CORE-SHELL PARTICLES

The present invention relates to core-shell particles.

Core-shell particles and in particular magnetic core-shell particles are well known in the art. Many authors have prepared magnetic core-shell particles which have particle sizes smaller than 10 μm such as for instance WO 90/15666, US 3,933,997, US 7,364,921, US 2005/0009002, US 2006/131542, US 2008/152939, US 2012/61608 and US 2023/352218. In these references magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) particles are used that have submicron sizes and generally multiple particles are included in the core of the core-shell particles. Although small core-shell particles provide a higher adsorption surface area for target compounds (and a high yield), these particles are prone to attrition loss and subsequent loss of magnetic material. The re-use possibilities of these particles will be limited.

Further publications reveal core-shell particles with similar size magnetic iron oxide particles with a shell that is generally non-porous. Examples of such publications are US 5,543,291, US 2004/197833, US 2006/003371, US 2006/280944, US 2008/283792, US 2009/92837, US 2009/17518, US 2010/300941, US 2014/17813, US 2021/139953 and US 2024/163462. The core-shell particles in these publications generally have insufficient surface area onto which a target compound can be adsorbed.

US 2009/17518, US 2006/188876 and WO 2006/125978 disclose core-shell particles where the magnetic metal particles are deposited on the core and generally do not form part of the core. In this way the attrition protection is less optimal and some of the magnetic particles may be lost during use. There is a need for core-shell particles which overcome the disadvantages of the core-shell particles of the prior art.

The objective of the present invention is to provide novel core-shell particles.

The invention pertains to core-shell particles comprising a core comprising a metal-containing particle and a shell comprising a polymer, wherein the average particle size of the core-shell particles is between 20 and 1000 μm, and the average particle size of the core is between 10 and 300 μm, and wherein the shell is porous and comprises a functional group. The core-shell particles of the invention can be used in separation and/or purification processes, in particular when a certain compound is selectively removed from a stream comprising said compound. Examples of such target compounds include proteins, enzymes, nucleic acids, complex organic molecules (e.g. alkaloids, antibiotics, lipids, vitamins) and synthetic complex organic molecules

and metal ions such as lithium. Examples of such streams include waste streams, chemnical reaction mixtures, liquid plant cell homogenates, food (e.g. egg and dairy) or juioe streams, downstream processing, salt water brine and fermentation or cell culture broths. The inventive particles are versatile and allow for different modifications, e.g. through ligands capable of binding specific compounds, to selectively remove specific compounds. The core comprises a metal-containing particle which enables easy separation from the stream, e.g. by a magnetic field when the metal-containing particle is magnetic or by gravitation when the metal-containing particle has a high density. The metal-containing particle in the core may have a relatively large particle size in order to obtain a large magnetic moment or a large mass, and enables an improved sedimentation velocity compared to core-shell particles comprising a multitude of very small metal-containing particles. In a preferred embodiment, the core comprises a single metal-containing particle. In this way, the particle size of the metal-containing particle can be chosen such that an optimal magnetic moment or core weight is obtained and an improved sedimentation velocity is achieved. The shell of the inventive core-shell particles protects the core and enables adsorption of the to be separated compound(s) to the functional groups and/or the ligands connected to the functional groups. Moreover, the polymeric shell allows for an efficient re-suspension of the separated core-shell particles in a liquid medium for regeneration of the core-shell particle and removal of the adsorbed compounds and/or for re-use of the core-shell particles in subsequent separation processes. The shell further prevents attrition of the metal-containing particle present in the core. The polymeric shell of the inventive particles is furthermore porous therewith increasing the surface area of the particles, the number and/or density of functional groups and ligands and/or increasing the adsorption capacity of the inventive particles.

The core-shell particles have an average particle size of between 20 and 1000 μm. Preferably, the average particle size of the core-shell particles is at least 25 μm and most preferably at least 30 μm, and preferably at most 300 μm, more preferably at most 250 μm and most preferably at most 200 μm. The average particle size of the core-shell particles can be determined using conventional methods including x-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), light microscopy and laser diffraction using a Malvern Mastersizer. Preferably, the average particle size is determined using light microscopy.

In one embodiment, the core-shell particles have a d50 of between 20 and 1000 μm. Preferably, the d90 of the core-shell particles of the invention is at least 25 μm and most preferably at least

30 μm, and preferably at most 300 μm, more preferably at most 250 μm and most preferably at most 200 μm. The d50 of the core-shell particles can be determined using conventional analytical techniques including laser diffraction using a Malvern Mastersizer and light microscopy.

The inventive core-shell particles comprise a core. The core comprises a metal-containing particle. The core may consist of the metal-containing particle or may further comprise a matrix in which the metal-containing particle is embedded. In one embodiment, such a matrix can be a surfactant bound to the particle surface and capable of chemically connecting to the polymeric shell. Examples of such surfactants include carboxylic acids in particular unsaturated carboxylic acids such as oleic acid; and silanes such as phenyl trimethoxysilane (PTMS) and methyl trimethoxysilane (MTMS). In another embodiment, such a matrix can be a dispersing polymer in which the metal-containing particle is embedded and which is capable of chemically connecting to the polymeric shell.

In one embodiment, the average particle size of the core is between 10 and 300 μm. Preferably, the average particle size of the core is at least 15 μm and most preferably at least 20 μm, and preferably at most 200 μm, more preferably at most 150 μm and most preferably at most 100 μm. The average particle size of the core can be determined using conventional methods including x-ray diffraction (XRD), transmission electron microscopy (TEM), light microscopy and scanning electron microscopy (SEM). Preferably, the average particle size is determined using light microscopy.

In one embodiment, the core has a d50 of between 10 and 100 μm. Preferably, the d90 of the core is at least 15 μm and most preferably at least 20 μm, and preferably at most 90 μm, more preferably at most 80 μm and most preferably at most 70 μm. The d90 of the core can be determined using conventional analytical techniques including laser diffraction using a Malvern Mastersizer and light microscopy. The particle size of the core is preferably determined prior to applying the (polymeric) shell of the core-shell particles of the present invention.

The inventive core-shell particles have a core comprising a metal-containing particle. In one embodiment, the metal-containing particle is magnetic. The magnetic metal-containing particle can be any magnetic metal-containing particle known in the art. The magnetic metal-containing particle can be metals such as iron, nickel and cobalt; metal oxides such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3); metal alloys such as steel (iron and carbon), stainless steel, alnico

(iron, nickel, cobalt and aluminium), permalloy (iron and nickel) and alloys of neodymium such as $Nd_2Fe_{14}B$; and metal sulfides such as pyrite (FeS_2), chalcopyrite ($CuFeS_2$), and bornite (Cu_5FeS_4). Preferably, the metal-containing particles comprise magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3). Most preferably, the metal-containing particles comprise magnetite (Fe_3O_4).

In another embodiment, the metal-containing particle has a density of at least 1 g/ml. Preferably, the density of the metal-containing particles is at least 1.5 g/ml, more preferably at least 2 g/ml and most preferably at 3 g/ml, and preferably at most 20 g/ml, more preferably at most 18 g/ml and most preferably at most 15 g/ml. The high-density metal-containing particles include tungsten-based compounds such as tungsten, tungsten trioxide and tungsten carbide; and tungsten-based alloys such as tungsten-iron alloys, tungsten-nickel alloys, tungsten-nickel-copper alloys and tungsten-iron-nickel alloys.

In one embodiment, the average particle size of the metal-containing particle of between 10 and 300 μm. Preferably, the average particle size of the metal-containing particle is at least 15 μm and most preferably at least 20 μm, and preferably at most 200 μm, more preferably at most 150 μm and most preferably at most 100 μm. The average particle size of the metal-containing particle can be determined using conventional methods including x-ray diffraction (XRD), transmission electron microscopy (TEM), light microscopy and scanning electron microscopy (SEM). Preferably, the average particle size is determined using light microscopy.

In one embodiment, the metal-containing particles have a d50 of between 10 and 300 μm. Preferably, the d50 of the metal-containing particles is at least 15 μm and most preferably at least 20 μm, and preferably at most 200 μm, more preferably at most 150 μm and most preferably at most 100 μm. The d50 of the metal-containing particles can be determined using conventional analytical techniques including laser diffraction using a Malvern Mastersizer and light microscopy. The particle size of the metal-containing particles is preferably determined prior to incorporation into the core-shell particles of the present invention.

In one embodiment, the inventive core-shell particles comprise at most 75 wt% metal-containing particles, based on the total weight of the core-shell particles. Preferably, the inventive core-shell particles comprise at most 60 wt% metal-containing particles, more preferably at most 50 wt% metal-containing particles and most preferably at most 40 wt% metal-containing particles, and preferably at least 1 wt% metal-containing particles, more preferably at least 5 wt% metal-

containing particles and most preferably at least 10 wt% metal-containing particles, based on the total weight of the core-shell particles.

The core-shell particles of the invention comprise a shell. Generally, the shell comprises a polymer. The polymer can be any polymer suitable for creating a shell around the core of the inventive core-shell particles. In one embodiment, the polymeric shell is prepared using hydrophobic monomers. Preferably, the hydrophobic monomer has a water solubility of at most 10 g/L at 20 °C and pH of 7, more preferably at most 5 g/L at 20 °C and pH of 7. In ne embodiment, the polymer comprises monomers selected from styrene, styrene derivatives, methacrylates, silanes, alkoxysilanes, diacids, diesters, diisocyanates and diols. Preferably, the polymeric shell is prepared from a monomer selected from an ethylenically unsaturated monomer, a diacid, a diester and a diisocyanate.

In one embodiment, the polymeric shell is prepared using ethylenically unsaturated monomers. Preferably, the polymer is prepared using an ethylenically unsaturated monomer and a cross-linking agent. Examples of such ethylenically unsaturated monomers include styrene and styrene derivatives such as styrene, p-hydroxystyrene and 3,4-dihydroxystyrene; and (meth)acrylates such as methacrylic acid, acrylic acid, glycidyl acrylate and glycidyl methacrylate; silanes such as tetrahydrosilane, vinyl silane, dimethyl vinyl silane, diphenyl vinyl silane, triphenyl vinyl silane and tetrachlorosilane; alkoxysilanes such as vinyltrimethoxy silane, vinyltriethoxy silane, 3-aminopropyl triethoxysilane, N-(2-amino ethyl)-3-aminopropyl trimethoxysilane, 3-methacryloxy propyltrimethoxysilane and 3-chloropropyltrimethoxysilane; and combinations of 2 or more ethylenically unsaturated monomers. The cross-linking agent can be any cross-linking agent suitable for cross-linking the ethylenically unsaturated monomers. Examples of cross-linking agents include vinyl compounds such as divinyl benzene (DVB), 2-vinylbenzyl chloride (2-VBC) and 4-vinyl benzyl chloride (4-VBC); and (meth)acrylate compounds such as ethylene glycol dimethacrylate (EGDMA) and trimethylolpopane triacrylate (TMPTA) and glycidyl methacrylate (GMA); and combinations of two or more cross-linking agents. Preferably, such cross-linking agents comprise a functional group. Examples of such functional groups include hydroxyl, amine and chloride.

In one embodiment, the polymeric shell is prepared using monomers comprising a diacid or a diester. Preferably, the polymer is prepared using a monomer comprising a diacid or a diester and a diol. Examples of such diacids include sebacic acid, dodecanedioic acid, azelaic acid, terephthalic acid, isophthalic Acid and phthalic Acid. Examples of such diesters include dimethyl

sebacate (DMS), dimethyl dodecanoate (dodecyl methyl ester), diethyl adipate, dimethyl terephthalate (DMT), dimethyl isophthalate (DMIP) and diethyl terephthalate (DETP). Examples of diols include 1,12-dodecanediol, 1,18-octadecanediol, 2,2,4,4-tetramethyl-1,3-cyclobutanediol and polydimethylsiloxane (PDMS) diol.

In one embodiment, the polymeric shell is prepared using monomers comprising a diisocyanate. Preferably, the polymer is prepared using a monomer comprising a diisocyanate and a diol. Examples of such diisocyanate include hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI), Desmodur® N (polymeric MDI) and methylene diphenyl diisocyanate (MDI). Examples of such diols include 1,12-dodecanediol, 1,18-octadecanediol, polypropylene glycol (PPG), polybutadiene diol, hydroxyl-terminated polydimethylsiloxane (HTPDMS), polycaprolactone diol (PCL diol), polysiloxane polyols such as polydimethylsiloxane (PDMS) diol.

In one embodiment, the polymeric shell is prepared using an alkyd resin. Examples of such alkyd resins include polyesters which are modified by fatty acids or corresponding triglycerides like for example the commercially available under tradenames Uralac AN621 S- 2 60 and Uralac AN637 S-2 60 (both ex DSM Resins). The alkyd resins may further be modified using phenolic resin, styrene, vinyl toluene, acrylic monomers and/or polyurethanes. More details of suitable alkyd resins and possible modifications can be found in US 2014/0360408.

In one embodiment, the functional groups may further react with a ligand. Such a ligand may provide further functionality to the core-shell particles of the invention. The ligand can be any ligand known in the art. Examples of such ligands include tertiary amines such as triethyl amine and triethanol amine; quaternary amines such as tetramethyl amine and tetraethyl amine; hydrophobic compounds such as ferulic acid and 4-amino benzamidine dihydrochloride.

In one embodiment, the shell is porous. Preferably, the shell of the inventive core-shell particles has a porosity of between 20 and 90%. Such porosity can be achieved by using a porogen during the preparation of the shell. Preferably, the porosity of the shell is at least 25%, more preferably at least 30% and most preferably at least 35% and preferably at most 85%, more preferably at most 80% and most preferably at most 75%. The porosity can be determined using any suitable method known in the art such as BET method (N_2) and helium pycnometry.

In one embodiment, the average thickness of the shell is between 10 and 700 μm. Preferably, the average thickness of the shell is at least 15 μm and most preferably at least 20 μm, and

preferably at most 500 μm, more preferably at most 200 μm and most preferably at most 100 μm. The thickness of the shell can be determined using conventional methods including light microscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM) and light microscopy. Preferably, the average thickness is determined using light microscopy.

In one embodiment, the inventive core-shell particles comprise at most 90 wt% shell, based on the total weight of the core-shell particles. Preferably, the inventive core-shell particles comprise at most 70 wt% shell, more preferably at most 50 wt% shell and most preferably at most 40 wt% shell, and preferably at least 1 wt% shell, more preferably at least 5 wt% shell and most preferably at least 10 wt% shell, based on the total weight of the core-shell particles.

The invention further pertains to a process for preparing core-shell particles comprising a core comprising a metal-containing particle and a shell comprising a polymer, wherein the average particle size of the core-shell particles is between 20 and 1000 mm, and the average particle size of the core is between 10 and 300 mm, and wherein the shell is porous and comprises a functional group, comprising the steps of:

(a) providing an organic mixture of a monomer, a cross-linking agent or a diol, a surfactant and/or a dispersing polymer, a porogen, an initiator or catalyst and the metal-containing particles;
(b) providing an aqueous mixture comprising water and a pickering stabilizer;
(c) contacting the organic mixture and the aqueous mixture to form an oil-in-water emulsion;
(d) polymerizing the ethylenically unsaturated monomer and the cross-linking agent to obtain a dispersion of core-shell particles;
(e) optionally washing the dispersion of the core-shell particles; and
(f) optionally reacting the core-shell particles with a ligand.

The process of the invention allows for the preparation of the core-shell particles of the invention. The core-shell particles may be prepared with a more uniform particle size distribution and effective encapsulation of the core by the polymeric shell. The inventive process is relatively simple and economically interesting.

In step (a) of the inventive process, an organic mixture of a monomer, a cross-linking agent or a diol, a surfactant and/or a dispersing polymer, a porogen, an initiator or catalyst and the metal-containing particles are provided. Preferably, the monomer is selected from an ethylenically unsaturated monomer, a diacid, a diester and a diisocyanate.

Examples of the ethylenically unsaturated monomer, the diacid, the diester, the diisocyanate and the cross-linking agent or diol have been described above. In one embodiment, the weight ratio of the monomer and the cross-linking agent or diol is at least 0.5, preferably at least 0.8 and most preferably at least 1, and preferably at most 10, more preferably at most 5 and most preferably at most 3.

In one embodiment, the organic mixture comprises at least 15 wt% monomer, preferably ethylenically unsaturated monomer, based on the total weight of the organic mixture. Preferably, the organic mixture of step(a) comprises at least 20 wt% monomer, preferably ethylenically unsaturated monomer, more preferably at least 25 wt% monomer, preferably ethylenically unsaturated monomer and most preferably at least 30 wt% monomer, preferably ethylenically unsaturated monomer, and preferably at most 60 wt% monomer, preferably ethylenically unsaturated monomer, more preferably at most 55 wt% e monomer, preferably ethylenically unsaturated monomer and most preferably at most 50 wt% monomer, preferably ethylenically unsaturated monomer, based on the total weight of the organic mixture.

In one embodiment, the organic mixture comprises at least 15 wt% cross-linking agent or diol, based on the total weight of the organic mixture. Preferably, the organic mixture of step(a) comprises at least 20 wt% cross-linking agent or diol, more preferably at least 25 wt% cross-linking agent or diol and most preferably at least 30 wt% cross-linking agent or diol, and preferably at most 60 wt% cross-linking agent or diol, more preferably at most 55 wt% cross-linking agent or diol and most preferably at most 50 wt% cross-linking agent or diol, based on the total weight of the organic mixture.

The surfactant and/or dispersing polymer can be any surfactant and/or dispersing polymer known in the art. The surfactant and/or dispersing polymer generally serve to disperse the metal-containing particles. Moreover, the surfactant and/or dispersing polymer generally connect or attach to the surface of the metal-containing particles. In addition, the surfactant and/or dispersing polymer are capable of reacting with the ethylenically unsaturated monomer and/or the cross-linking agent used to create the polymeric shell. Examples of the surfactant and/or dispersing polymer have been described above.

In one embodiment, the weight ratio of the metal-containing particles and the surfactant and/or dispersing polymer is at least at least 0.5, preferably at least 0.8 and most preferably at least 1, and preferably at most 10, more preferably at most 5 and most preferably at most 3.

In one embodiment, the organic mixture comprises at least 0.5 wt% surfactant and/or dispersing polymer, based on the total weight of the organic mixture. Preferably, the organic mixture of step(a) comprises at least 1 wt% surfactant and/or dispersing polymer, more preferably at least 1.5 wt% surfactant and/or dispersing polymer and most preferably at least 2 wt% surfactant and/or dispersing polymer, and preferably at most 8 wt% surfactant and/or dispersing polymer, more preferably at most 6 wt% surfactant and/or dispersing polymer and most preferably at most 5 wt% surfactant and/or dispersing polymer, based on the total weight of the organic mixture.

The organic mixture further comprises a porogen. The porogen serves to provide porosity to the polymeric shell. The porogen can be any porogen known in the art. Examples of such porogens include toluene, benzyl alcohol and cyclohexanol.

In one embodiment, the weight ratio of the monomer, preferably ethylenically unsaturated monomer, and the porogen is at least at least 0.5, preferably at least 0.8 and most preferably at least 1, and preferably at most 10, more preferably at most 5 and most preferably at most 3.

In one embodiment, the organic mixture comprises at least 15 wt% porogen, based on the total weight of the organic mixture. Preferably, the organic mixture of step(a) comprises at least 20 wt% porogen, more preferably at least 25 wt% porogen and most preferably at least 30 wt% porogen, and preferably at most 60 wt% porogen, more preferably at most 55 wt% porogen and most preferably at most 50 wt% porogen, based on the total weight of the organic mixture.

The organic mixture further comprises an initiator and/or a catalyst. The initiator serves to initiate the addition polymerization reaction. The catalyst serves to initiate the condensation polymerization reaction. The initiator can be any suitable initiator known in the art. Examples of suitable initiators include organic peroxides such as di(t-butyl) peroxide, dilauroyl peroxide, dibenzoyl peroxide, dicumyl peroxide, methyl ethyl ketone peroxide, t-butyl hydroperoxide t-butylperoxy benzoate; azo compounds such as azo bisisobutyronitrile (AIBN) and 1,1′-azobis(cyclohexanecarbonitrile) (ACHN); and inorganic peroxides such as sodium persulfate, potassium persulfate and ammonium persulfate. Examples of suitable catalysts include Ti-based catalysts such as titanium isopropoxide (TTIP); Sn-based catalysts such as dibutyl tin oxide (DBTO), dibutyl tin dilaurate (DBTL), dibutyltin dilaurate (DBTDL), dioctyltin dilaurate and organic catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and N-methylmorpholine (NMM).

In one embodiment, the weight ratio of the monomer, preferably ethylenically unsaturated monomer, and the initiator is at least at least 0.01, preferably at least 0.05 and most preferably at least 0.1, and preferably at most 1, more preferably at most 0.5 and most preferably at most 0.3.

In one embodiment, the organic mixture comprises at least 0.01 wt% initiator and/or catalyst, based on the total weight of the organic mixture. Preferably, the organic mixture of step(a) comprises at least 0.02 wt% initiator and/or catalyst, more preferably at least 0.05 wt% initiator and/or catalyst and most preferably at least 0.1 wt% initiator and/or catalyst, and preferably at most 10 wt% initiator and/or catalyst, more preferably at most 5 wt% initiator and/or catalyst and most preferably at most 3 wt% initiator and/or catalyst, based on the total weight of the organic mixture.

The organic mixture of step (a) further comprises metal-containing particles. Such metal-containing particles have been described above.

In one embodiment, the weight ratio of the monomer, preferably ethylenically unsaturated monomer, and the metal-containing particles is at least at least 0.5, preferably at least 0.8 and most preferably at least 1, and preferably at most 10, more preferably at most 5 and most preferably at most 3.

In one embodiment, the organic mixture comprises at least 15 wt% metal-containing particles, based on the total weight of the organic mixture. Preferably, the organic mixture of step(a) comprises at least 20 wt% metal-containing particles, more preferably at least 25 wt% metal-containing particles and most preferably at least 30 wt% metal-containing particles, and preferably at most 60 wt% metal-containing particles, more preferably at most 55 wt% metal-containing particles and most preferably at most 50 wt% metal-containing particles, based on the total weight of the organic mixture.

The remaining part of the organic mixture may be comprised of other components commonly used in such organic mixtures. With the monomer, preferably ethylenically unsaturated monomer, the cross-linking agent, the surfactant and/or dispersing polymer, the porogen, the initiator, the metal-containing particles and the other components add up to 100 wt% of the total weight of the organic mixture.

In one embodiment, the temperature in step (a) is at most 60 °C, preferably the temperature is at most 50°C, more preferably at most 40°C and most preferably at most 30°C, and preferably at least 10°C, more preferably at least 15°C and most preferably at least 20°C.

Preferably, the organic mixture is stirred.

In step (b) of the inventive process, an aqueous mixture comprising water and a pickering stabilizer is provided. The pickering stabilizer generally serves to stabilize an emulsion of the organic mixture in the aqueous mixture by forming a pickering emulsion. The pickering stabilizer comprises particles capable of stabilizing the emulsion. The pickering stabilizer can be any pickering stabilizer known in the art. Examples of such pickering stabilizers include clays such as hydroxyapatite and laponite, silica, calcium carbonate, tricalcium phosphate, starch, emulsifying proteins such as soy protein and whey protein, and carbon nanostructures such as microcrystalline cellulose.

In one embodiment, the average particle size of the pickering stabilizer is smaller than the average particle size of the metal-containing particles. Preferably, the ratio of the average particle sizes of the metal-containing particles and the pickering stabilizer is at least 5, more preferably at least 8, and more preferably at least 10, and preferably at most 100, more preferably at most 50 and most preferably at most 30.

In one embodiment, the average particle size of the pickering stabilizer is between 0.01 and 15 μm. Preferably, the average particle size of the core is at least 0.05 μm and most preferably at least 0.1 μm, and preferably at most 10 μm, more preferably at most 8 μm and most preferably at most 5 μm. The particle size of the core can be determined using conventional methods including x-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), light microscopy and laser diffraction.

In one embodiment, the pickering stabilizer has a d50 of between 0.01 and 15 μm. Preferably, the d50 of the core is at least 0.05 μm and most preferably at least 0.1 μm, and preferably at most 10 μm, more preferably at most 8 μm and most preferably at most 5 μm. The d50 of the core can be determined using conventional analytical techniques including laser diffraction using a Malvern Mastersizer and light microscopy. The particle size of the pickering stabilizer is preferably determined prior to applying the (polymeric) shell of the core-shell particles of the present invention.

In one embodiment, the aqueous mixture comprises at least 0.1 wt% pickering stabilizer, based on the total weight of the aqueous mixture. Preferably, the aqueous mixture of step (b) comprises at least 0.5 wt% pickering stabilizer, more preferably at least 1 wt% pickering stabilizer and most preferably at least 15 wt% pickering stabilizer, and preferably at most 10 wt% pickering stabilizer, more preferably at most 8 wt% pickering stabilizer and most preferably at most 5 wt% pickering stabilizer, based on the total weight of the aqueous mixture.

The aqueous mixture further comprises water. In one embodiment, the aqueous mixture comprises at least 85 wt% water, based on the total weight of the aqueous mixture. Preferably, the aqueous mixture of step (b) comprises at least 90 wt% water, more preferably at least 92 wt% water and most preferably at least 95 wt% water, and preferably at most 99.9 wt% water, more preferably at most 99.5 wt% water and most preferably at most 99 wt% water, based on the total weight of the aqueous mixture.

The remaining part of the aqueous mixture may be comprised of other components commonly used in such aqueous mixtures. With the pickering stabilizer, water and the other components add up to 100 wt% of the total weight of the aqueous mixture.

In one embodiment, the temperature in step (b) is at most 60 °C, preferably the temperature is at most 50°C, more preferably at most 40°C and most preferably at most 30°C, and preferably at least 10°C, more preferably at least 15°C and most preferably at least 20°C.

Preferably, the aqueous mixture is stirred.

In step (c) of the inventive process, the organic mixture of step (a) and the aqueous mixture of step (b) are contacted to form an oil-in-water emulsion. The pickering stabilizer stabilizes droplets of the organic mixture in water. The size of the oil droplets generally depends on the temperature and the stirring speed. The stirring speed can be chosen such that each oil droplet comprises one metal-containing particle.

In one embodiment, the temperature in step (c) is at most 60 °C, preferably the temperature is at most 50°C, more preferably at most 40°C and most preferably at most 30°C, and preferably at least 10°C, more preferably at least 15°C and most preferably at least 20°C.

In step (d) of the inventive process, the monomer, preferably ethylenically unsaturated monomer and the cross-linking agent are polymerized to obtain a dispersion of core-shell particles in accordance with the invention. The polymerization is generally started by activating the initiator.

Such activation can be performed by increasing the temperature, increasing the pressure and/or exposure to UV radiation. Preferably, the temperature of the emulsion is increased to initiate the polymerization reaction. The advantage of having captured all reactants taking part in the polymerization reaction is that the oil droplet is the reaction vessel, and the size of the resulting core-shell particles are generally limited to the size of the oil droplet.

In one embodiment, the temperature in step (d) is at least 50 °C, preferably the temperature is at least 55°C, more preferably at least 60°C and most preferably at least 65°C, and preferably at most 90°C, more preferably at most 85°C and most preferably at most 80°C.

In optional step (e) of the inventive process, the dispersion of the core-shell particles of step (d) is washed. In this washing step, the remaining monomer, preferably ethylenically unsaturated monomer, cross-linking agent or diol, porogen and/or pickering stabilizer is generally removed. The washing step of (e) can be performed using any suitable solvent known in the art. Examples of suitable solvents include alcohols such as methanol, ethanol and isopropanol; water; acidic aqueous solutions such as aqueous hydrogen chloride solutions; alkaline aqueous solutions such as phosphate-buffered saline (PBS); and aromatic solvents such as toluene. In one embodiment, the washing step is repeated twice or more times. In a preferred embodiment, two or more solvents are used to wash the inventive core-shell particles.

In one embodiment, the temperature in step (e) is at least 20 °C, preferably the temperature is at least 30°C, more preferably at least 50°C and most preferably at least 60°C, and preferably at most 90°C, more preferably at most 85°C and most preferably at most 80°C.

In optional step (f) of the inventive process, the core-shell particles of the invention are reacted with a ligand. In particular, the functional groups present in the core-shell particles can be reacted with a ligand to form a second functional group. The second functional group enables the selective adsorption of functional compounds such as proteins. Suitable ligands have been described above.

In one embodiment, the molar ratio of the functional groups in the shell and the ligand is at least 0.5, preferably at least 0.8 and most preferably at least 1, and preferably at most 5, more preferably at most 3 and most preferably at most 2.

In one embodiment, the temperature in step (f) is at least 60 °C, preferably the temperature is at least 70°C, more preferably at least 80°C and most preferably at least 85°C, and preferably at most 140°C, more preferably at most 130°C and most preferably at most 125°C.

The invention further pertains to the use of the core-shell particles of the invention for selectively adsorbing target compound, e.g. a protein. Preferably, the inventive core-shell particles are used to separate and isolate a target compound from (complex) process streams, e.g. a fermentation broth. The invention further pertains to a process for separating a target compound from a process stream comprising the steps of:

(a) contacting a process stream comprising the target compound and core-shell particles comprising a core comprising a metal-containing particle and a shell comprising a polymer, wherein the average particle size of the core-shell particles is between 20 and 1000 μm, and the average particle size of the core is between 10 and 300 μm, and wherein the shell is porous and comprises a functional group to obtain loaded core-shell particles to which the target compound is selectively adsorbed;

(b) separating the loaded core-shell particles from the process stream;

(c) regenerating the loaded core-shell particles to desorb the target compound to obtain a stream comprising the target compound and regenerated core-shell particles;

(d) optionally removing solvent from the stream comprising the target compound and drying the target compound;

(e) optionally re-suspending the regenerated core-shell particles in the process stream and repeating steps (a) to (d).

The inventive process allows for selective adsorption of a target compound from a process stream, and subsequent isolation of the target compound. A process stream may consist of many different compounds, and separating may not be easy when using conventional methods such as precipitation and (ultra)filtration. The inventive core-shell particles combine selective adsorption, a relatively large surface area due in part to the porosity of the shell and easy separation from the process stream. Moreover, regeneration of the core-shell particles is generally efficient allowing a good yield of the target compound and simple re-use of inventive core-shell particles.

In step (a) of the inventive process, the core-shell particles of the invention are contacted with a process stream comprising the target compound to obtain loaded core-shell particles to which the target compound is selectively adsorbed. The process stream can be any process stream known in the art from which a target compound is to be isolated. Examples of such process streams include fermentation or cell culture broths, chemical reaction mixture, liquid plant cell homogenate, food processing streams such as egg or milk, co-products from the food industry, waste water streams, salt water brine, process streams from chemical reactions and biorefinery

process streams. In one embodiment, the process stream is a fermentation broth. Such a fermentation broth is the result of microbial fermentation process in which the target compound is a specific protein produced during the fermentation. Examples of such proteins include bovine serum albumin (BSA), Subtilisin A and lactoferrin. The target compound can be any compound known in the art that requires isolation. In one embodiment, the target compound is a protein, an enzyme, a nucleic acid, alkaloids, antibiotics, lipids, vitamins, a (synthetic) oligomer or polymer or a metal ion such as lithium.

In one embodiment, the temperature in step (a) is at most 80 °C, preferably the temperature is at most 70°C, more preferably at most 60°C and most preferably at most 50°C, and preferably at least 0°C, more preferably at least 10°C and most preferably at least 15°C.

In step (b) of the process of the invention, the loaded core-shell particles are separated from the process stream. The separation of the loaded core-shell particles can be performed using any method known in the art. Preferably, when the core-shell particles comprise magnetic metal-containing particles, a magnetic field can be applied to collect the loaded core-shell particles. This separation can be relatively quick and is easy. Alternatively or additionally, the core-shell particles comprise metal-containing particles with a high density (e.g. a density exceeding 5 g/ml), which can sediment to the bottom of the reactor allowing the removal of the process stream.

In one embodiment, the temperature in step (b) is at most 80 °C, preferably the temperature is at most 70°C, more preferably at most 60°C and most preferably at most 50°C, and preferably at least 0°C, more preferably at least 10°C and most preferably at least 15°C.

In step (c) of the inventive process, the loaded core-shell particles of step (b) can be regenerated to desorb the target compound to obtain a stream comprising the target compound and the regenerated core-shell particles. Such regeneration can be carried out using any regeneration method known in the art. In one embodiment, the target compound is released from the core-shell particles using a buffer solution having a pH that enables desorption of the target compound from the core-shell particles, e.g. a pH below the isoelectric point of the target compound (e.g. a protein) may change the charge on the target compound.

In one embodiment, the temperature in step (c) is at most 80 °C, preferably the temperature is at most 70°C, more preferably at most 60°C and most preferably at most 50°C, and preferably at least 0°C, more preferably at least 10°C and most preferably at least 15°C.

In optional step (d) of the process of the invention, solvent is removed from the stream comprising the target compound and optionally the target compound is dried. The solvent, preferably water, is removed from the stream to concentrate the stream comprising the target compound. Such concentration may be performed using any method known in the art. Examples of such methods include ultrafiltration, decanting and evaporation. Such concentration generally leads to a stream comprising a more concentrated target compound and a solvent or water content below 40 wt%, which allows for more cost effective further drying of the target compound to a dried form (water content below 10 wt%).

In one embodiment, the solvent or water removal or concentration temperature in optional step (d) is at most 120 °C, preferably the temperature is at most 100°C, more preferably at most 90°C and most preferably at most 80°C, and preferably at least 30°C, more preferably at least 40°C and most preferably at least 50°C. The temperature in step (d) is chosen such that the target compound is not affected or deteriorated.

The drying of the target compound can be performed using any drying method known in the art. Such drying methods include oven drying, spinning flash drying, IR drying, microwave drying, vacuum drying, drum drying, fluidized bed drying and spray drying.

In one embodiment, the drying temperature in optional step (d) is at most 120 °C, preferably the temperature is at most 100°C, more preferably at most 90°C and most preferably at most 80°C, and preferably at least 30°C, more preferably at least 40°C and most preferably at least 50°C. The drying temperature is chosen such that the target compound is not affected or deteriorated. The drying temperature may be the same or different from the temperature at which solvent (e.g. water) is removed. Preferably, the drying temperature is higher than the temperature at which solvent (e.g. water) is removed.

In optional step (e), the regenerated core-shell particles can be re-suspended in the process stream and steps (a) to (d) are repeated. In this way a higher yield of the target compound can be obtained. The regenerated core-shell particles of the invention can be effectively and easily re-suspended in the process stream. Due to the (very) low abrasion level of the core-shell particles and the metal-containing particles remaining in the core (no loss of metal), the inventive core-shell particles can be re-used many times. In this way, the core-shell particles can be used in a cost-effective manner.

The invention is exemplified in the following Examples.

Examples

Examples 1 to 5 and Comparative Example A: magnetic core-shell particles

0.13 g magnetite particles (particle size from 25 to 50 μm) are placed in a 2 mL plastic container and subsequently 1.14 mL 4-vinylbenzyl chloride, 0.67 mL divinylbenzene, 114 mg dilauroyl peroxide and 0.01 g Solsperse 36600 were added to obtain the organic phase. The container is then sealed and gently mixed by shaking (utilizing an end-to-end shaker) for 30 minutes. Next, the water (10 mL) was charged to a 20-milliliter reactor and the tricalcium phosphate (1.3 wt% dispersion; average particle size is 4 μm) was added under stirring to obtain the aqueous phase. After 5 minutes, the stirring was stopped and the magnetite-containing organic phase was added to the aqueous phase. Subsequently, the resulting mixture was thoroughly mixed. The resulting dispersion was heated to 70 °C and kept at this temperature for 6 hours while stirring. After cooling, the resulting core-shell particles (Comparative Example A) were washed with diluted hydrochloric acid, water and isopropyl alcohol. The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Comparative Example A ranges from 125 to 250 μm.

The same procedure was followed as for Comparative Example A except that 0.72 mL toluene was added to the organic phase. The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 1 ranges from 125 to 250 μm. Scanning electron microscopy (SEM) revealed that the core-shell particles were porous.

The core-shell particles of Example 1 were functionalized with a ligand by immersion in an aqueous solution of 4-amino benzamidine (5 wt%) and incubated for 24 hours at 60 °C (Example 2). The presence of amino-benzamidine groups was confirmed using FT-IR.

The same process as for Example 1 was used. 700 mg of the resulting core-shell particles were reacted with 2.91 g ferulic acid, 0.32 g tetraethyl ammonium bromide and 50 ml dimethyl formamide at 120°C for 16 hours (Example 3). The presence of ferullate groups was confirmed using FT-IR.

The same process as for Example 1 was used. 700 mg of the resulting core-shell particles were reacted with 6.7 mL de-ionized water, 3.3 mL isopropyl alcohol and 540 mg potassium

hydroxide at 80°C for 3 hours (Example 4). The presence of hydroxyl groups was confirmed using FT-IR.

The same process as for Example 1 was used. 700 mg of the resulting core-shell particles were reacted with 5.0 mL de-ionized water, 2.0 mL isopropyl alcohol and 3 mL of an aqueous trimethyl amine (45 wt%) solution at room temperature for 3 hours (Example 5). The presence of trimethyl amine groups was confirmed using FT-IR.

Example 6: binding of ovalbumin

To an aqueous solution of ovalbumin (2.5 mg/ml) which was buffered using a 10 mM phosphate buffer (pH is 6.47) about 5 mg of the core-shell particles of Example 5 were added. The resulting dispersion was stirred by shaking for 16 hours at room temperature. Subsequently, the loaded core-shell particles were separated using a magnet and decanting the supernatant. The loaded particles were exposed to a 300 mM aqueous sodium chloride solution to release the adsorbed ovalbumin. The binding capacity was 50.4 mg ovalbumin per gram of core-shell particles.

Examples 7 to 11: magnetic core-shell particles

0.20 g magnetite particles (particle size from 25 to 50 μm) are placed in a 2 mL plastic container and subsequently 0.45 mL glycidyl methacrylate, 0.45 mL trimethylolpropane triacrylate, 0.9 mL toluene, 45 mg dilauroyl peroxide and 0.02 g Solsperse 36600 were added to obtain the organic phase. The container is then sealed and gently mixed by shaking (utilizing an end-to-end shaker) for 30 minutes. Next, the water (10 mL) was charged to a 20-milliliter reactor and the tricalcium phosphate (2.0 wt% dispersion; average particle size is 4 μm) was added under stirring to obtain the aqueous phase. After 5 minutes, the stirring was stopped and the magnetite-containing organic phase was added to the aqueous phase. Subsequently, the resulting mixture was thoroughly mixed. The resulting dispersion was heated to 70 °C and kept at this temperature for 6 hours while stirring. After cooling, the resulting core-shell particles (Example 7) were washed with diluted hydrochloric acid, water and isopropyl alcohol. The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 7 ranges from 125 to 250 μm.

The same process is used as for Example 7 except that 1-dodecanol is used instead of toluene (Example 8). The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 8 ranges from 125 to 250 μm.

The same process is used as for Example 7 except that benzyl alcohol is used instead of toluene (Example 9). The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 9 ranges from 125 to 250 μm.

The same process is used as for Example 7 except that cyclohexanol is used instead of toluene (Example 10). The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 10 ranges from 125 to 250 μm.

The same process is used as for Example 7 except that hydroxyapatite (average particle size is 4 μm) is used instead of tricalcium phosphate (Example 11). The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 11 ranges from 125 to 250 μm.

Examples 12: magnetic core-shell particles using 500 nm magnetite particles

0.30 g magnetite particles (particle size from 200 to 500 nm) are placed in a 2 mL plastic container and subsequently 0.45 mL glycidyl methacrylate, 0.45 mL ethylene glycol dimethacrylate, 0.9 mL toluene, 45 mg dilauroyl peroxide and 0.06 g Solsperse 36600 were added to obtain the organic phase. The container is then sealed and gently mixed by shaking (utilizing an end-to-end shaker) for 30 minutes. Next, the water (10 mL) was charged to a 20-milliliter reactor and the tricalcium phosphate (2.5 wt% dispersion; average particle size is 4 μm) was added under stirring to obtain the aqueous phase. After 5 minutes, the stirring was stopped and the magnetite-containing organic phase was added to the aqueous phase. Subsequently, the resulting mixture was thoroughly mixed. The resulting dispersion was heated to 70 °C and kept at this temperature for 6 hours while stirring. After cooling, the resulting core-shell particles (Example 12) were washed with diluted hydrochloric acid, water and isopropyl alcohol. The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles

were observed. The particle size of the core-shell particles of Example 12 ranges from 60 to 120 μm with core sizes ranging from 50 to 80 μm.

Examples 13: core-shell particles up to 750 μm

0.20 g magnetite particles (particle size from 25 to 50 μm) are placed in a 2 mL plastic container and subsequently 0.45 mL 4-vinylbenzyl chloride, 0.45 mL divinylbenzene, 0.9 mL toluene, 114 mg dilauroyl peroxide and 0.08 g Solsperse 36600 were added to obtain the organic phase. The container is then sealed and gently mixed by shaking (utilizing an end-to-end shaker) for 30 minutes. Next, the water (10 mL) was charged to a 20-milliliter reactor and the tricalcium phosphate (1.0 wt% dispersion; average particle size is 6 μm) was added under stirring to obtain the aqueous phase. After 5 minutes, the stirring was stopped and the magnetite-containing organic phase was added to the aqueous phase. Subsequently, the resulting mixture was thoroughly mixed. The resulting dispersion was heated to 70 °C and kept at this temperature for 6 hours while stirring. After cooling, the resulting core-shell particles (Example 13) were washed with diluted hydrochloric acid, water and isopropyl alcohol. The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 13 ranges from 450 to 750 μm.

Examples 14: core-shell particles using metallic iron particles

0.20 g iron particles (particle size from 72 to 90 μm) are placed in a 2 mL plastic container and 1.8 mL of diluted hydrochloric acid (0.1 M) were added. The mixture was stirred by shaking at room temperature. After 3 hours, 61 μL of ammonia solution (28%) were added and the mixture stirred again for 30 minutes. Subsequently, the iron particles were separated using a magnet, decanting the supernatant and washed with water. Subsequently, 1.8 mL of oleic acid were added and the mixture stirred by shaking for 16 hours. The iron particles were again separated by magnetic decantation, washed with water and isopropyl alcohol and dried at 70 °C for 4 hours.

Subsequently 0.45 mL 4-vinylbenzyl chloride, 0.45 mL divinylbenzene, 0.9 mL toluene and 114 mg dilauroyl peroxide were added to obtain the organic phase. The container is then sealed and gently mixed by shaking (utilizing an end-to-end shaker) for 30 minutes. Next, the water (10 mL) was charged to a 20-milliliter reactor and the tricalcium phosphate (1.3 wt% dispersion; average particle size is 4 μm) was added under stirring to obtain the aqueous phase. After 5 minutes, the stirring was stopped and the magnetite-containing organic phase was added to the aqueous phase. Subsequently, the resulting mixture was thoroughly mixed. The resulting dispersion was

heated to 70 °C and kept at this temperature for 6 hours while stirring. After cooling, the resulting core-shell particles (Example 14) were washed with diluted hydrochloric acid, water and isopropyl alcohol. The polymerization yield was above 90% and no separated (non-encapsulated) magnetite particles were observed. The particle size of the core-shell particles of Example 14 ranges from 125 to 250 μm.

CLAIMS

1. Core-shell particles comprising a core comprising a metal-containing particle and a shell comprising a polymer, wherein the average particle size of the core-shell particles is between 20 and 1000 μm, and the average particle size of the core is between 10 and 300 μm, and wherein the shell is porous and comprises a functional group.

2. Core-shell particles according to claim 1 wherein the metal-containing particle is magnetic.

3. Core-shell particles according to any one of claims 1 and 2 wherein the core comprises a single metal-containing particle.

4. Core-shell particles according to any one of the preceding claims wherein the core comprises magnetite.

5. Core-shell particles according to any one of the preceding claims wherein the polymer comprises monomers selected from styrene, styrene derivatives, methacrylates, silanes, alkoxysilanes, diacids, diesters, diisocyanates and diols.

6. Core-shell particles according to any one of the preceding claims wherein the shell has a porosity of between 20 and 95%.

7. Core-shell particles according to any one of the preceding claims wherein the functional group is selected from unsaturated carboxylic acid, alkoxysilanes, polyalkylene imines and polyalkylene glycols.

8. A process for preparing core-shell particles comprising a core comprising a metal-containing particle and a shell comprising a polymer, wherein the average particle size of the core-shell particles is between 20 and 1000 μm, and the average particle size of the core is between 10 and 300 μm, and wherein the shell is porous and comprises a functional group, comprising the steps of:
   (a) providing an organic mixture of a monomer, a cross-linking agent or a diol, a surfactant and/or a dispersing polymer, a porogen, an initiator or a catalyst and metal-containing particles;

(b) providing an aqueous mixture comprising water and a pickering stabilizer;
(c) contacting the organic mixture and the aqueous mixture to form an oil-in-water emulsion;
(d) polymerizing the monomer and the cross-linking agent or diol to obtain a dispersion of core-shell particles;
(e) optionally washing the dispersion of the core-shell particles; and
(f) optionally reacting the core-shell particles with a ligand.

9. A process for separating a target compound from a process stream comprising the steps of:
(a) contacting a process stream comprising the target compound and core-shell particles comprising a core comprising a metal-containing particle and a shell comprising a polymer, wherein the average particle size of the core-shell particles is between 20 and 1000 mm, and the average particle size of the core is between 10 and 300 mm, and wherein the shell is porous and comprises a functional group to obtain loaded core-shell particles to which the target compound is selectively adsorbed;
(b) separating the loaded core-shell particles from the process stream;
(c) regenerating the loaded core-shell particles to desorb the target compound to obtain a stream comprising the target compound and regenerated core-shell particles;
(d) optionally removing solvent from the stream comprising the target compound and optionally drying the target compound;
(e) optionally re-suspending the regenerated core-shell particles in the process stream and repeating steps (a) to (d).