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(54) **Eljárás alginátot tartalmazó porózus formázott testek előállítására**

Description

PRIOR ART

[0001] The invention relates to a method for producing alginate-containing porous or spongy moulded articles, as well as the moulded articles obtained thereby and their use.

[0002] It is known that alkali metal alginates, such as for example Na alginate, are water-soluble, whereas alkaline earth alginates, such as for example Ca alginate, are water-insoluble. Thin, water-insoluble layers can therefore be produced for example by spraying a thin Na alginate film with a $CaCl_2$ solution. If on the other hand it is desired to produce thicker layers, then there is the difficulty that the homogeneous incorporation of free Ca ions into an Na alginate solution is complicated by a marked increase in the viscosity of the solution, so that no uniform products but instead non-coherent Ca alginate agglomerates are formed.

[0003] In order to overcome this problem US 5718916 proposes for example to add to the aqueous solution of the water-insoluble alginate composition a water-soluble complex-forming agent, such as for example sodium citrate. If for example a readily soluble calcium salt such as calcium chloride is then added, the immediate precipitation of calcium alginate is thus delayed by the presence of the complex-forming agent, whereby the formation of small insoluble calcium alginate globules in the product should be prevented. The examples of the aforementioned US patent specification are limited however to a scale of a few millilitres. The gelling time of the alginate solution after addition of the calcium chloride is merely 30 to 60 seconds. If an attempt is made to scale up this method, then it is found that the desired delay by addition of the complex-forming agent to the solution of the sodium alginate is not sufficient, and a relatively large-size product with a high homogeneity cannot be obtained. Furthermore, in the aforementioned method the use of surfactants is obligatory in order to achieve a sufficient dispersion of the components. The use of such surfactants can however lead to incompatibility problems, for example when used on the skin. The fact that in the method of US 5718916 a sufficient delay in the precipitation cannot be achieved by the prior addition of the complex-forming agent is also confirmed in GB 235 7765 of the same inventor, in which the method of US 5718916 is consequently described as disadvantageous. GB 2357765 discloses a method for producing water-insoluble alginate sponges or foamed products for the production of adhesive plasters or dressings or surgical products, in which also water-soluble alginate is crosslinked by the addition of polyvalent

metal ions in the presence of a foaming agent. The presence of a complexing agent is in this case intentionally avoided. In a preferred variant the process is carried out in the presence of ammonium hydroxide in order to lower the viscosity of the calcium alginate. In the examples calcium sulphate and then acetic acid for example are added. The method requires the presence of a foam-forming agent, a surfactant, a borate buffer, as well as the aforementioned ammonium compounds. This complex mixture of substances makes it difficult to control the process and the resultant products contain a large number of components whose physiological effects have to be taken into account.

[0004] From DE 202 19 666 U1 pads or dressings for dermatological applications are described, containing a polymer-based, in particular, alginic acid-based, carrier material. Specific examples describing the production of these pads cannot be obtained from the utility model. GB 621 230 A, WO 2004/104076 and JP 02 208332 A disclose possible modifications of these pads, such as the admixture of calcium salts.

[0005] Furthermore DE 43 28 329 discloses freeze-dried biological matrices for moisturising the skin and for topical transdermal application of pharmaceutical cosmetically active substances containing natural polysaccharides and modified polysaccharides. Also, this printed specification already mentions the stabilisation of the biological matrix by formation of calcium alginate frameworks by addition of calcium ions. However, this printed specification does not disclose how homogeneous thicker alginate layers can be produced.

[0006] The production of small-size alginate sponges for oral ingestion by adding a soluble calcium salt (calcium gluconate) to a Na alginate solution is described in WO 01/17377. This method is however not suitable for producing large-size alginate sponges for the reasons already mentioned above (no homogeneous incorporation of calcium ions). Owing to the resultant inhomogeneities the incorporation of active ingredients proposed there is furthermore complicated.

[0007] From WO94/00512 a method is known for forming polysaccharide foams, in particular alginate-based foams. This patent specification discloses in one embodiment also the variant in which an insoluble carbonate or hydrogen carbonate salt of polyvalent metal cations is dispersed in the foamed polysaccharide, and the foam is then treated with a strong acid in order to release carbon dioxide and through the cations that are formed to crosslink the polysaccharide with the formation of a dimensionally stable foamed structure. In this way, according to the details given in the printed specification foam thicknesses of up to 5 mm can be stabilised. These thicknesses are, however, in particular insufficient if it is then desired to cut the foamed articles into thinner layers. Also, the use of calcium carbonate

leads to an undesirable formation of gas during the production, which means that the pore sizes can hardly be controlled, resulting in marked inhomogeneities in the foam.

[0008] A further method for producing alginate sponges is known from US 3653383. In this, first of all Ca alginate is produced from alginic acid and calcium carbonate, the formed Ca alginate is then comminuted and the resulting gel is subjected to freeze-drying. In this way although relatively large-size spongy materials can be produced, the resultant products however decompose fairly rapidly in water. The alginate sponges – in particular even if they are cut into thin layers – have an insufficient wet strength, in particular wet tensile strength, for cosmetic or medicinal pads or dressings.

[0009] In the still unpublished German patent application DE 10323794.1 a method for producing porous alginate moulded articles is described, which requires the addition of complex-forming agents for polyvalent metal ions or a salt of a polyvalent metal ion with a multidentate complexing anion. The use of calcium sulphate and a mineral acid in the production of the porous alginate moulded articles is not disclosed.

[0010] The object of the present invention therefore consisted in providing relatively large-sized, extremely homogeneous moulded articles based on compounds formed between alginates and polyvalent metal ions, which have a high wet strength, in particular a high wet tensile strength, which can be cut with normal cutting tools into thin layers, which are optically pleasing, i.e. have in particular a high whiteness, and which can therefore be used in cosmetic or medicinal applications, such as a cosmetic skin pad or medicinal dressing or wound pad, etc. In addition the method for producing the moulded articles should be able to be easily controlled, and additives that are not completely physiologically harmless, such as foam-forming agents, surfactants, borate buffers and also ammonium compounds, should be avoided as far as possible.

[0011] Furthermore the method should enable homogeneous thick porous alginate layers to be prepared from which suitable, also orally applicable, cosmetic or medicinal application forms, such as for example implant moulded articles, satiation compressed articles, agents for the control, in particular delayed release of active constituents or the like, can be produced in a simple manner by pressing and/or punching.

[0012] The inventors of the present patent application were surprisingly able to successfully provide homogeneous, relatively thick, large-size moulded articles based on alginates of polyvalent metal salts, which can be obtained by the special method, likewise forming the subject matter of the present invention, which solve the aforementioned problems of the moulded articles of the prior art and which are therefore eminently suitable for the production

of cosmetic or medicinal products. The moulded articles preferably contain neither foam-forming agents, nor surfactants, nor borate buffers, nor ammonium compounds.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The present patent application thus provides a method for producing alginate-containing porous moulded articles, which method comprises mixing an aqueous alginate solution with calcium sulphate in the presence of at least one mineral acid, pouring the mixture obtained into a mould, and drying the mixture. Mineral acids include for example hydrochloric acid, sulphuric acid and phosphoric acid. Hydrochloric acid is preferred.

[0014] The water-soluble alginates used according to the invention are preferably alkali metal alginates, such as alginates of sodium, potassium, etc.

[0015] The underlying alginic acid is a natural acidic polysaccharide, which is extracted in particular from so-called brown algae (phaecophyceae) with a high molecular weight varying from about 30 000 to 200 000 Daltons, and contains chains that are formed from D-mannuronic acid and L-guluronic acid. The degree of polymerisation varies depending on the type of algae used for the extraction, the time of year at which the algae were collected, and the origin of the algae, as well as the age of the plants. The main species of brown algae from which alginic acid is obtained are for example Macrocystis pyrifera, Laminaria cloustoni, Laminaria hyperborea, Laminaria flexicaulis, Laminaria digitata, Ascophyllumnodosum and Fucus serratus. Alginic acid or alkaline alginates can however also be obtained microbiologically, for example by fermentation with Pseudomonas aeruginosa or mutants of Pseudomonas putida, Pseudomonas fluorescence or Pseudomonas mendocina (see for example EP-A-251905 and Römpp Chemie Lexikon "Natural substances" Thieme Verlag, 1997 and the documents cited there).

[0016] According to the invention alginates are preferred having an average particle size of up to about 0.2 mm and a viscosity in aqueous solution (1% solution, pH 7, 20°C) of 300 to 800 mPas.

[0017] According to the invention sodium alginate is particularly preferred.

[0018] The employed aqueous solution of the water-soluble alginate preferably has a concentration such that in the aqueous suspension formed after addition of the calcium sulphate and mineral acid, a concentration of 0.2 to 3.0%, preferably 0.3 to 2.5%, more preferably 0.4 to 1.2% (weight/weight) of alginate referred to the employed amount of water

is obtained. The solution can be prepared by suspending the desired amount of alginate for example in distilled water. The concentration of the alginate in the aqueous suspension has an influence on the hardness of the formed porous moulded articles. Concentrations of more than 2% (w/w) lead to relatively hard or brittle moulded articles, which is less desirable. Concentrations lower than 2% (w/w) lead to less brittle moulded articles, which is more preferred.

[0019] In a further preferred embodiment the porous moulded articles according to the invention contain carboxymethylcellulose, in particular sodium carboxymethylcellulose. The addition of sodium carboxymethylcellulose surprisingly leads to an improvement in the optical density of the porous moulded articles according to the invention without at the same time increasing the hardness or the brittleness of the moulded articles. On the other hand, the addition of sodium carboxymethylcellulose leads to an improvement of the flexibility of the obtained porous moulded articles. Furthermore the addition of carboxymethylcellulose, in particular sodium carboxymethylcellulose, leads to a stabilisation of the moulded articles. In the production of carboxymethylcellulose-containing moulded articles the carboxymethylcellulose, in particular sodium carboxymethylcellulose, surprisingly also prevents a sedimentation of the sparingly soluble salt, in particular $CaSO_4$, and thus allows a more homogeneous incorporation of the latter into the aqueous suspension and an increase in the homogeneity of the obtained moulded articles. In the method according to the invention a slurry of $CaSO_4$ and sodium carboxymethylcellulose in water is therefore formed, and to this is added the aqueous sodium alginate solution that contains the mineral acid and optionally further constituents, as described in more detail hereinafter.

[0020] The carboxymethylcellulose, in particular sodium carboxymethylcellulose, can be present in the moulded articles according to the invention in an amount of up to 90 wt.% referred to the dry content of the moulded article. This corresponds to the preferred ranges to be adjusted in the aqueous suspension of about up to 3 wt.%, preferably 0.2 to 3 wt.%.

[0021] A preferred embodiment of the moulded article according to the invention contains carboxymethylcellulose, in particular sodium carboxymethylcellulose, and hyaluronic acid or its salts or derivatives.

[0022] In the method according to the invention it is in principle also possible to add a complex-forming agent for calcium, in order to reduce the concentration of the calcium ions in the solution and thus inhibit the cross-linking of the alginate, although this is not absolutely essential. Such a complex-forming agent may be a carboxylate of an α-

hydroxypolycarboxylic acid, such as a citrate or malate, which however can serve as a cosmetically active constituent, such as a skin moisturiser.

[0023] According to the invention it is surprisingly found that the pH value adjusted by the mineral acid has an influence on the tensile strength of the obtained porous moulded articles. In order to achieve a higher tensile strength a pH value of less than 6, preferably less than 5, is therefore preferred. These low pH values are in turn particularly preferred in combination with a low alginate concentration of less than 2% (w/w) in the obtained suspension.

[0024] The amount of $CaSO_4$ is conveniently chosen so that the concentration of the salt in the resulting suspension is about 0.1 to 500 mmol/litre, in which the total amount of the salt refers here to the volume of the suspension.

[0025] The amount of added $CaSO_4$ referred to the amount of the soluble alginate in the solution is preferably chosen so that the molar ratio of alginate to $CaSO_4$ is 0.001 to 1.

[0026] The formation of the sparingly soluble alginates is conveniently controlled so that a flowability of the alginate solution, expressed as a viscosity at room temperature (20°C) of below about 1 000 mPas, is achieved within at least 1 minute, preferably about 2 minutes and more preferably within at least 3 minutes .

[0027] The mixing together of aqueous alginate solution, calcium sulphate and at least one mineral acid can preferably be carried out in mixers with a stator/rotor system, for example in a colloid mill.

[0028] According to the invention the (still) flowable alginate composition is poured into a mould suitable for the subsequent drying. In this connection layer thicknesses of the flowable alginate composition of up to about 50 cm are possible. Preferred moulds are box moulds of rectangular horizontal section. The pouring step can take place at any suitable stage of the method. Thus, the solution of the water-soluble alginate can already be poured into the mould subsequently used for the drying if a sufficient thorough mixing can be ensured in this mould. Preferably however the pouring takes place after the start of the crosslinking or precipitation of the sparingly soluble alginate.

[0029] The drying of the aqueous alginate suspension poured into the mould takes place in a manner known *per se*, particularly preferably by freeze-drying. This can also be carried out in a manner known *per se*, and here reference may be made for example to DE 4328329 C2 or DE 4028622 C2, to which reference should specifically be made as regards the drying

step of the method according to the invention, and which are therefore part of the method according to the invention.

[0030] In a preferred embodiment of the method according to the invention, before the casting of the suspension into a mould at least one further component, selected from the group consisting of: cosmetic or medicinal active substances, further natural or synthetic hydrocolloid-forming polymers and cosmetic or medicinal auxiliaries and additives, is additionally added.

[0031] Further natural or synthetic hydrocolloid-forming polymers include (partially) water-soluble, natural or synthetic polymers that form gels or viscous solutions in aqueous systems. They are conveniently selected from further natural polysaccharides, synthetically modified derivatives thereof or synthetic polymers. Further polysaccharides include for example homoglycans or heteroglycans, such as for example carrageen, pectins, tragacanth, guar gum, carob bean kernel flour, agar-agar, gum Arabic, xanthan, natural and modified starches, dextrans, dextrin, maltodextrins, chitosan, glucans such as β-1,3-glucan, β-1,4-glucan, cellulose, mucopolysaccharides, such as in particular hyaluronic acid, etc. Synthetic polymers include for example: cellulose ether, polyvinyl alcohol, polyvinylpyrrolidone, synthetic cellulose derivatives such as methylcellulose, carboxycellulose, carboxymethylcellulose, in particular sodium carboxymethylcellulose, cellulose esters, cellulose ethers such as hydroxypropylcellulose, polyacrylic acid, polymethacrylic acid, poly(methyl methacrylate) (PMMA), polymethacrylate (PMA), polyethylene glycols, etc. Mixtures of these polymers may also be used. The use of hydrocolloid-forming proteins, such as e.g. collagen, is however not preferred since some end users increasingly prefer to use purely plant products, especially in cosmetics.

[0032] According to the invention hyaluronic acid and/or its salts and/or its derivatives are particularly preferably added in addition. Hyaluronic acid is a highly viscous natural glucosaminoglycan with alternating β_{1-3} glucoronic acid and β_{1-4}-glucosamine fractions; its molecular weight is between 50 000 and a few million. Hyaluronic acid is often used as sodium salt, for example in therapy, mainly in ophthalmology, surgery and cosmetics. The salts of hyaluronic acid that are formed with alkali, alkaline earth, magnesium, aluminium, ammonium or substituted ammonium ions can be used as carriers in order to increase the absorption of medicaments (see e.g. Römpp Chemie Lexikon "Natural substances", Thieme Verlag, 1997 and the documents cited there). According to the invention sodium hyaluronate with a molecular weight of about 1 000 000 to 2 500 000 Daltons, is particularly preferred The addition of hyaluronic acid in the method according to the invention leads completely surprisingly to an increased whiteness of the obtained alginate-containing porous

moulded articles. This is particularly preferred for aesthetic reasons, especially in cosmetic use. Furthermore, hyaluronic acid however also exhibits its therapeutic action especially in topical or external use, such as for example as a skin moisturiser or to promote cicatrisation.

[0033] The hyaluronic acid or its salts are added to the alginate-containing porous moulded articles according to the invention in an amount, referred to the dried moulded articles, of about 0.1 to 90 wt.%, preferably 1 to about 67 wt.%.

[0034] Active substances added according to the invention include in particular cosmetic or therapeutic or pharmaceutical active substances, in particular those suitable for external use. The moulded article produced according to the invention preferably contains at least one cosmetic and/or pharmaceutical active substance. Accordingly, the preferred moulded articles according to the invention are preferably cosmetic or therapeutic agents. Cosmetic moulded articles and moulded articles in the meaning of the invention produced using cosmetic active substances are essentially agents within the meaning of the foodstuffs and consumer goods act (LMBG), i.e. substances or preparations of substances that are intended to be used externally on the human body for cleansing, care or to influence the appearance or body odour, or to transmit olfactory impressions, unless they are predominantly intended to alleviate or eliminate diseases, suffering, physical injuries or pathological conditions. In this context the cosmetic moulded articles produced according to the invention are for example cosmetic pads, such as for example face masks, etc., that can be used for example as skin washing and cleansing agents, skincare applications, in particular face skincare applications, eye cosmetics, lip care agents, nail care agents, foot care agents as well as hair or dental care agents.

[0035] Examples of cosmetically, optionally also for example dermatological, therapeutically active compounds include: anti-acne agents, antimicrobial agents, antiperspirants, astringent agents, deodorants, depilatories, skin conditioners, skin-smoothing agents, agents for improving skin hydration, such as for example glycerine or urea, sunscreen agents, keratolytics, free radical traps, antiseptics, active substances for treating signs of skin ageing and/or means that modulate the differentiation and/or proliferation and/or pigmentation of the skin, vitamins such as vitamin C, active substances with an irritant side effect, such as α-hydroxy acids, β-hydroxy acids, α-ketoacids, β-ketoacids, retinoids (retinol, retinal, vitamin A), anthralins (dioxyanthranol), anthranoids, peroxides (in particular benzoyl peroxide), minoxidil, lithium salts, antimetabolites, vitamin D and its derivatives; catechols, flavonoids, ceramides, fatty substances such as mineral oil, for example paraffin oils or Vaseline oils, silicone oils, vegetable oils such as coconut oil, sweet almond oil, apricot oil, maize oil, jojoba oil, olive oil, avocado oil, sesame oil, palm oil, eucalyptus oil, rosemary oil, lavender

oil, pine oil, thyme oil, mint oil, cardamom oil, orange flower oil, soya oil, bran oil, rice oil, rapeseed oil and castor oil, wheat germ oil and vitamin E isolated therefrom, evening primrose oil, plant lecithins (e.g. soya lecithin), sphingolipids/ceramides isolated from plants, animal oils or fats, such as tallow, lanolin, butter oil, fatty acid esters, esters of fatty alcohols and waxes with a melting point corresponding to skin temperature (animal waxes such as beeswax, carnauba wax and candelilla, mineral waxes such as microcrystalline waxes, and synthetic waxes such as polyethylene or silicone waxes), as well as all oils suitable for cosmetic purposes, such as for example those mentioned in the CTFA Agreement, Cosmetic Ingredient Handbook, 1st Edition, 1988, The Cosmetic, Toiletry and Fragrance Association, Inc., Washington, polyunsaturated fatty acids, essential fatty acids (e.g. gamma-linolenic acid), enzymes, co-enzymes, enzyme inhibitors, hydrating agents, skin calming agents, detergents or foam-forming agents, and inorganic or synthetic matting fillers, and abrasive agents.

[0036] Furthermore, plant active substance extracts or extracts or individual substances obtained therefrom may be mentioned, which can be added to the porous moulded articles produced according to the invention. In general the plant active substance extract is as a rule selected from the group consisting of solid plant extracts, liquid plant extracts, hydrophilic plant extracts, lipophilic plant extracts, individual plant constituents; as well as their mixtures, such as flavonoids and their aglycones: rutin, quercetin, diosmin, hyperoside, (neo)hesperidine, hesperitin, gingko biloba (e.g. gingko flavone glycosides), crataegus extract (e.g. oligomeric procyanidines), buckwheat (e.g. rutin), sophora japonica (e.g. rutin), birch leaves (e.g. quercetin glycosides, hyperosid and rutin), elderflower (e.g. rutin), lime blossom (e.g. ethereal oil with quercetin and farnesol), St John's wort oil (e.g. olive oil extract), calendula, arnica (e.g. oily extracts of the flowers with ethereal oil, polar extracts with flavonoids), Melissa (e.g. flavones, ethereal oil); immunostimulants; Echinacea purpurea (e.g. alcoholic extracts, fresh plant juice, pressed juice), eleutherococcus senticosus; alkaloids; rauwolfia (e.g. prajmalin), evergreen (e.g. vincamine); further phytopharmaceuticals: aloe, conkers (e.g. aescin), garlic (e.g. garlic oil), pineapple (e.g. bromelaine), ginseng (e.g. ginsenosides), milk thistle fruit (e.g. extract standardised to silymarin), butcher's broom extract (e.g. ruscogenin), baldrian (e.g. valepotriates, tinct. valerianae), cava-cava (e.g. cavalactones), hop flowers (e.g. hop bitters), passiflorae extract, gentian (e.g. ethanol extract), anthraquinone-containing drug extracts, e.g. aloin-containing aloe vera juice, pollen extract, algae extracts, liquorice extracts, palm extract, galphimia (e.g. mother tincture), mistletoe (e.g. aqueous-ethanolic extract), phytosterols (e.g. beta-sitosterol), wool flower (e.g. aqueous-alcoholic extract), drosera (e.g. liqueur wine extract),

sea buckthorn fruits (e.g. juice or buckthorn oil sap obtained therefrom), marshmallow root, primrose root extract, fresh plant extracts from mallow, comfrey, ivy, equisetales, common yarrow, ribwort (e.g. pressed juice), stinging nettle, celandine, parsley; plant extracts from Norolaena lobata, Tagetes lucida, Teeoma siems, Momordica charantia, and aloe vera extracts.

[0037] Preferred cosmetic active substances are natural and synthetic moisturising factors such as e.g. glycerine, urea and ceramides, skin protection products, skin whiteners, vitamins, antioxidants, so-called anti-ageing agents, anti-irritant agents, sunscreen products, etc.

[0038] Further preferred cosmetic active substances are natural fats and oil, i.e. triglycerides of natural fatty acids, for example on account of their rehydrating and caring effect on the skin.

[0039] A particularly preferred cosmetic active substance is urea, with regard to which it is assumed that it also acts as a local anaesthetic.

[0040] In contrast to the afore-described moulded articles essentially used in cosmetics, the therapeutically employed moulded articles (medicaments/medicinal products) are preferably those that contain at least one pharmaceutical and/or therapeutic, in particular also dermatological, active substance and that in the meaning of the medicines law are intended *inter alia* for healing, alleviating or preventing diseases, suffering, physical injuries or diseases. Furthermore, alginate itself can however also be regarded *per se* as a pharmaceutically/therapeutically active substance. The agents and active substances are intended for external application, in which connection they may be skin-active substances or also transdermal active substances. They include for example: means for treating skin diseases, externally applicable analgesics, e.g. dextropropoxyphen, pentazocin, pethidine, buprenorphine; antirheumatics/antiphlogistics (NSAR), e.g. indomethacin, diclofenac, naproxen, ketoprofen, ibuprofen, flurbiprofen, salicylic acid and derivatives such as acetylsalicylic acid, oxicams; steroid hormones, e.g. betamethasone, dexamethasone, methylprednisolone, ethinyl oestradiol, medroergotamine, dihydroergotoxin; gout medication, e.g. benzbromarone, allopurinol; external dermatological ointments, including antibacterial agents, antimycotics, antiviral substances, anti-inflammatories, antipruitic substances, anaesthetising substances, e.g. benzocain, corticoids, acne treatments, antiparasitics; externally applicable hormones; venous therapeutic agents; immunosuppressants, etc. all for external application.

[0041] Preferred therapeutic agents are analgesics, e.g. immunosuppressants, hormones, agents for treating skin diseases such as neurodermatitis, atopic dermatitis, etc., and anti-herpes agents.

[0042] The porous moulded articles produced according to the invention can furthermore optionally contain one or more auxiliary substances. Auxiliary substances include: fillers, pH adjustment agents such as buffers, stabilisers, co-solvents, pharmaceutically and cosmetically customary or other dyes and pigments, preservatives, plasticisers, lubricants, etc. A particularly preferred auxiliary substance is squalane. Squalane has a skin calming and skin smoothing effect.

[0043] Porous moulded articles containing alginates of polyvalent metal ions, which have a thickness of at least one centimetre, preferably at least 2 cm, and which are obtained by crosslinking (or precipitation) of alginate-containing aqueous solutions with salts of polyvalent metal ions and subsequent drying of the aqueous suspension of the obtained, crosslinked alginate, can be produced by the present invention. The thickness of a moulded article denotes in this connection the shortest distance between two points in such a moulded article. The production of such thick large-size moulded articles having the desired wet strength, in particular wet tensile strength, cutting ability, etc., was not possible hitherto in the prior art. These porous moulded articles are preferably obtained by the method according to the invention. The methods that include the freeze-drying of comminuted insoluble alginates lead to readily decomposable porous or spongy materials unsuitable for the application envisaged here.

[0044] The porous moulded articles according to the invention have on suspending 1 g of the moulded article in 100 g of water at 20°C a pH value of the aqueous phase of less than 7, preferably less than 6. Such an acidic pH value is preferred especially in cosmetic use on the skin.

[0045] The porous moulded article according to the invention preferably has a density of 0.005 to 1 g/cm^3, preferably 0.01 to 0.5 g/cm^3 (determined according to DIN 53420).

[0046] The porous moulded article according to the invention preferably has a wet tensile strength of at least about 10 mN/mm layer thickness (determined according to DIN 53328).

[0047] The porous moulded article according to the invention does not, or not substantially, consist of spun alginate fibres, e.g. calcium alginate fibres.

[0048] The aforementioned porous moulded articles according to the invention can, as previously mentioned, contain in addition at least one further component selected from the

group consisting of: cosmetic or medicinal active substances, further natural or synthetic hydrocolloid-forming polymers and cosmetic or medicinal auxiliary substances or additives. These can be contained in the porous moulded articles according to the invention in amounts of up to 0.75 g/g, preferably less than 0.5 g/g of the moulded article.

[0049] The porous moulded articles according to the invention are particularly suitable for producing layered moulded articles by cutting the porous moulded articles according to the invention in a manner known *per se*. This is not possible for example with the spongy materials produced by freeze-drying comminuted insoluble alginates. Layer thickness of 0.5 to 20 for example are obtained by cutting the porous moulded articles according to the invention. The invention also relates to the layered porous moulded articles thereby obtained. Such layered porous moulded articles are suitable in particular for external application, such as a cosmetic or medicinal pad, as a wound dressing or bandage, as an implant material, as a cell culture medium, etc.

[0050] The porous moulded articles according to the invention are furthermore particularly suitable for producing collagen-base compressed, expandable, spongy moulded articles, such as are described for example in EP 0901 792 of the applicant. They can be produced in a simple manner from the large-size porous moulded articles obtained in particular after freeze-drying, by stamping and/or pressing, in particular also on an industrial scale, which hitherto was not easily possible according to the methods of the prior art.

[0051] Such compressed products are suitable in particular for oral, buccal or nasal application, for example as satiation compressed products, which may optionally contain in addition active substances, food supplements or vitamins (e.g. DE 19942417).

[0052] On account of the sparingly soluble nature of the porous moulded articles according to the invention they are furthermore suitable for producing forms loaded with active substances, from which the active substance is released in a controlled, in particular delayed manner. Such forms include sponges containing active substances, such as implants, vaginal suppositories, as well as orally applicable forms, the latter in particular as compressed products, which in the moistened state, such as in the stomach, expand to a multiple of their compressed volume and release the contained active substance from the spongy matrix (e.g. WO 98/0961 7).

[0053] The present invention furthermore relates to porous moulded articles containing alginates of polyvalent metal ions and hyaluronic acid and/or their salts and/or their derivatives, which are obtained by the method according to the invention. As already mentioned hereinbefore, these moulded articles completely unexpectedly have an increased

whiteness, which is particularly preferred especially in cosmetic but also in medicinal uses. The preceding description for example may be referred to as regards the composition of such hyaluronic acid-containing porous moulded articles. The hyaluronic acid-containing porous moulded articles are preferably produced by the method according to the invention.

[0054] The present invention also relates to the use of the porous moulded articles according to the invention or the moulded articles obtained by the method according to the invention, as cosmetic agents.

[0055] The use of the porous moulded articles according to the invention in cosmetics is preferably in the form of cosmetic skin pads, which are applied moist to the skin and can be removed after a certain action time, for example after the active substances contained therein have been absorbed by the skin. Also, the alginate itself already manifests a cosmetic effect, such as the hydration and smoothing of the skin.

[0056] The present invention also relates to the use of the porous moulded articles according to the invention or the moulded articles obtained by the method according to the invention, for the production of a medicinal product. Such medicinal products include for example wound dressings and bandages, transdermal pads, adhesive plasters, implants, substrates for cultivating cells, means for the controlled, in particular delayed, administration of active substances in the form of the aforementioned implants, but also orally applicable retard preparations, or as so-called satiation compressed products, which by expansion of the compressed porous moulded article in the stomach produce a satiation effect. The latter can also contain nutritional supplements, vitamins, minerals or other active substances.

[0057] The porous moulded articles according to the invention or the moulded articles obtained by the method according to the invention are preferably used for external application, in particular as a cosmetic or medicinal pad. In addition, as previously mentioned oral, buccal, vaginal or nasal application, etc., is however also possible. The homogenous thick porous alginate moulded articles obtainable according to the invention enable, as previously mentioned, the production of arbitrary application forms on an industrial scale by known methods, such as cutting, pressing, compression and/or stamping.

[0058] Particularly preferred moulded articles according to the invention contain, referred to the dry substance, i.e. without residual moisture:

About 6 to 100 wt.% alginate

0 to about 90 wt.% carboxymethylcellulose, in particular the sodium salt,

0 to about 70 wt.% hyaluronic acid or its salts or derivatives,

0 to about 90 wt.% natural or synthetic oils,

0 to about 70 wt.% citric acid or its salts,

which preferably corresponds in the aqueous suspension in to be freeze-dried step c) to

about 0.2 to 3 wt.% alginate,

0 to about 3 wt.% carboxymethylcellulose, in particular its sodium salt,

0 to about 1 wt.% hyaluronic acid or its salts or derivatives,

0 to about 3 wt.% natural or synthetic oils,

0 to about 1 wt.% citric acid or its salts.

[0059] The porous moulded articles according to the invention preferably exist in the form of a layer, i.e. the length and width of the moulded article are at least 10 times, preferably at least 20 times as great as the thickness of the moulded article. Such layers can also be cut into shapes, for example into the shape of a face mask. The layers have a surface area of preferably at least about 25 cm^2, preferably at least about 50 cm^2, more preferably of at least about 100 cm^2.

[0060] The invention furthermore also relates to laminates containing at least one layer, as described hereinbefore, which is laminated on at least one side with at least one further carrier layer. Preferably the layer according to the invention is laminated only on one side with preferably only one carrier layer. The carrier layer preferably consists of a rayon network (of viscose). Such laminates are preferably used as a wound dressing or adhesive plaster and particularly preferably as a cosmetic mask.

[0061] The invention also relates to a combination containing at least one of the porous moulded articles according to the invention as well as at least an aqueous solution containing one or more active substances and/or auxiliary substances, in a coherent, spatial arrangement (application pack, set, kit-of-parts, etc.). The active substances solution can for example be solutions of highly volatile active substances and/or auxiliary substances, which on account of the production method by freeze-drying should not be or cannot be incorporated into the moulded article, such as for example certain fractions of ethereal oils, perfume, fragrance, etc. Furthermore the solution may contain temperature-sensitive pharmaceutical or cosmetic active substances.

[0062] The invention is described in more detail with the aid of the following examples:

Step 1:

2500 g	RO water (deionised water, reverse osmosis)
32.5 g	Na alginate
10.0 g	Citric acid

HCl

[0063] The alginate powder and citric acid are incorporated by means of a mixer into the RO water until a homogeneous mixture is formed. HCl is then added. (At this point cosmetic and/or medicinal active substances and/or oils or other substances, etc., may conveniently or optionally be incorporated into this mixture).

Step 2:

50 g	RO water
10.0 g	Calcium sulphate
10.0 g	Sodium carboxymethylcellulose

[0064] The calcium sulphate and sodium carboxymethylcellulose are added while stirring to 50 ml of RO water.

Step 3:

[0065] The solutions from step 1 and step 2 are thoroughly mixed for ca. 30 seconds.

Step 4:

[0066] The mixture from step 3 is poured into a mould and allowed to react for ca. 1 hour.

Step 5:

[0067] The gelled moulded article is shock frozen and freeze-dried.

Step 6:

[0068] The freeze-dried, large size, porous or spongy moulded article, optionally containing additional substances, can be processed further as described above.

Szabadalmi igénypontok

1.Eljárás porózus öntött termékek előállítására, amely tartalmazza vizes alginát oldat összekeverését kalcium-szulfát és nátrium-karboximetil-cellulóz iszapszerű keverékével legalább egy ásványi sav jelenlétében, a kapott keveréknek az öntését egy öntőformába és a keverék szárítását.

2. Az 1. igénypont szerinti eljárás, ahol az ásványi sav a hidrogén-klorid.

3. Az 1. vagy 2. igénypontok bármelyike szerinti eljárás, ahol a vizes alginát oldat egy alkálifém-alginát oldat.

4. Az 1-3. igénypontok bármelyike szerinti eljárás, ahol a szárítást fagyasztva szárítással hajtjuk végre.

5. Az 1-4. igénypontok bármelyike szerinti eljárás, ahol a szárítást megelőzően legalább egy további komponenst adagolunk a következőkből álló csoportból választva: kozmetikai és gyógyászati aktív anyagok, további természetes vagy szintetikus hidrokolloid-formáló polimerek és kozmetikai vagy gyógyászati hordozóanyagok vagy adalékanyagok.

6. Az 5. igénypont szerinti eljárás, ahol a további komponens legalább egy természetes poliszacharid vagy annak módosított származéka.

7. Az 5. vagy 6. igénypontok bármelyike szerinti eljárás, ahol a további komponens hialuronsav vagy sója.

8. Az 5-7. igénypontok bármelyike szerinti eljárás, ahol karbamidot adagolunk további komponensként.

9. Az 5-8. igénypontok bármelyike szerinti eljárás, ahol szkvalént adagolunk további komponensként.

10. Eljárás réteges öntött termékek előállítására az 1-9. igénypontok bármelyike szerint előállítható öntött termékek darabolásával, ahol az öntött termék egy réteg formájában van, azaz az öntött termék hossza és a szélessége legalább 10-szerese az öntött termék vastagságának, és amennyiben alkalmazható, a kapott öntött terméknek legalább egy oldalára legalább egy további támasztó réteget laminálunk.