# GREEN SYNTHETIC STRATEGY FOR OXIDE MATERIALS: POLYSACCHARIDES-ASSISTED SYNTHESIS. PART III.

## DEXTRAN-ASSISTED SYNTHESIS OF NANOSIZED METAL-OXIDES

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Dextran is an attractive biopolymer suitable in biomedical fields, especially due its non-toxicity, biocompatibility and biodegradability. Its unique characteristics make the dextran an interesting starting material for the design of nanosized metal oxide materials. This article presents the implications of the dextran in co-precipitation and gel template synthesis of some metal oxide nanoparticles.

## INTRODUCTION

Metal – oxide nanoparticles present a great interest among researchers owing to their applications in ceramics, coatings, catalysts, sensors, semiconductors, magnetic data storage, solar energy devices, ferrofluids, but also in medical field such as hyperthermia, bioimaging, cell labeling, drug delivery systems etc. However, these applications are limited, being related to their surface nature, particle size, and also shape. Polymers have been extensively used to control particle size, acting as stabilizers and preventing the spontaneous agglomeration of nanoparticles, in order to be used in pharmaceutical and biomedical products. In this context, natural biopolymers, such as polysaccharides, are attractive candidates for use in the biomedical fields, especially due to their non-toxicity, biocompatibility and biodegradability.[1,2] Among others, dextran appears to be one of the most popular polysaccharides involved in these important fields.

Dextran is the collective name given to a large class of α-1,6- linked glucose polymers.[3] It is a branched polysaccharide composed from a majority of α-1,6- and a minority of α-1,3- or α-1,4- glycosidic linked glucose units, with molecular weight that can vary between 1000 and several hundred thousand daltons (fig. 1). The exact structure of each type of dextran depends on its specific microbial strain of origin. The linkage in dextran molecules varies from 50% to 97% α-1,6- of total linkages and the linkages of a α-1,2-, α-1,3- and α-1,4- are usually at branch points.[4]

It has the following unique characteristics appropriate to prepare nanoparticle through solution procedures: (1) flexibility of the random structure; (2) high solubility due to the high proportion of the D-glucose units linked by α-1,6-bonds; (3) high stability; (4) the of reductive character owing to the aldehyde groups that make possible an *in situ* reducing of the metallic cations;[5-7] and (5) its controlled release using dextranase.[8]

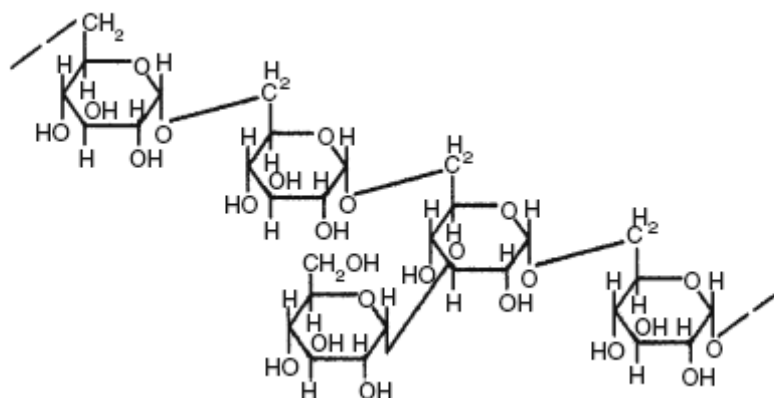* Corresponding author: dr_oana_carp@yahoo.com

Fig. 1 – Molecular formulation of dextran with α -1,3- branching.

Dextran is an attractive biopolymer suitable in medical fields, as drug delivery vehicle[9,10] and blood volume expander[11]. Such others polysaccharides, the dextran readily forms hydrogels with diverse properties and applications.[9a,9b] The swelling properties, enzymatic degradability and release behavior of dextran hydrogels have been also studied.[9c,9d]

## DEXTRAN ASSISTED CO-PRECIPITATION METHODS OF METAL OXIDES

The stabilization/capping of iron oxides, magnetite, and maghemite, has been the main application of dextran in metal oxide field.[6] Likewise, dextran coating have been considered as an alternative to the poly(ethylene glycole), many of the clinically approved superparamagnetic iron oxide nanoparticles (SPIONs) preparations being dextran-coated.[12-14] Along with its biocompatibility,[15-17] the polysaccharide and its derivatives have a high affinity (polar interactions, complexation/chelation and hydrogen bonding) for iron oxide surfaces.[18] Dextran-coated colloidal magnetic iron oxides are used in magnetic resonance imaging,[14,19] cell labeling and tracking[20-22] and cell sorting[23,24]. Most of the dextran coating procedures are performed *in situ*[25,26] but the grafting of the polymer on the magnetic particles, the post-synthesis coating methods, are also used.[27,28]

The *in situ* dextran coating was first used by Molday and Mackenzie[26], the procedure being also applied for various dextran derivatives, including carboxydextran and carboxymethyl dextran.[6]

Carp *et al.*[29] have investigated the thermal behaviour of two types of dextran (with the molecular mass of 40 000 and 70 000) - coated magnetites obtained by a post synthesis procedure, the polysaccharide being connected to the iron oxide surface by means of hydrogen-bonds, with a lower thermal stability and through the coordination bonds with higher thermal stability.

Since, the most iron oxide-dextran interactions are hydrogen-bonds, the detachment of polymer may easily occurs. In these conditions, in order to improve the coatings stability, dextran crossslinking strategies involving for example epichlohydrin were elaborated.[30] The toxicity of epichlohydrin has led to the development of other cross-linking strategies. An interesting method to obtain ultrasmall supermaramagnetic iron oxides (VUSPIO) was developed by Duguet *et al.*[31,32] and consists in a succession of oxidation/reduction reactions involving silane compounds and dextran. The maghemite surface is modified with aminopropylsilane (APS) groups that are subsequently coupled with partially oxidized dextran *via* condensation reaction and the formation of the Schiff bases. The versatility of the VUSPIO arises from the easiness of dextran derivatization, *e.g.* by polyethylene glycole.

Single domain magnetites with a homogeneous spatial distribution were formed via an *in situ* co-precipitation using dextran-based nanoparticles carboxyl-functionalized (DANP) as coating agent and template[33] as it is represented in Scheme 1. The DANP hosts for the growing and organization of $Fe_3O_4$ nanoparticles (DAMNP), were previously synthesized by a one-pot approach, without using any organic solvent and surfactants.[34] The obtained magnetic nanocomposites exhibit saturation magnetizations similar with whose of the magnetite and have great potential in many biomedical fields.
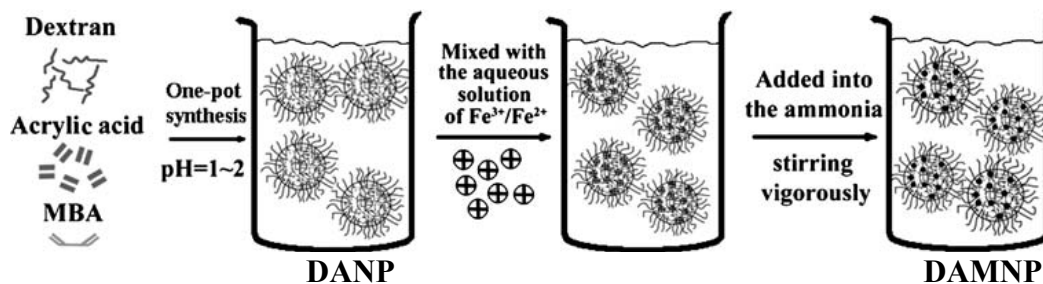
Scheme 1 – The schematic illustration of the synthesis of dextran-based nanoparticles containing carboxyl group (DANP) and dextran-Fe$_3$O$_4$ nanoparticles (DAMNP)[34] (N,N'-methylenebisacrylamide (MBA)).

A biocompatible ferrofluid containing dextran-modified magnetic nanoparticle (MNPs) has been prepared following an one step method which involve hydrazine hydrate as reducing and also precipitator agent.[35] The dextran to MNPs weigh ratio and the molecular weight of dextran strongly influence the coating efficiency, the size, dispersibility and magnetic properties of coated oxides.

Walsh *et al.*[8] have recently reported a general and simple synthetic route of dextran stabilized oxides (Fe$_3$O$_4$, Co$_3$O$_4$ and Mn$_3$O$_4$) involving a combination of co-precipitation and microwave heating procedures developed previously.[36] The obtained stable suspensions of dextran - metal oxide particles (with average diameters of ca. 10 nm) could be cast as flexible transparent films. The enzymatic treatment of the coated metal oxides with dextranase provides an effective and simple method to remove the bounded dextran.[8] Monodisperse metal oxide cores, with diameters lower than 6 nm and stabilized by a low level of residual polysaccharide have been obtained. The amount of the remained dextran is still sufficient to inhibit the particles aggregation and growth, being also a basis for new nanoparticle assays.

Dextran assisted precipitation methods were used also to obtain iron oxide nanorods. Perez *et al.*[37] have reported a simple, high-yield, room-temperature and water-based post synthesis method of dispersed dextran-coated iron oxide nanorods. This procedure differs from the above-mentioned methods by the quick addition of dextran, in the time range 1- 60 s, after the nucleation process is complete. The geometry of the oxides is strongly influenced by polymer purity, a high degree of purity affording the rod-shape development.[38]

The iron oxides properties, especially the magnetic properties, could be modified by various substitution of iron cations localized either on the octahedral and tetrahedral sites. Dextran-coated iron oxides doped with rare-earth cations can be prepared using methods that are essentially identical to those used to prepare the analogous iron oxide colloids. Therefore, using an *in situ* synthesis, in which octahedral Fe$^{3+}$ cations are partially substituted with lanthanide ions (Ln$^{3+}$ = Er, Sm, Tb and Gd), doped lanthanide oxides have been obtained.[39] The substitution of the iron cations with trivalent lanthanide ions had minimal effects on colloid size. The effective diameters of most ultrasmall mixed ferrite iron oxides (USMIOs) colloids range between 20 and 40 nm. The presence of lanthanides ions (europium and terbium) in the iron oxide matrix generates interesting optical properties for the long-term multilabelings. These oxides have high photostability, a narrow emission band, and a broad absorption band combining the high sensitivity of time resolved fluorescence with the high spatial resolution of MRI.[40]

The substitution of the tetrahedral iron cations with manganese, gadolinium and zinc metal ions tailors the superparamagnetic properties of the iron oxides nanoparticles and would provide control over properties that are important for biological applications.[39,41-43] In addition, the doping process could allow an additional control of the used material amount and implicit its toxicity in some therapeutic applications.

**DEXTRAN IN GEL TEMPLATE SYNTHESIS OF NANOSIZED OXIDES**

The structural complexity of dextran, in particular the multi-branched nature of the polymer, has made it an interesting biotemplate molecule.

Choosing the dextran as a soft sacrificial template, Mann *et al.*[44] were first who developed a processing route for the fabrication of metals and metal oxides sponges without the requirement of any extraneous support materials. Self-supporting

macroporous frameworks of silver, gold, copper and magnetic iron oxide, as well as composites of silver/copper oxide or silver/titania can be prepared by decomposition of the metals salt containing dextran 70.000 gels shaped and patterned through the use of appropriate moulds, in a temperature range of 500 and 900°C. In each case, expansion of the dextran matrix during thermal degradation gives rise to an open framework template and associated spatial patterning of interconnecting metal/metal oxide rods or filaments between 1 and 20 μm thickness, depending on the calcination temperature.
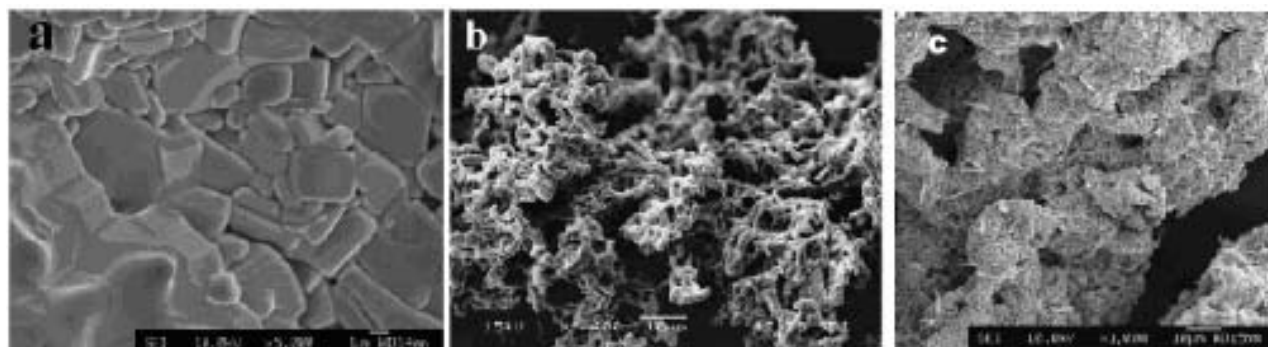
A similar method was used in the synthesis of the high-temperature superconductor $YBa_2Cu_3O_7$ (Y123) sponges (fig. 2a), obtained after a calcination at 920°C.[45] The semiconductor Y123 synthesized in the absence of the polysaccharide exhibits the typical polydispersity in terms of crystal size and morphology, while the Y123 dextran templated sponge (fig. 2b) has a uniform, macroporous and opened architecture. The inclusion of silver or sodium metal ions into the precursor dextran gels improves the structural stability of the oxidic sponges (fig. 2c).



Fig. 2 – SEM images of (a) $YBa_2Cu_3O_7$ sample; (b) a dextran templated $YBa_2Cu_3O_7$ sponge and (c) a silver-doped dextran templated $YBa_2Cu_3O_7$ sponge; scale bar in part a is 1 μm, in parts b and c is 10 μm.

Another strategy to obtain patterned sponges containing a network of capillaries and pore structures from polysaccharide/inorganic components, have been developed by Bilgainya *et al.*[46] The authors have encapsulated gold, $Fe_3O_4$ and $TiO_2$ nanoparticles in the patterned gels obtained by freeze drying of $Ca^{2+}$ ion cross-linked sodium carboxymethylcellulose (CMC)/sodium alginate hydrogels with or without addition of dextran. This synthesis route exploiting the property of used polysaccharides to form hydrogels.[9,47] The dextran influences the viscosity and subsequent patterning behaviour of the hydrogel composites, also. In addition, the freeze drying methods transform the patterned hydrogels into self - supporting polysaccharide sponges.

The preparation of sponge CMC/alginate hydrogel in presence of the dextran shows disordered capillaries with diameters varied from 4 to 9 μm, along with pores sizes 3 to 9 μm in size (fig. 3a), significantly decreased in comparison with those of polysaccharide sponges prepared from cross-linked and freeze-dried CMC/alginate composite hydrogels. Encapsulation of a $Fe_3O_4$ into the CMC/alginate/dextran sponges increased the capillary diameters (15–20 μm), with the pore sizes of 1–7 μm (fig. 3b). A similar increasing in

the capillary diameters (20–25 μm) and pore diameters values (10-20 μm) was also observed for sponges prepared in the presence of $TiO_2$ nanoparticles (fig. 3c).

Coral - like microcrystals of porous MgO nanoparticles, were also obtained by a single-step self-assembly of porous nanoparticles *via* a template process in the presence of dextran 40 000.[48] The morphologies of the final products are strongly dependent on the experimental conditions, for example the concentration of the raw materials. In the absence of the polysaccharide or to a lower concentration of dextran, MgO is formed either as irregular and imporous nanoparticles, or as a mixture of porous and imporous nanoplates. A high concentration of dextran obstructs the formation of pure MgO phase. On the other hand the replacement of the nitrate salt of magnesium(II) with the chloride magnesium(II) determines the formation of a web-like morphology, with many polygonal pores with diameters ranging from 250 to 700 nm. The proposed mechanism implies the formation of inorganic polymer complex through the self-assembly behavior of the hydrophilic groups of dextran.[44,49,50]
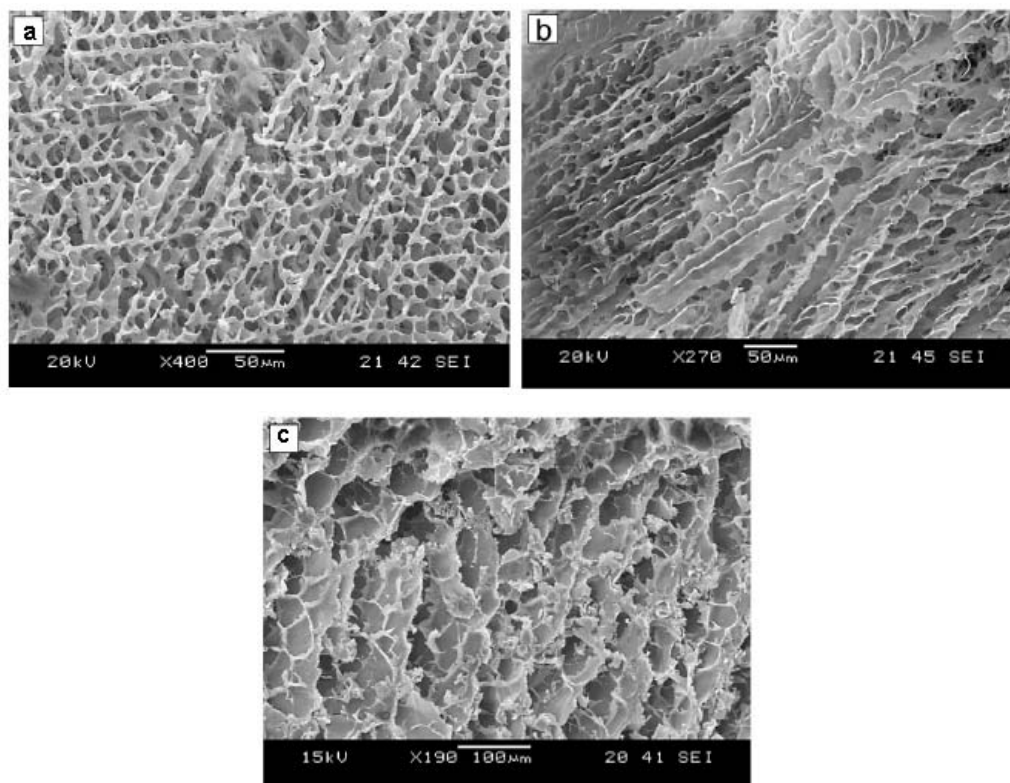
Fig. 3 – SEM images of (a) CMC/alginate/dextran sponge; scale bar = 50 μm (b) CMC/alginate/dextran/Fe$_3$O$_4$ sponges; scale bar = 50 μm (c) CMC/alginate/dextran/TiO$_2$ sponges; scale bar = 100 μm.

## CONCLUSIONS

The presented implications of the dextran in some polysaccharides-based green strategies to metal oxides synthesis evidence its ability to play diverse role as stabilizer and biotemplate. In comparison with other polysaccharides, such as starch or cellulose, the benefit of dextran coatings is especially important in terms of biomedical and pharmacological fields. On the other hand, the involvement of dextran during the synthesis route have a significant relevance, being related to the structural stability and parameters.

Polysaccharides have a great contribution to the origin of life, but also to a research field always in progress, meaning the future biomaterials. Paraphasing a Voltaire's statement, "There is nothing more powerful than a new material whose time has come…"

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