new therapeutically agents and their improved administration mechanisms. From practical point of view a DDS is the component that controls the quantity and the delivery period of a drug (*e.g.* released dose in time) in some places of the body. In comparison with traditional therapy, that presents an oscillatory curve of drug concentration in plasma, DDS with controlled release are made to maintain the same concentration at a therapeutic level during the treatment.These unique characteristics recommend mesoporous materials for DDS with controlled release, thus there were made serious researches last years (Vallet-Regi et al., 2007).

Commercial DDS, especially based on polymers technology, are successful DDS with a large spectrum of application like implanted drugs, with oral, transdermal and i.v. administrations. These systems are used in other medical and pharmaceutical applications such as orthopedic and stomatology. However, one of the main specific problems of DDS is lowering the activity of some drugs before it gets to the tissue, due to premature degradation of the active agent. Thus, systems responding to stimuli without spontaneous full release can have an essential contribution in solving this problem. Other specific treatments used for long term may require an increase or a decrease of release rate, according to the disease evolution. For this purpose, implanted systems capable to respond on external stimuli (*e.g.* magnetic field) or internal pH variations are interesting even if there is or not spontaneous full release (Vallet-Regi et al., 2007; Ahmed et al., 2013).

DDS interacts with physiological medium when its functions are fulfilled during oral administration or implantation. While the oral administration presents non-toxicity, the implants must be biomaterials, that is non-viable material that became part of the body for long or short period, having the purpose to recover, improve or replace the natural functions of living tissue or organs. Therefore, adequate functioning of implanted materials depends on its long term compatibility, a dynamic process with two characteristics: host effects on the material in time and material effects on the host. In addition, implanted material biocompatibility is based on some parameters like the implantation place, shape and dimension of the material and its surface chemistry (Friess, 2004; Ding et al., 2006).

There is a large field of intelligent DDS with controlled release. Most common delivery graphs for mesoporous materials presents

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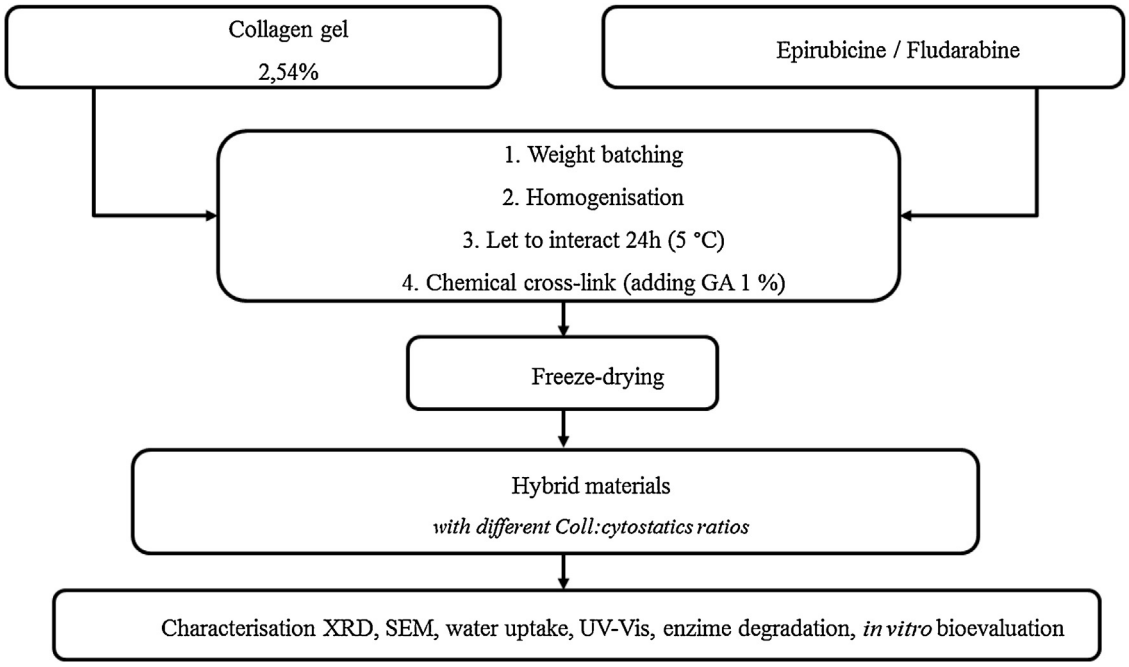

Fig. 1. Scheme of the synthesis of Coll/cytostatic hybrid materials with desired morphology and biological activity.

four profiles. The first profile, obtained for unfunctionalized matrix, has initially a maximum and then a long and lent release period. This first profile can be used for emergency high dose in acute infections or inflammations. The second profile is associated with the diffusion or dissolution process, which generally has first order kinetics, maintaining the drug concentration. The third profile corresponds to a process with zero order kinetics, in other words, the release process is time dependent. This profile is used for long term DDS. The last process is more complex, depending on external stimuli as pH, temperature, magnetic field (Vallet-Regi et al., 2007).

DDS mechanisms of multicomponent materials with the four presented profiles are: drug-solution diffusion through the coat (when the fluid gets to membrane and solubilize the active substance); erosion-system gradual destruction which allows drug delivery; osmosis based on water penetration which leads to an osmotic pressure in the particle, followed by release of the medicament on the outside (Dey et al., 2008; Kumari et al., 2010).

One of the most important problems of medical field is the cancer treatment. Cancer therapy is one of the three pylons of this type of treatment with chirurgical treatment and radiation therapy. Generally, antitumor drugs are classified in three categories: cytotoxic, biological and hormonal agents. Cytotoxic agents are the traditional treatment which affects cancerous cells, by interfering with DNA, inhibiting cells division. This type of treatment has the big disadvantage of killing healthy cells with the cancerous ones. The major classes of cytotoxic agents include alkylating agents, antimetabolites and plant alkaloids. Biological agents include monoclonal antibodies and cancer vaccines. This therapy (also called immunotherapy or biotherapy) uses the body's immune system to treat cancer. Hormonal therapy interferes with hormone dependent routes which allow the growth of cancer cells and plays an important role in the treatment of prostate cancer and breast cancer. It includes tamoxifen and aromatase inhibitors (Mazzaferro et al., 2013).

Collagen is an excellent material which can be used in applications such as controlled drug delivery systems due to the high biocompatibility properties and hemostatic and wound healing. Drug controlled release systems that have collagen matrix as support are often used as skin and bones, being the main component of these tissues (Lungu et al., 2013; Voicu et al., 2013; Wallace and Rosenblatt, 2003).

Cytotoxic agents used in the preparation hybrid materials were epirubicin ($C_{27}H_{29}NO_{11}$) and fludarabine ($C_{10}H_{13}FN_5O_7P$), both being used (usually in a mixture with other compounds) in chemotherapy to treat various types of cancer like breast, stomach,

Table 1
Composition of synthesized hybrid materials.

Code of hybrid material	Conc. Epirubicin (%)	Conc. collagen (%)
A	1	2.54
A1		1.5
A2		1
A3		0.5
B	3	2.54
B1		1.5
B2		1
B3		0.5
C	5	2.54
C1		1.5
C2		1
C3		0.5
Code of hybrid material	**Conc. Fludarabine (%)**	**Conc. collagen (%)**
D	1	2.54
D1		1.5
D2		1
D3		0.5
E	3	2.54
E1		1.5
E2		1
E3		0.5
F	5	2.54
F1		1.5
F2		1
F3		0.5

These materials were weighted as dried components.