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(54) IMPROVED NANOCARRIER
MANUFACTURING

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(71) Applicant: Evonik Operations GmbH, Essen
(DE)(72) Inventors: Jürgen Erwin Lang, Karlsruhe (DE);
Mario Gomez, Darmstadt (DE);
Marcel Arndt, Moerfelden-Walldorf
(DE)(73) Assignee: Evonik Operations GmbH, Essen
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(2013.01)

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(57) ABSTRACT

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An apparatus may be for producing nanocarriers and/or nanoformulations. A process may be for producing a nanocarrier and/or a nanoformulation with this apparatus. According to the preparation, a first liquid phase and a second liquid phase are mixed first to give a primary mixture using a static mixer. In a subsequent mixing step the primary mixture is diluted with a third liquid. An aspect of apparatus may be that the arrangement of the static mixer inside a linear pipe conducting a third liquid phase. Thus, the primary mixture exiting the mixer is instantaneously diluted with to give secondary mixture. The volume flow of the third mixture is chosen larger than the volume flow of the primary mixture. By these measures, nanocarriers with improved morphology and homogeneity are produced. Encapsulation efficiency was enhanced as well.

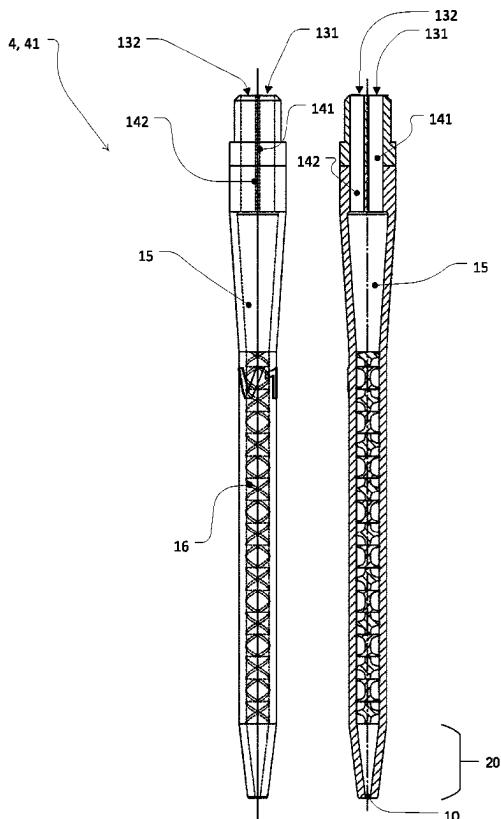
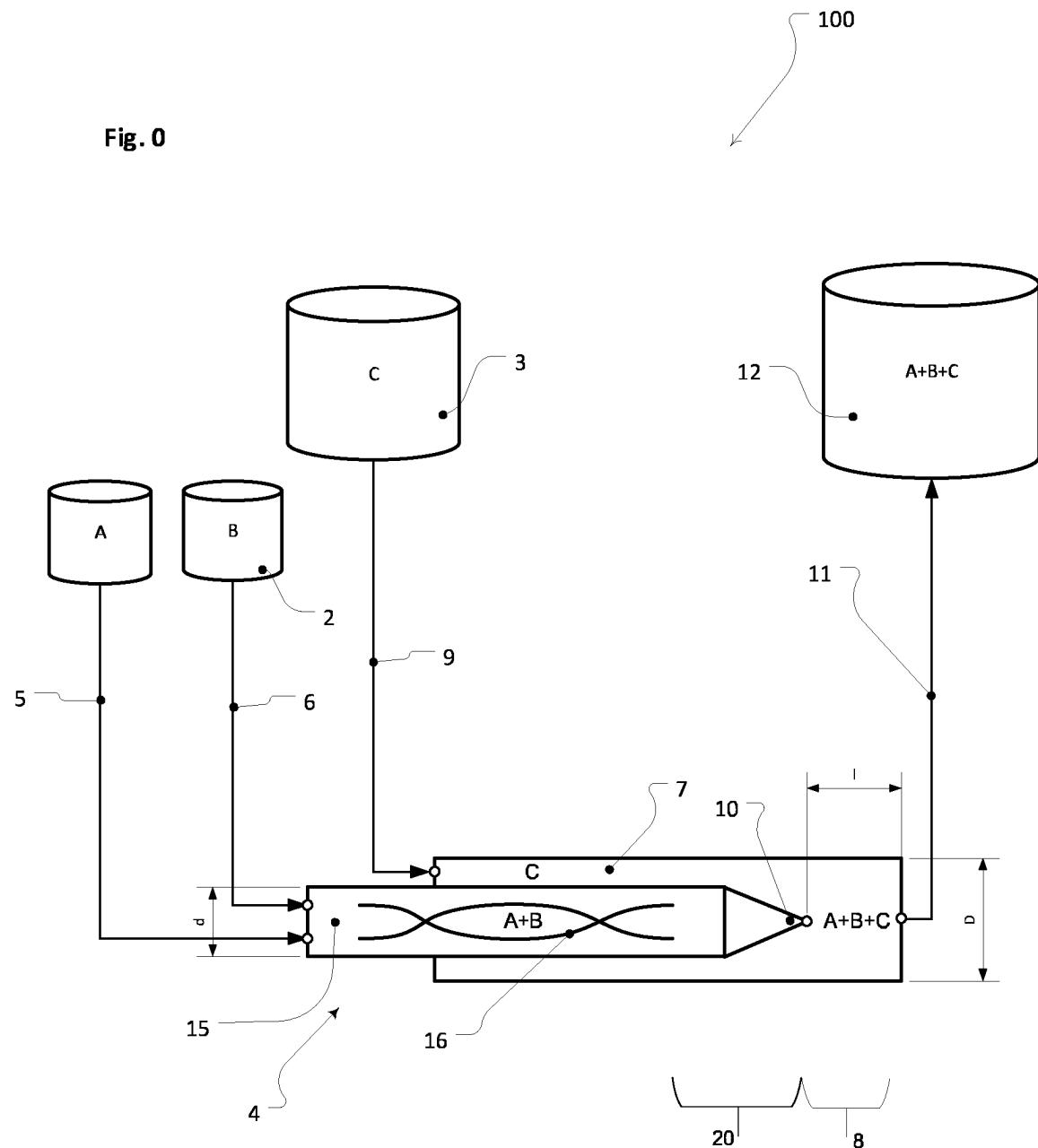
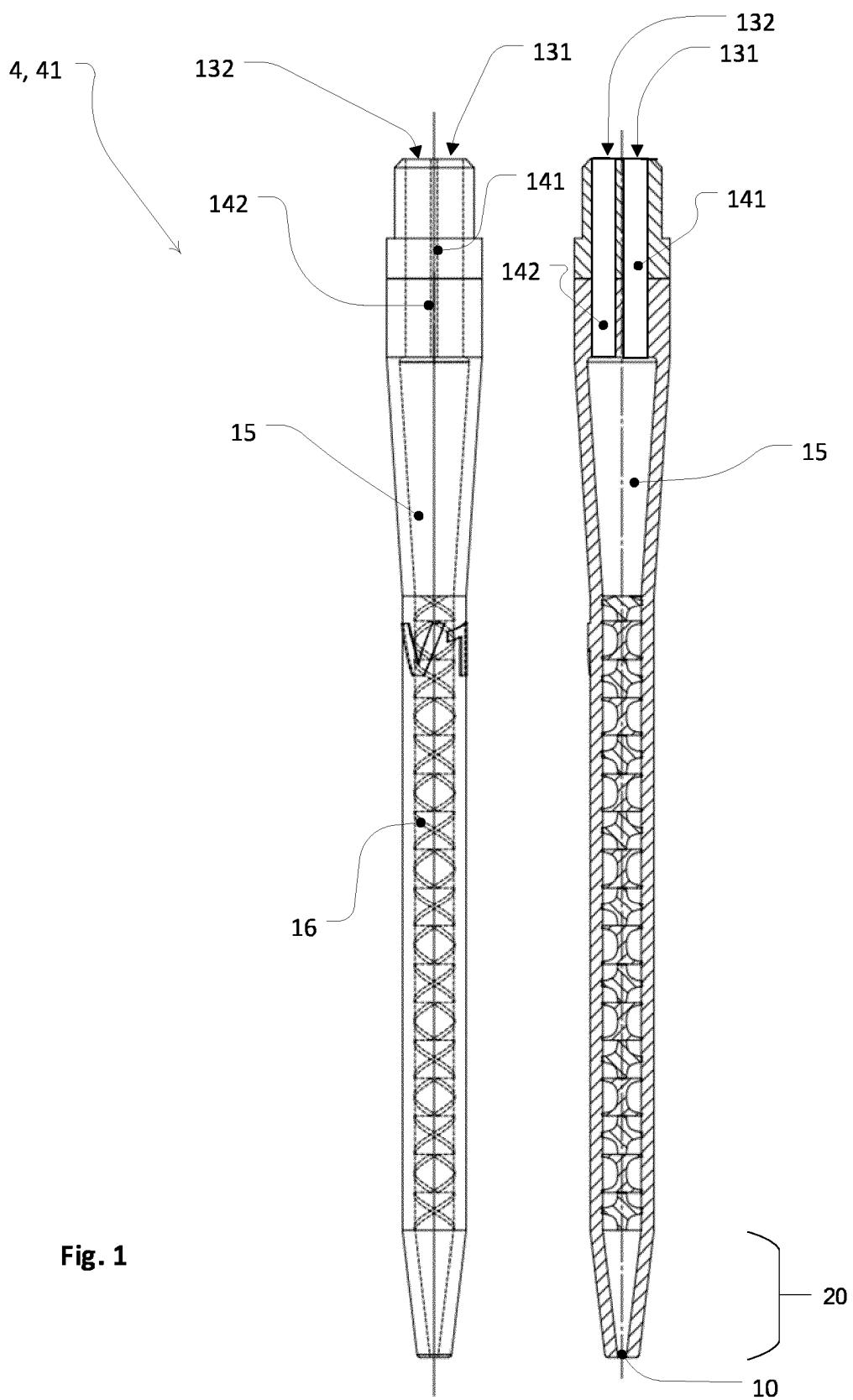


Fig. 0





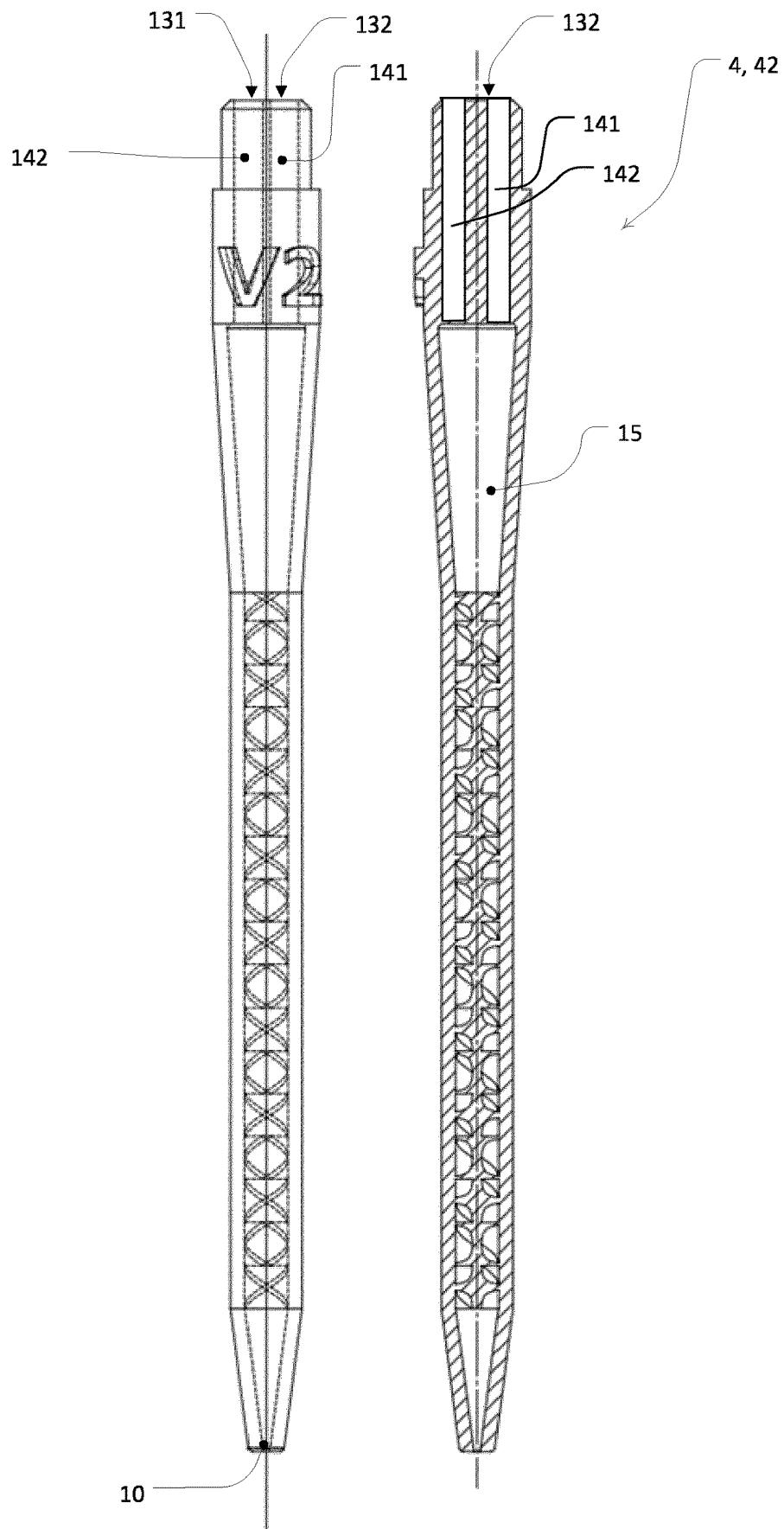


Fig. 2

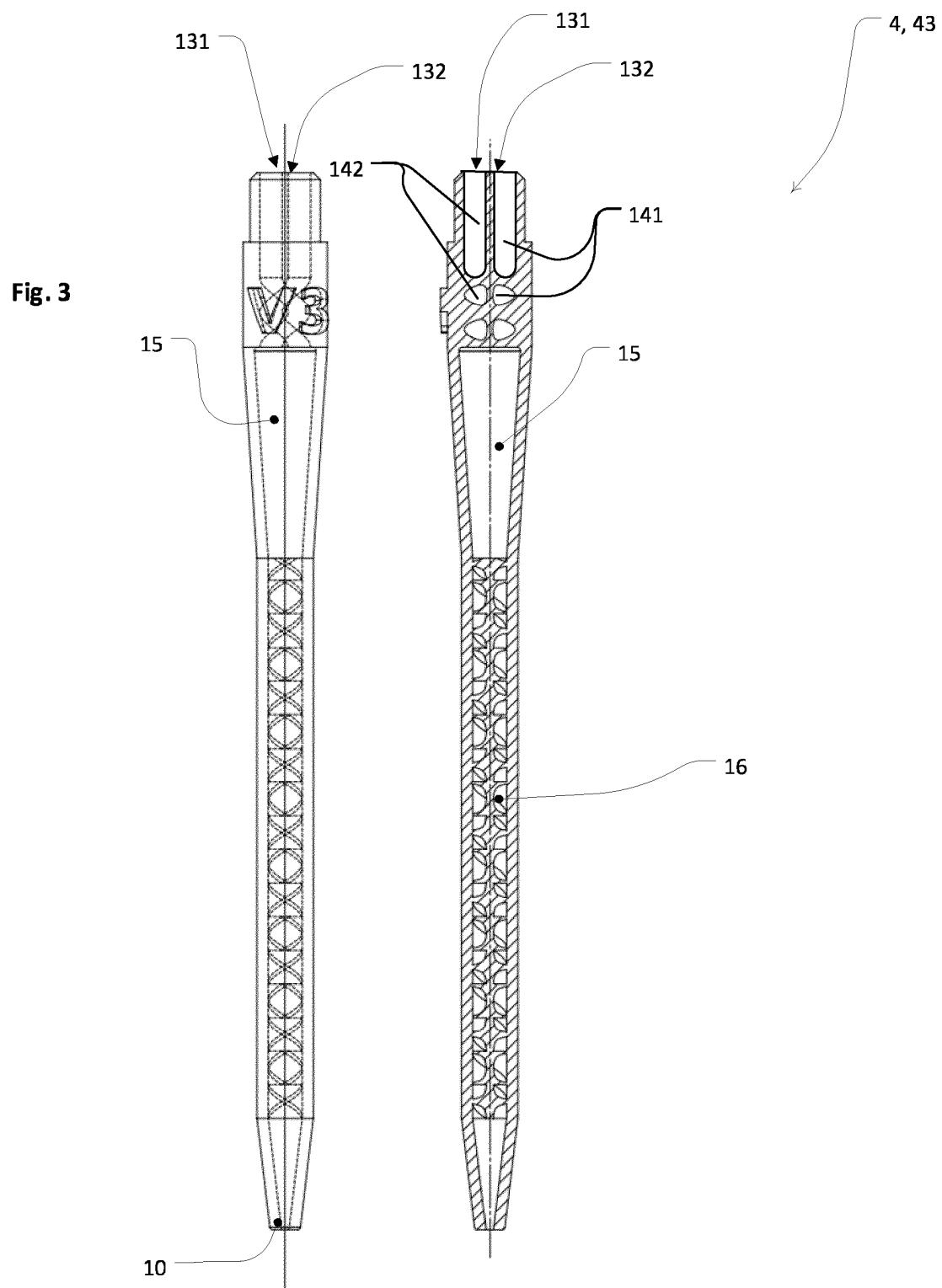
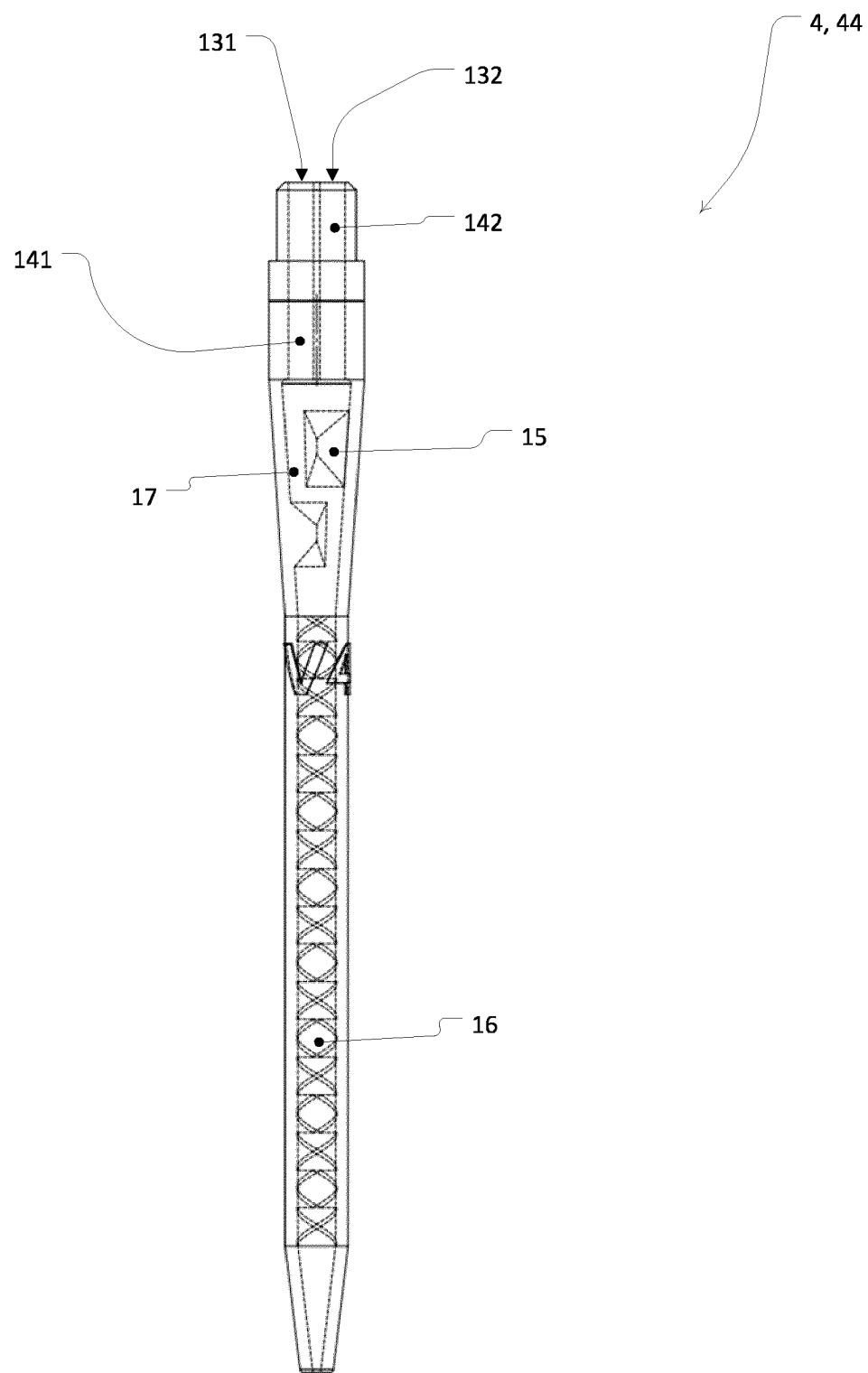


Fig. 4



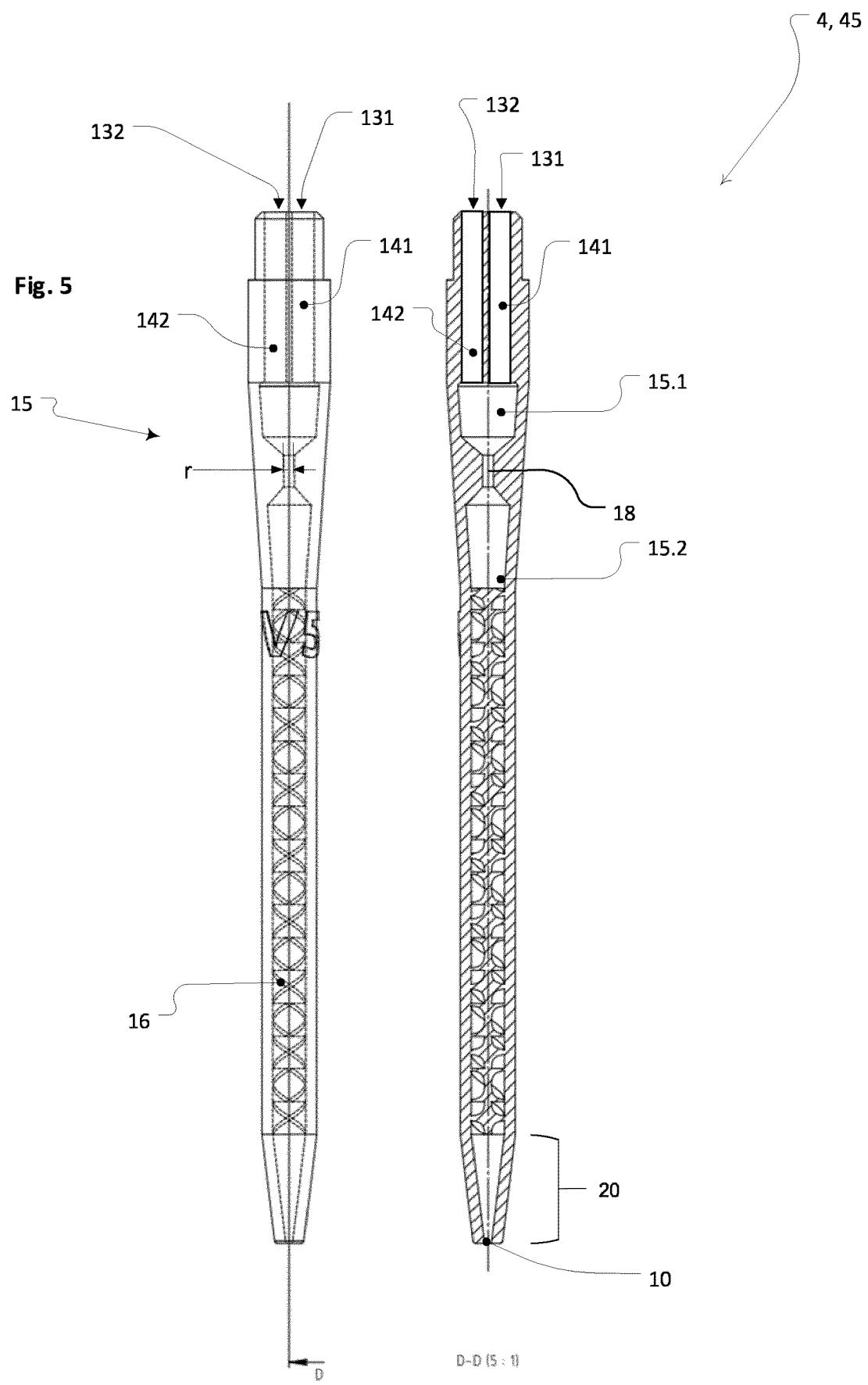
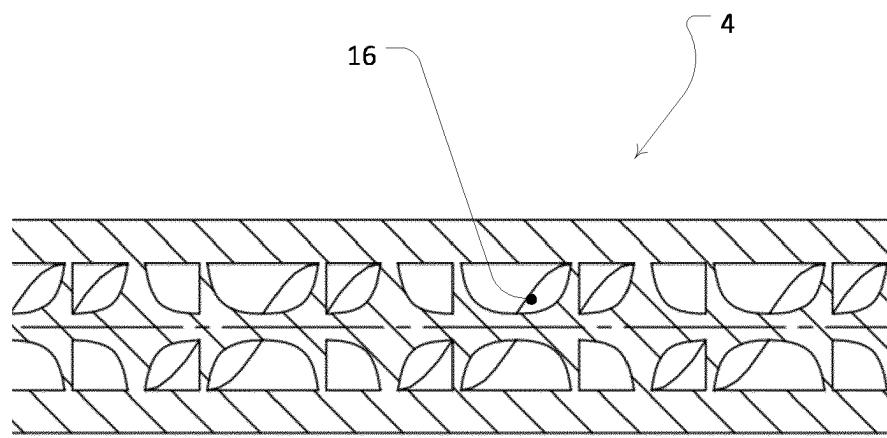
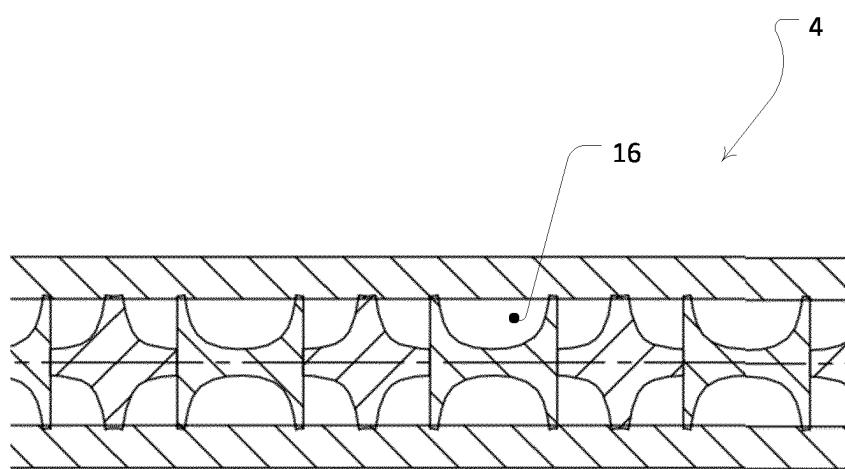
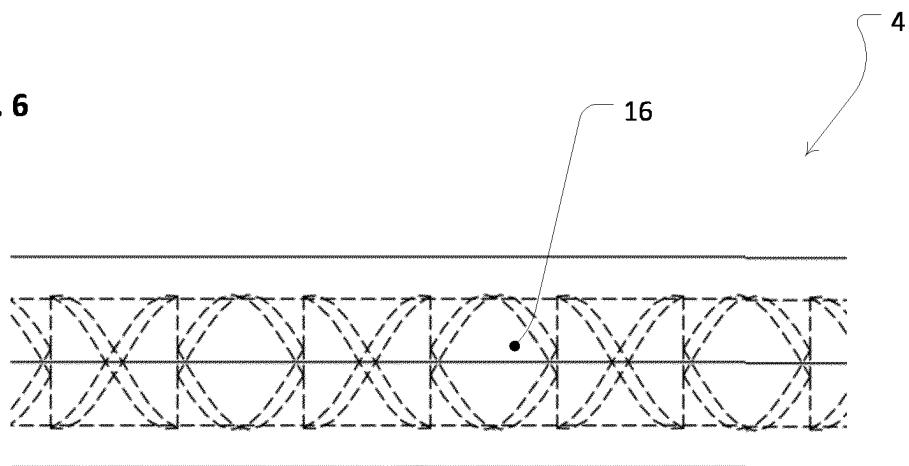


Fig. 6



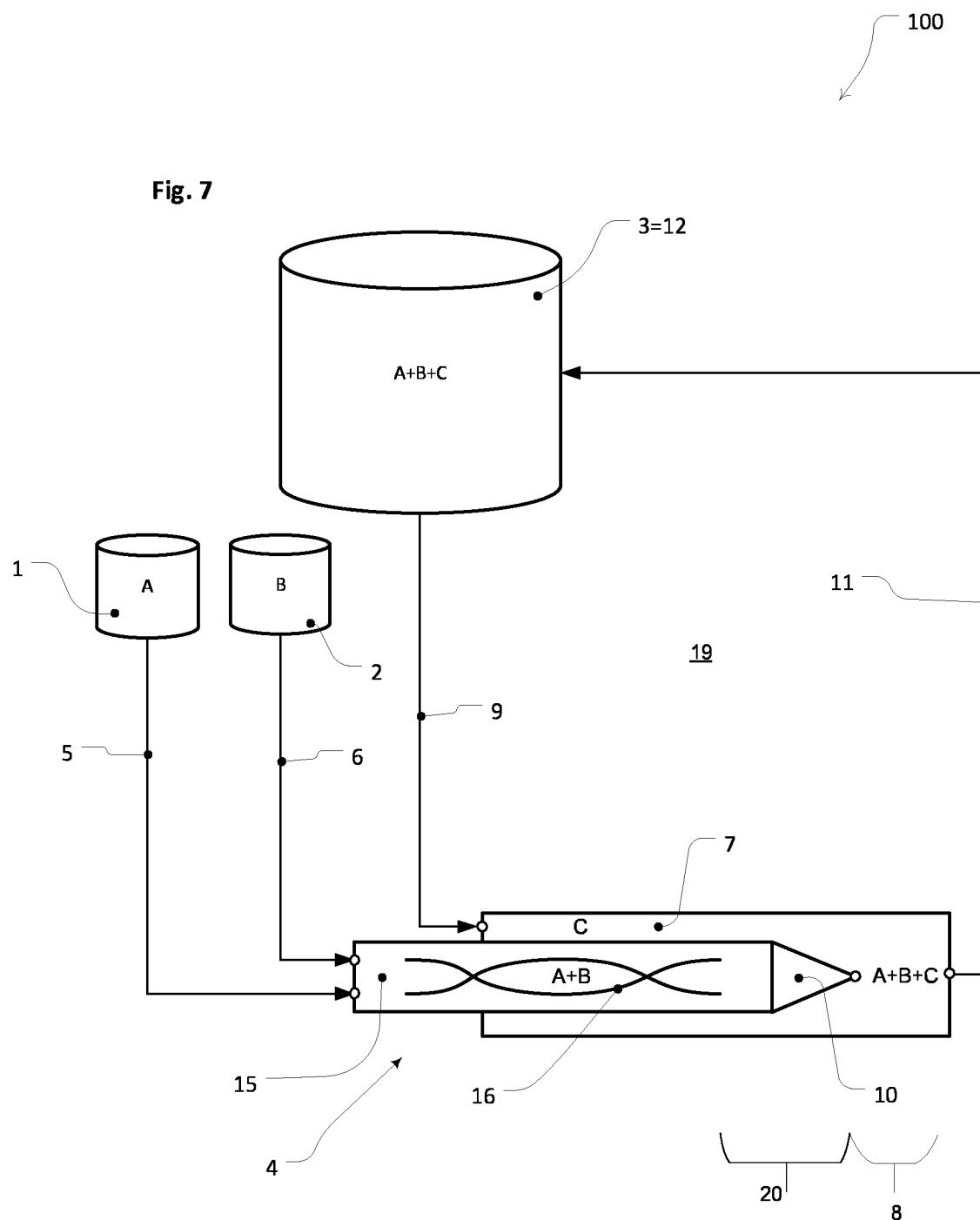
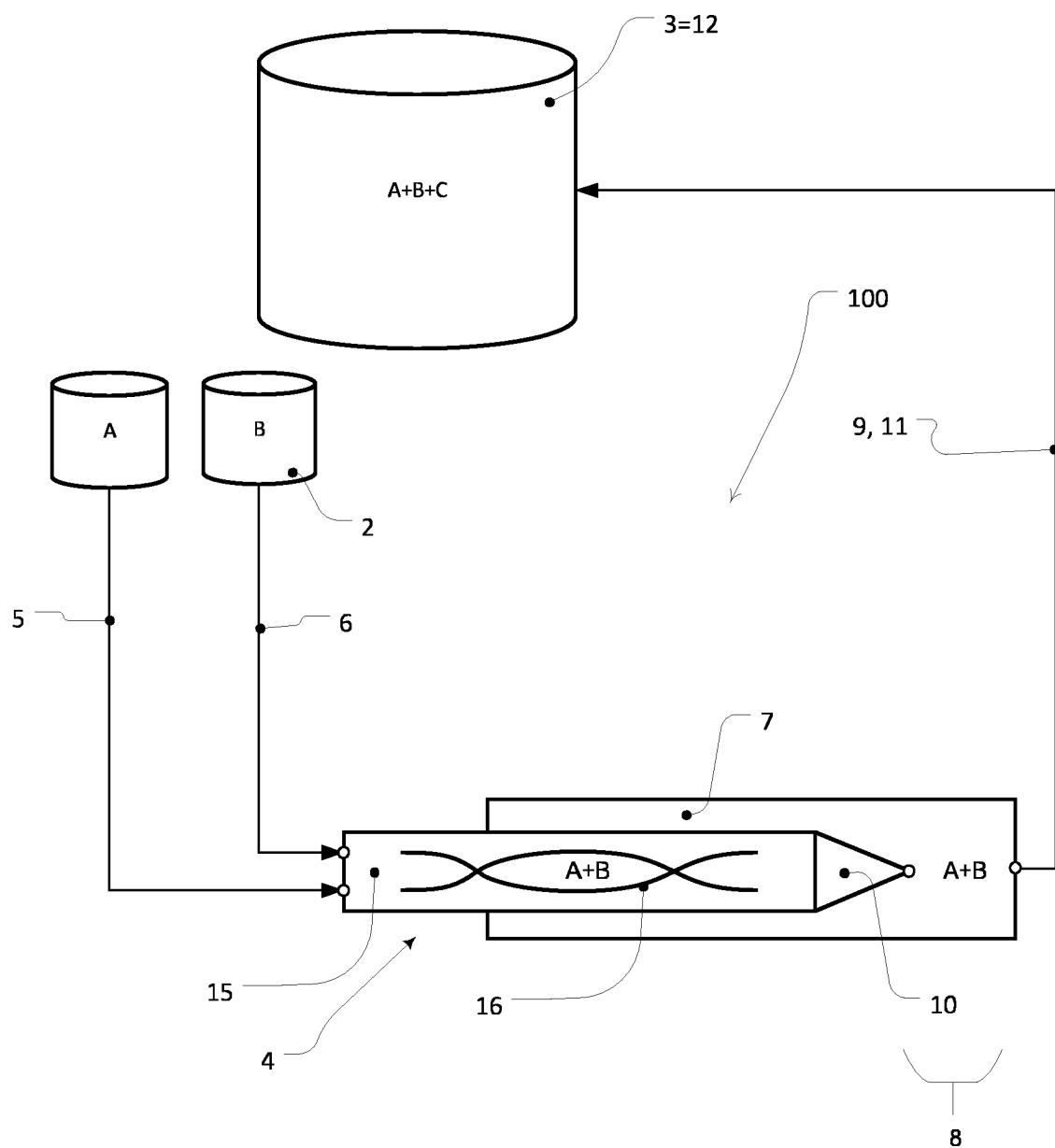


Fig. 8



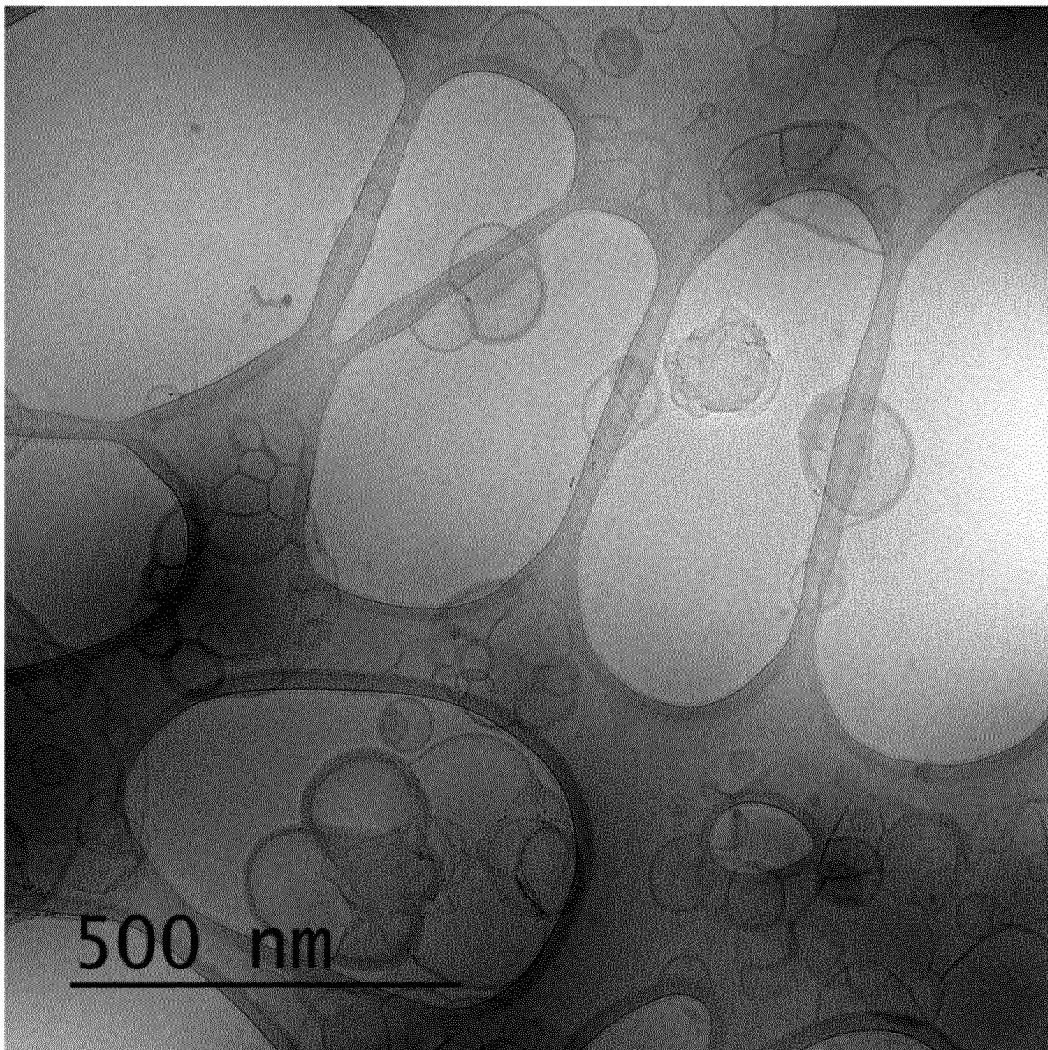


Fig. 9
(prior art)

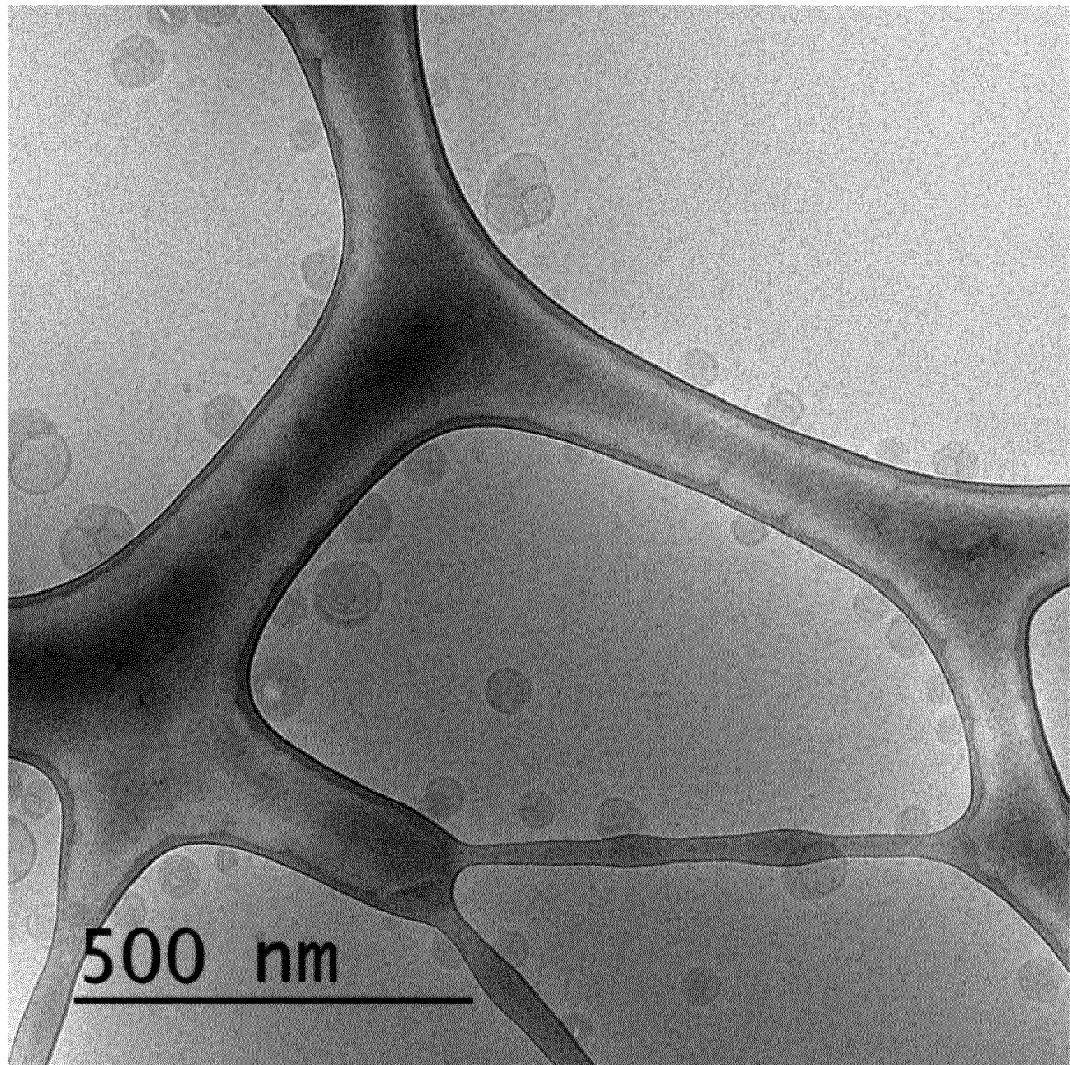


Fig. 10

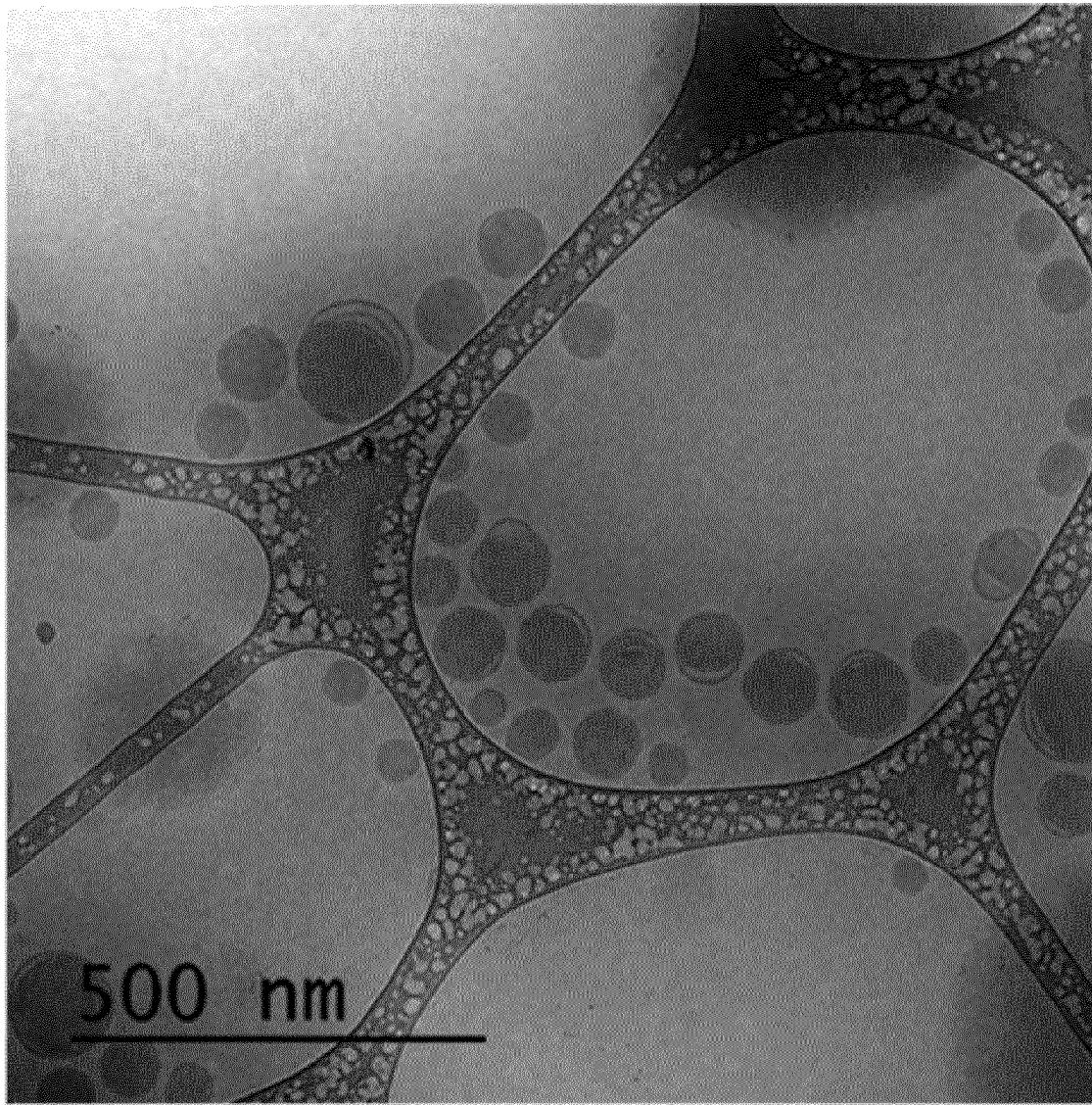


Fig. 11

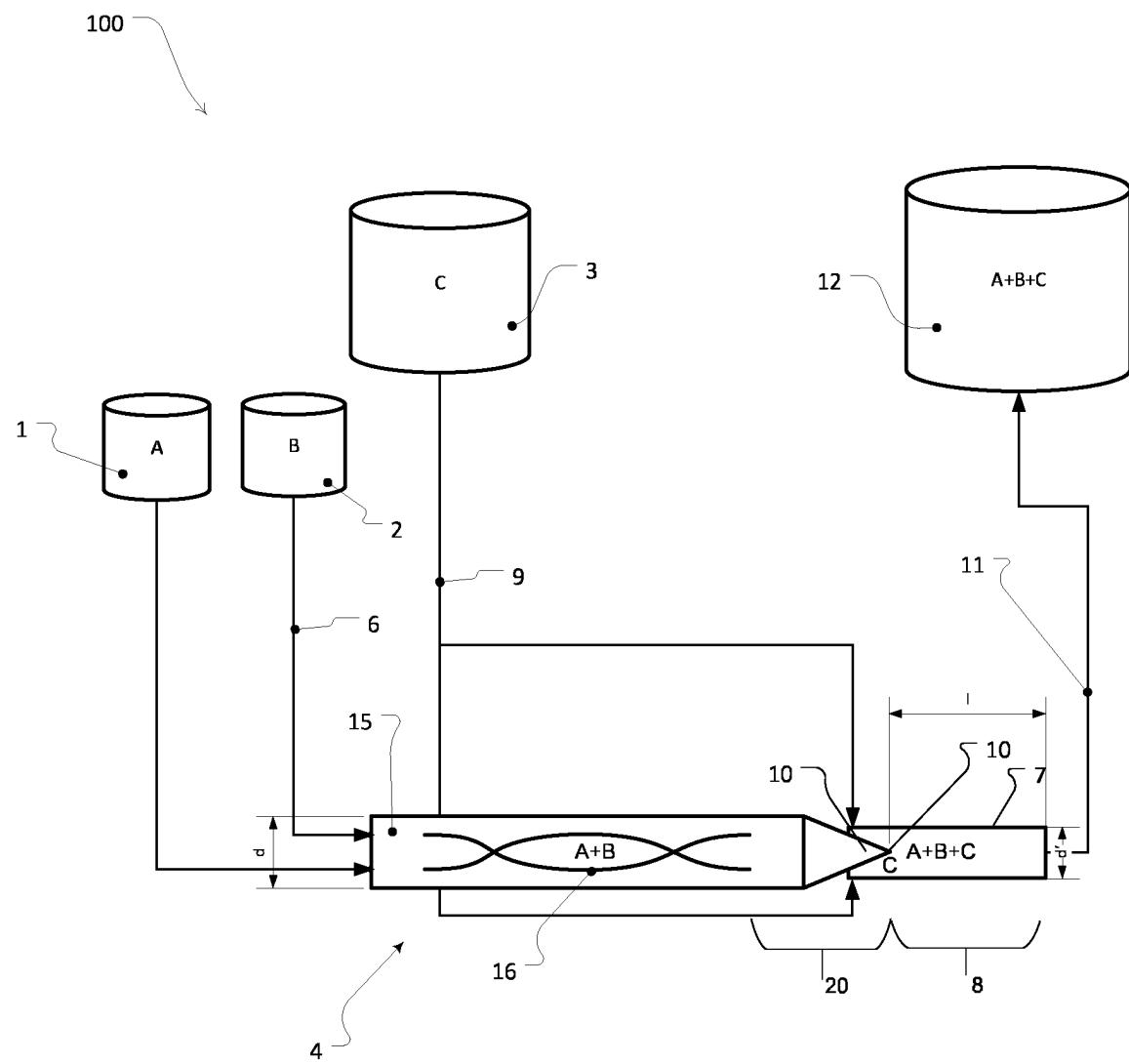
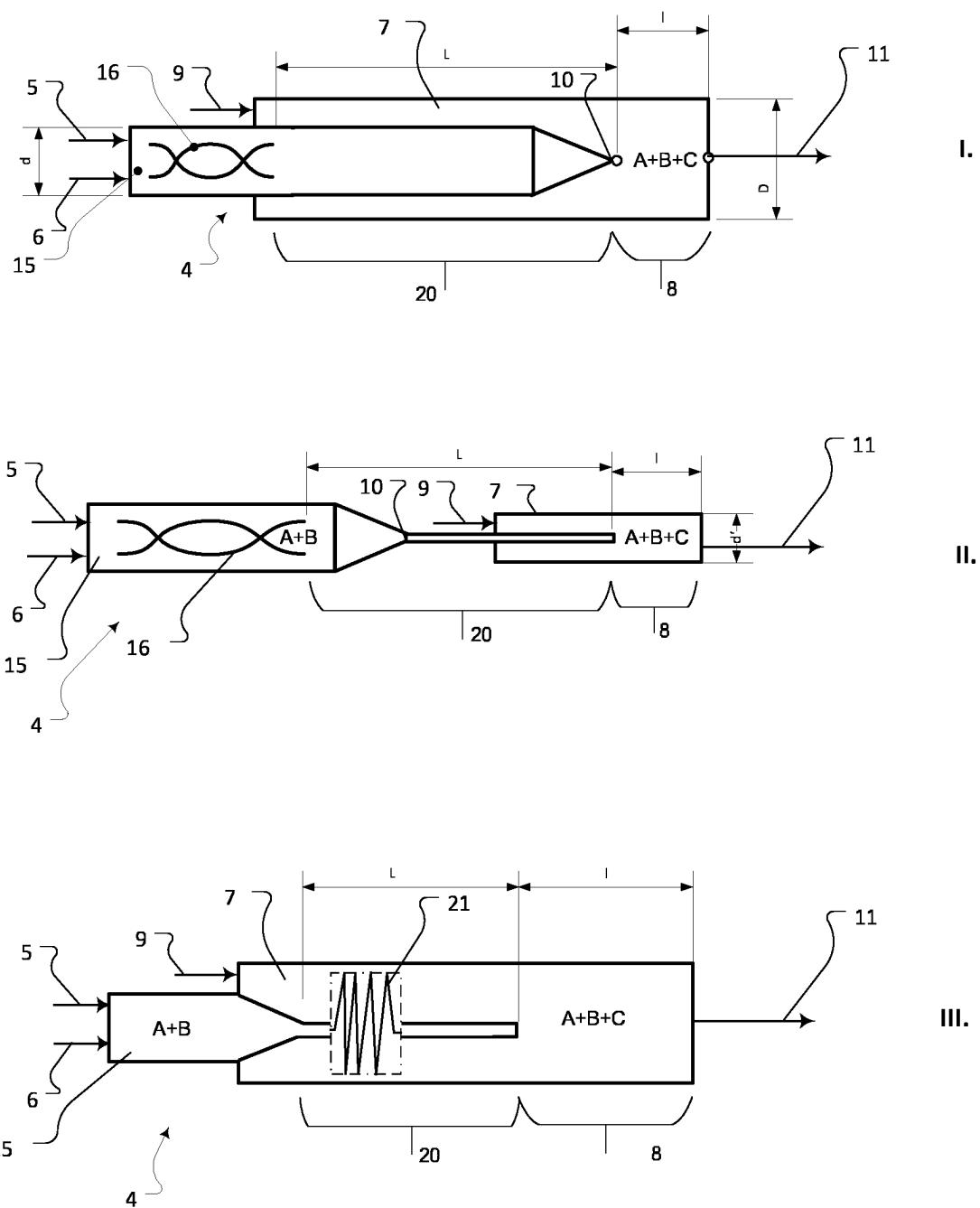


Fig. 12

Fig. 13



IMPROVED NANOCARRIER MANUFACTURING

[0001] In the context of the present invention a nanocarrier is a composition for carrying pharmaceutical, cosmetic or nutraceutical active ingredients. The nanocarrier may consist of a pure substance or may be a mixture of two or more substances. The substances may be solid, semi-fluid or liquid. The substances may be single-phase or multi-phase substances: In all cases nanocarriers are in particulate form, wherein the average particle size is smaller than 300 nm.

[0002] Examples of nanocarriers are particles of natural or synthetic polymers, lipids (lipid nanoparticles—LNP), liposomes and micelles and nanoemulsions.

[0003] Nanocarriers composed of two or more substances are generally produced by providing the individual substances or precursors thereof as dispersions or as solutions in liquid media and mixing these with one another. The mixing results in physical interactions between the individual substances or precursors to form the nanocarrier. The nanocarrier may optionally be subjected to subsequent workup, for example by separation from the liquid medium. The obtained nanocarrier may then either be used as a placebo or is laden with an active ingredient to form a nanoformulation.

[0004] In the context of the present invention a nanoformulation is a dosage form of a pharmaceutical, cosmetic or nutraceutical active ingredient carried by a nanocarrier. The active ingredient may be on the surface of the nanocarrier, may be inside the nanocarrier or may be complexed with the nanocarrier.

[0005] Examples of nanoformulations include inter alia so-called lipoplexes or polyplexes, i.e., complexes of polymers or lipids with for example DNA, RNA, proteins, peptides etc. Within these complexes the polymers/lipids form the nanocarrier while the DNA/RNA form the active ingredient.

[0006] As described above the production of nanoformulations may be carried out by loading a nanocarrier with active ingredient.

[0007] However, in pharmaceutical technology it is in the interest of process economy that the production of the nanocarrier and the loading thereof with active ingredient is carried out in an integrated process:

[0008] In such an integrated process the nanocarrier is produced first and loaded with active ingredient in the nascent state. This is generally carried out by providing and mixing the individual components of the nanoformulation as a dispersion or solution in liquid media. The components include the substances forming the nanocarrier/precursors to these substances and also the active ingredient or its precursors. The mixing results in physical interactions between the individual components to form the nanoformulation. If required, the nanoformulation is subsequently subjected to further workup, for instance removal of organic solvents or separation of the nanoformulation from the liquid medium.

[0009] Especially nanoformulations using LNP or polyplexes as carrier are always produced in an integrated process where the loading of the carrier with active ingredient is carried out in the nascent state.

[0010] In commercial processes, loading of the nanocarrier is often realized by impingement mixers.

[0011] EP1519714B1 discloses a process for producing nanoformulations employing an apparatus comprising a T-shaped impingement mixer. The two fluids to be mixed are passed through coaxial feed conduits to a collision point,

mixed there and withdrawn through a discharge offset by 90°. The volume flow of the two fluids into the active element is the same.

[0012] Beyond that, there are processes known that make use of so-called microfluidic mixers. Microfluidic mixers are usually static mixers working without any moving organs. The mixture is rather prepared by impingement (T- or Y-angle) or dividing and recombining streamlines of the components by a multitude of baffles or intersections. Microfluidic mixers have been developed for small scale chemical processes and are therefore operated at a very low throughput.

[0013] An introduction to microfluidic mixers and their production by means of additive manufacturing is provided by Enders et al:

[0014] Enders, A., Siller, I. G., Urman, K., Hoffmann, M. R., Bahnemann, J.: 3D Printed Microfluidic Mixers-A Comparative Study on Mixing Unit Performances. *Small* 2019, 15, 1804326. DOI 10.1002/smll. 201804326

[0015] From patent literature there are some items derivable disclosing the use of microfluidic mixers for preparing nanocarriers:

[0016] For instance, EP 3271057 B1 discloses the use of static mixers in liposome production.

[0017] U.S. Pat. No. 7,811,603 B2 discloses the microfluidic preparation of liposomes on a droplet basis.

[0018] WO 0105373 A1 discloses static mixer for mixing two liquids in NLP production. In particular, static mixer is used for mixing the buffer phase (e.g., RNA in buffer) but not for the particle formation during mixing the buffer phase and the organic lipid phase.

[0019] A distinctive kind of arrangement of micromixers named "herringbone" is known in LNP production from WO 2013059922 A1.

[0020] A certain type of micromixer named "caterpillar mixer" is known to be employed in liposome production from WO 2017103268 A1.

[0021] Liposome production with microfluidic device having a baffle is disclosed in WO 2021224205 A1.

[0022] WO 2022/194615 A1 relates to an apparatus for preparing nanoformulations and/or microformulations from up to three liquid phases. The apparatus is equipped with three linear ducts, all arranged vertically. The third duct is surrounding the first and the second duct. The third duct is part of a liquid cycle. No micromixer is used.

[0023] A drawback of known processes for producing nanoformulations and/or nanocarriers (in particular lipid nanoparticles formed with the use of cationic or ionizable lipids) employing microfluidic mixers is that particles are not stabilized after mixing in acidic conditions and e.g. tend to agglomerate right after the microfluidic mixing process. In particular, it has been observed in field of LNP production, that a delay of subsequent change in acidity to a more neutral pH of the dispersion medium causes deformation of the LNP, thus a transport and prolonged storage of an intermediate is currently not possible. Thus, particle morphology and homogeneity are less stable. Further, residual solvent concentration in the product before downstream processing may be a reason for instability after production. Particle deformation leads to loss of active ingredient. This results in poor encapsulation efficiency.

[0024] In light of this, it is object of present invention to prepare nanocarriers/nanoformulations that shall have an

improved stability in regard to particle morphology and homogeneity. Encapsulation efficiency shall be improved. Beyond that, the obtained nanocarriers shall not agglomerate to larger particles.

[0025] The objective is achieved by an apparatus according to claim 1 and by a process according to claim 11 performable using this apparatus.

[0026] The present invention thus provides an apparatus for producing nanocarriers and/or nanoformulations which has the following features:

- [0027] a) a static mixer having a contacting section and downstream of contacting section for providing an at least biphasic primary mixture, meaning mixing a first liquid phase with a second liquid phase in absence of a third phase;
- [0028] b) a linear pipe, whereby at least the distal section of the static mixer is surrounded by the linear pipe;
- [0029] c) a longitudinal mixing section, whereby the static mixer and linear pipe establish a longitudinal mixing section, which extends downstream from the static mixer inside the linear pipe up to its end;
- [0030] d) a first inlet of the static mixer for accommodating a first liquid phase from a first reservoir vessel via a first feed;
- [0031] b) a second inlet of the static mixer for accommodating a second liquid phase from reservoir vessel via a second feed;
- [0032] d) an inlet for a third feed of the linear pipe for accommodating a third liquid phase to the longitudinal mixing section from a third reservoir vessel via the third feed;
- [0033] e) a linear pipe forming at least a part of said third feed and said longitudinal mixing section;
- [0034] d) whereby the first inlet and second inlet are in fluid communication with the contacting section, the contacting section is receiving the first liquid phase and the second liquid phase in absence of the third phase, and whereby the static mixer is providing an at least biphasic primary mixture by mixing the first liquid phase with the second liquid phase in absence of the third phase
- [0035] g) the longitudinal mixing section is providing an at least triphasic secondary mixture by mixing said primary mixture with said third liquid phase;
- [0036] i) a collection vessel for accommodating the secondary mixture;
- [0037] k) a conduct, by means of which the longitudinal mixing section is in fluid communication with the collection vessel;
- [0038] l) whereby at least a distal section of said the static mixer is arranged inside said linear pipe, whereby the static mixer having a conical contacting section.
- [0039] The distal section shall mean the part closer to the output side of the static mixer.
- [0040] An beneficial aspect of present apparatus is the arrangement of the static mixer inside the linear pipe (7) of the third feed to establish the longitudinal mixing section. Thanks to this arrangement, the first liquid phase A and the second liquid phase B are mixed first to give the primary mixture A+B. The static mixer is designed to mix A and B in absence of C. Thus, there is no inlet for the third liquid phase C into the static mixer. On the other hand, the static mixer is situated at least partly in the feed of the third phase

C, namely in its linear pipe. Thus, the primary mixture A+B exiting the static mixer is instantaneously diluted with C flowing through the third feed line to give secondary mixture A+B+C.

[0041] According this invention, static mixer is equipped with a conical contacting section (15). Inside said contacting section, first liquid phase A and second liquid phase B are contacted for establishing primary mixture A+B. Due to conical shape of contacting section, contact angle is impressed to cone angle.

[0042] According to a preferred embodiment conical contacting section is equipped with a restrictor. The diameter of the restrictor shall be in range between 0.1 mm and 3 mm, preferable between 0.2 and 1.5 mm. A mixer with up to 1 mm restrictor seems to provide best particle stability.

[0043] Preferably, linear pipe and static mixer are arranged vertically. Thus, dilution of primary mixture A+B in third phase is not influenced by gravity.

[0044] It has been found that particle stability can be improved by means of a helically twisted channel having e.g., a rectangular cross section and/or a staggered arrangement of static mixing elements.

[0045] Primary mixture A+B flows through this distinctively designed channel to intimate contact of components of later nano particles or nanoformulations.

[0046] According to a preferred embodiment apparatus is characterized by two inlet ducts arranged in parallel inside of the static mixer (4) and preferably one aperture projecting into direction of central axis of linear pipe. Each inlet duct is dedicated to one liquid phase. After leaving inlet ducts, mixing of first and second liquid phase to primary mixture is performed. As inlet ducts are arranged in parallel, contact angle of first liquid phase A and second liquid phase B is 0°.

[0047] According to yet another preferred embodiment, static mixer is equipped with a pinhole aperture projecting into direction of central axis of linear pipe, wherein pinhole aperture marks the most-narrow constriction of the mixer. The diameter of pinhole aperture amounts from 0.1 to 1 mm. As most-narrow constrictions of usual microfluidic devices is below 0.1 mm, static mixer is not considered as a microfluidic device. Having a most-narrow constriction in range from 0.1 to 1 mm, it is rather considered as a millifluidic device.

[0048] Mentioned design elements of static mixer are to be arranged in the following sequence in downstream direction: pair of parallel inlet ducts, conical contact section with restrictor, helically twisted channel having a rectangular cross section and/or a staggered arrangement of static mixing elements, pinhole aperture.

[0049] According to a preferred embodiment of the apparatus, the static mixer comprises a dwelling section for the primary mixture A+B, preferably a dwelling section formed as a capillary having a length of minimum double the length of the contact section and/or the helically twisted channel, preferably 2 to 25 times in length of the contacting section, ideally 10 to 25 times in length. According to a further opinion the dwelling section is even partly formed as a helix. The outlet of the dwelling section is placed inside the linear pipe and/or forms at least one of the feeds of the linear pipe. According to an improved embodiment, a aperture plate is placed between the contact section and the subsequent dwelling zone formed as a capillary and/or a helically

twisted channel. Adventurously the aperture of the aperture plate has an open diameter of 0.8 to 5 mm, ideally 0.8 to 2.5 mm.

[0050] Preferably the extended dwelling section comprises no inner mixing element. The primary mixture A+B flows continuously, preferably having at least for a defined distance a laminar flow inside the extended dwelling section, ideally having at least for more than $\frac{2}{3}$ of the length a laminar flow inside the extended dwelling section.

[0051] According to a preferred embodiment of the overall apparatus, collection vessel for accommodating the secondary mixture and third reservoir vessel for accommodating a third liquid phase are designed as a combined vessel, such as combined vessel, third feed, longitudinal mixing section and conduct forming a circle line. Such circle line helps running production process continuously.

[0052] Circle line may require circulating pump for circulating secondary mixture.

[0053] Inventive apparatus may be equipped with at least one of the following:

- [0054] i) first feed including a metering device for dosing first liquid phase into static mixer;
- [0055] ii) second feed including a metering device for dosing second liquid phase into static mixer;
- [0056] iii) third feed including a metering device for dosing third liquid phase into longitudinal mixing section.

[0057] The metering devices are used to control the quantity of each liquid phase for realizing desired shares in the mixtures.

[0058] It has been observed that dosing primary mixture A+B directly into third liquid C without further mixing means allows production of nanoparticles that are stabilized e.g. do not tend to agglomerate. Thus, the particle size distribution of obtained nanocarriers is constant over time.

[0059] For achieving this effect at its best, choosing a volume flow of the third liquid C that is larger than the volume flow of the primary mixture A+B is recommended.

[0060] Such optimized usage of inventive apparatus for providing nanoformulations or nanocarriers is a second object of the inventive.

[0061] Hence, yet another object of the invention is a process for producing a nanocarrier and/or a nanoformulation, comprising the steps of:

- [0062] a) providing an inventive apparatus as outlined above;
- [0063] b) providing a first liquid phase in the first reservoir vessel, wherein the first liquid phase comprises a first liquid dispersion medium and at least one component selected from the group consisting of precursor to a nanocarrier, active ingredient, precursor to an active ingredient;
- [0064] c) providing a second liquid phase in the second reservoir vessel, wherein the second liquid phase comprises a second liquid dispersion medium and at least one component selected from the group consisting of precursor to a nanocarrier, precursor to an active ingredient, active ingredient;
- [0065] d) providing a third liquid phase in the third reservoir vessel, wherein the third liquid phase comprises a third liquid dispersion medium;
- [0066] e) establishing a first liquid flow from the first reservoir vessel via the first feed into the static mixer;

[0067] f) establishing a second liquid flow from the second reservoir vessel via the second feed into the static mixer;

[0068] g) establishing a third liquid flow from the third reservoir vessel via the third feed into the longitudinal mixing section, wherein the volume flow of the third liquid flow is larger than the sum of the volume flow of the first liquid flow and the volume flow of the second liquid flow;

[0069] h) mixing the first liquid phase and the second liquid phase in the static mixer in absence of the third phase so as to obtain an at least biphasic mixture containing the nanocarrier and/or a nanoformulation or precursors thereof;

[0070] i) mixing the biphasic mixture with the third liquid phase by means of the longitudinal mixing section so as to obtain an at least triphasic mixture containing the nanocarrier and/or nanoformulation and third liquid dispersion medium;

[0071] k) conducting triphasic mixture from longitudinal mixing section to collection vessel by means of the conduct;

[0072] l) collecting the triphasic mixture in the collection vessel;

[0073] m) withdrawing the triphasic mixture from the apparatus;

[0074] n) optionally: working up the triphasic mixture, in particular separating the nanocarrier and/or the nanoformulation from the triphasic mixture.

[0075] Substantial aspect of the inventive process is that the volume flow of the third liquid phase is larger than the sum of the volume flow of first liquid phase and second liquid phase. This sum is equal to the volume flow of the primary mixture.

[0076] Dispersing the primary, biphasic mixture in the larger volume of third liquid leads to improved particle stability in terms of morphology and homogeneity. In addition to that, if an active ingredient is to be laden on the nanocarrier to give a nanoformulation, encapsulation efficiency is enhanced when using inventive device.

[0077] As the volumetric amount of the third phase is larger than the first and second phase, the third phase can be used to adjust the pH value of the secondary mixture.

[0078] According to a first option, the pH of the first liquid phase is between 3 and 5, preferably 4, whereas the pH of the third liquid phase is between 6 and 8, preferably 7. As the pH of the third (large) phase is higher than the first (small) phase, the pH is raised radically in the moment of contact of the primary mixture with the third liquid phase. This pH shift particularly stabilizes LNPs.

[0079] According to a second option, the pH of the first liquid phase is between 3 and 5, preferably 4, whereas the pH of the third liquid phase is between 3 and 5, preferably 4. Thus, pH of first liquid phase and third liquid phase is quite similar but not necessarily identical. Accordingly, there is no radical pH shift when providing the secondary mixture, the pH values is rather maintained. This option is chosen if a pH shift shall be performed in a subsequent downstream step. However, in view of production efficiency and particle stability, performing pH shift while mixing primary mixture with third liquid phase is preferred.

[0080] Given pH values are to be measured at 25° C. with a glass electrode. The latter shall be calibrated with a reference liquid of defined pH value. It is worth to mention

was added at 25 ml/min and the aqueous buffer containing the RNA-surrogate at 75 ml/min.

[0183] As a result the encapsulation efficiency of Clean-Cap Fluc mRNA was increased from 51.8% without dwelling section for the static mixture A+B to 91.2%, if an extended dwelling section was introduced to the setup.

REFERENCES

- [0184] 0 Apparatus
- [0185] 1 first reservoir vessel
- [0186] 2 second reservoir vessel
- [0187] 3 third reservoir vessel
- [0188] 4 static mixer
- [0189] 41 first embodiment of static mixer
- [0190] 42 second embodiment of static mixer
- [0191] 43 third embodiment of static mixer
- [0192] 44 forth embodiment of static mixer
- [0193] 45 fifth embodiment of static mixer
- [0194] 5 first feed
- [0195] 6 second feed
- [0196] 7 linear pipe
- [0197] 8 longitudinal mixing section
- [0198] 9 third feed
- [0199] 10 pinhole aperture
- [0200] 11 conduct
- [0201] 12 collection vessel
- [0202] 131 first inlet
- [0203] 132 second inlet
- [0204] 141 first inlet duct
- [0205] 142 second inlet duct
- [0206] 15 contacting section (also 15.1, 15.2)
- [0207] 16 helically twisted channel
- [0208] 17 baffle
- [0209] 18 restrictor
- [0210] 19 cycle
- [0211] 20 dwelling section
- [0212] 21 helix section of dwelling section
- [0213] A first liquid phase
- [0214] B second liquid phase
- [0215] C third liquid phase
- [0216] A+B primary mixture
- [0217] A+B+C secondary mixture
- [0218] d outer diameter of static mixer
- [0219] d' outer diameter of linear pipe
- [0220] D inner diameter of linear pipe
- [0221] l length of linear mixing section
- [0222] L length of dwelling section
- [0223] r diameter of restrictor
- 1. An apparatus for producing nanocarriers and/or nano-formulations, the apparatus comprising:
 - a static mixer having a contacting section and downstream of contacting section, a helically twisted channel extends;
 - a linear pipe, whereby at least a distal section of the static mixer is surrounded by the linear pipe;
 - a longitudinal mixing section, whereby the static mixer and linear pipe establish a longitudinal mixing section, which extends downstream from the static mixer inside the linear pipe up to an end of the linear pipe;
 - a first inlet of the static mixer for accommodating a first liquid phase from a first reservoir vessel via a first feed;
 - a second inlet of the static mixer for accommodating a second liquid phase from a second reservoir vessel via a second feed;
- an inlet of the linear pipe for accommodating a third liquid phase to the longitudinal mixing section from a third reservoir vessel via a third feed;
- a linear pipe forming at least a part of said third feed and said longitudinal mixing section;
- wherein the first inlet and second inlet are in fluid communication with the contacting section, the contacting section is receiving the first liquid phase and the second liquid phase in absence of the third phase, and whereby the static mixer is providing an at least biphasic primary mixture by mixing the first liquid phase with the second liquid phase in absence of the third phase;
- the longitudinal mixing section is providing an at least triphasic secondary mixture by mixing said primary mixture with said third liquid phase;
- a collection vessel for accommodating the secondary mixture;
- a conduct, by which the longitudinal mixing section is in fluid communication with the collection vessel;
- wherein at least a distal section of said the static mixer is arranged inside said linear pipe, wherein static mixer has a conical contacting section.
- 2. The apparatus as claimed in claim 1, wherein conical contacting section comprises a restrictor.
- 3. The apparatus as claimed in claim 1, characterized in that wherein linear pipe and static mixer are arranged vertically.
- 4. The apparatus as claimed in claim 1, wherein static mixer comprises a helically twisted channel having a rectangular cross section and/or a staggered arrangement of static mixing elements.
- 5. The apparatus as claimed in claim 1, characterized by two inlet ducts arranged in parallel inside of the static mixer.
- 6. The apparatus as claimed in claim 1, wherein static mixer has an extended dwelling section at the distal end.
- 7. The apparatus as claimed in claim 1, wherein the static mixer has a pinhole aperture projecting into direction of central axis of linear pipe, wherein the pinhole aperture marks a most-narrow constriction of the static mixer, wherein a diameter of the pinhole aperture is from 0.1 to 1 mm.
- 8. The apparatus as claimed in claim 1, wherein the collection vessel for accommodating the secondary mixture and third reservoir vessel for accommodating a third liquid phase are designed as a combined vessel.
- 9. The apparatus as claimed in claim 8, wherein the combined vessel the third feed the longitudinal mixing section, and the conduct form a circle line including a circulating pump for circulating secondary mixture.
- 10. The apparatus as claimed in claim 1, fulfilling at least one feature selected from the group consisting of features (i), (ii), and (iii):
 - (i) the first feed comprises a metering device for dosing the first liquid phase into the static mixer;
 - (ii) the second feed comprises a metering device for dosing the second liquid phase into the static mixer; and
 - (iii) the third feed comprises a metering device for dosing the third liquid phase into the longitudinal mixing section.

- 11.** A process for producing a nanocarrier and/or a nanoformulation, the process comprising:
- a) providing an apparatus according to claim 1;
 - b) providing the first liquid phase in the first reservoir vessel, wherein the first liquid phase comprises a first liquid dispersion medium and at least one component selected from the group consisting of a precursor to a nanocarrier, an active ingredient, and a precursor to an active ingredient;
 - c) providing the second liquid phase in the second reservoir vessel, wherein the second liquid phase comprises a second liquid dispersion medium and at least one component selected from the group consisting of a precursor to a nanocarrier, a precursor to an active ingredient, and an active ingredient;
 - d) providing the third liquid phase in the third reservoir vessel, wherein the third liquid phase comprises a third liquid dispersion medium;
 - e) establishing a first liquid flow from the first reservoir vessel via the first feed into the static mixer;
 - f) establishing a second liquid flow from the second reservoir vessel via the second feed into the static mixer;
 - g) establishing a third liquid flow from the third reservoir vessel via the third feed into the longitudinal mixing section, wherein a volume flow of the third liquid flow is larger than a sum of a volume flow of the first liquid flow and a volume flow of the second liquid flow;
 - h) mixing the first liquid phase and the second liquid phase in the static mixer in absence of the third phase so as to obtain an at least biphasic mixture containing the nanocarrier and/or a nanoformulation or precursors thereof;
 - i) mixing the biphasic mixture with the third liquid phase in the longitudinal mixing section so as to obtain an at least triphasic mixture containing the nanocarrier and/or nanoformulation and the third liquid dispersion medium;
 - k) conducting the triphasic mixture from the longitudinal mixing section to the collection vessel through the conduct;
 - l) collecting the triphasic mixture in the collection vessel;
 - m) withdrawing the triphasic mixture from the apparatus;
 - n) optionally working up the triphasic mixture.
- 12.** The process as claimed in claim 11, wherein a pH of the first liquid phase is between 3 and 5; wherein a pH of the third liquid phase is either between 6 and 8 or between 3 and 5; all pH values are as measured at a temperature of 25° C. by a glass electrode.
- 13.** The process as claimed in claim 12, wherein the first dispersion medium is water or an aqueous buffer, the second dispersion medium is an organic substance, and the third dispersion medium is water or an aqueous buffer.
- 14.** The process as claimed in claim 13, wherein the organic substance is a monohydric or polyhydric alcohol.
- 15.** The process as claimed in claim 13, wherein the second liquid phase comprises at least one precursor to a nanocarrier, wherein said precursor to a nanocarrier is a natural or artificial lipid.
- 16.** The process as claimed in claim 15, whereby the natural or artificial lipid is selected from the group consisting of cholesterol, 1,2-dioleyloxy-3-dimethylaminopropane (DODMA), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyoxyethylene (PEG-DMG), dilinoleylmethyl-4-dimethylaminobutyrate (Dlin-MC3-DMA), and 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC).
- 17.** The process as claimed in claim 11, wherein the third liquid phase comprises a buffer.
- 18.** The process as claimed in claim 11, wherein the collection vessel for accommodating the secondary mixture and third reservoir vessel for accommodating a third liquid phase are designed as a combined vessel, and wherein the third liquid phase is circulated before or during a metered addition of the first liquid phase and the second liquid phase.
- 19.** The process as claimed in claim 11, wherein lipid nanoparticles are produced.
- 20.** (canceled)

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