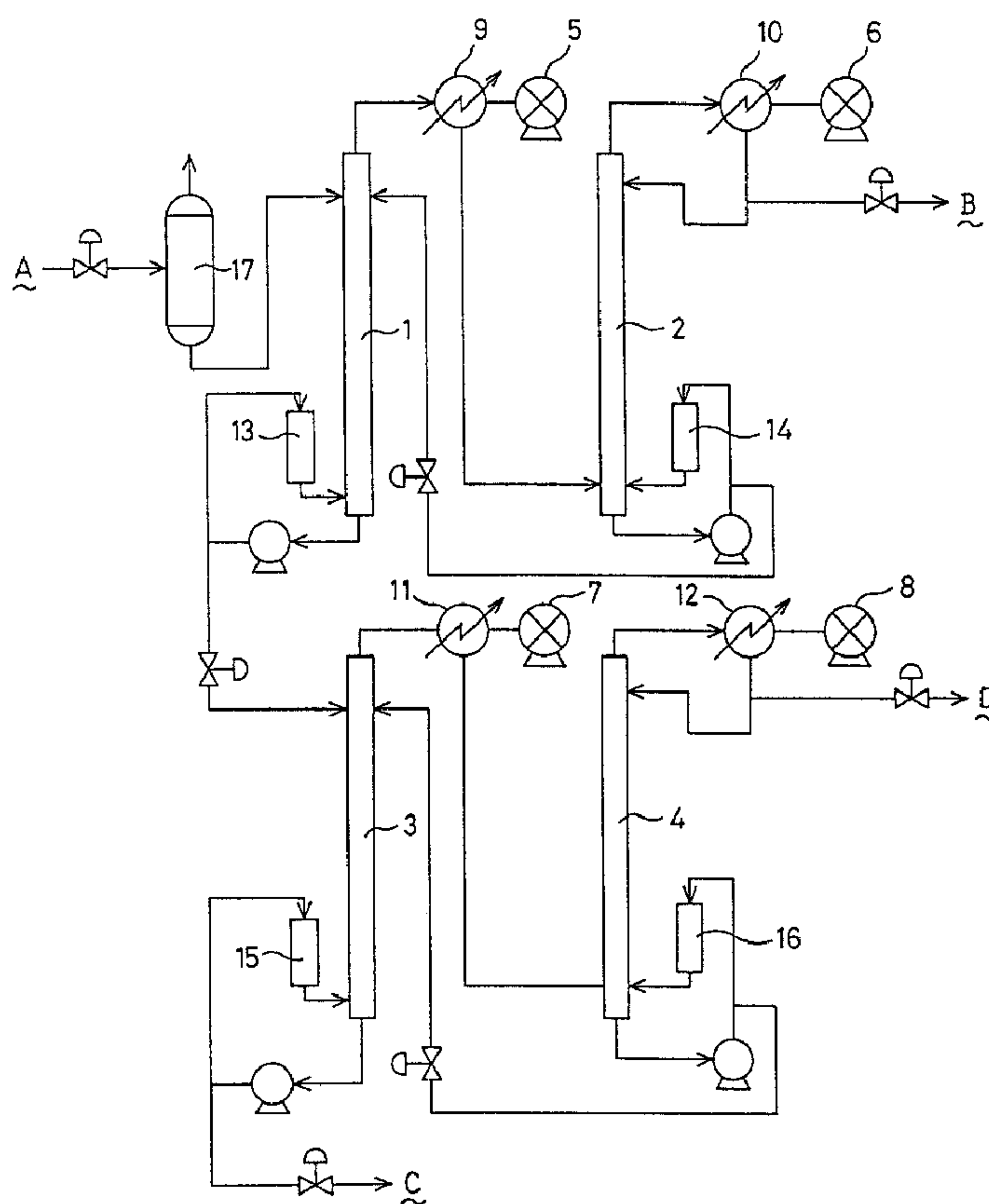




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 (72) Inventeurs/Inventors:
 Hata, Kazuhiko, JP;
 Noda, Hideo, JP;
 Makuta, Masahiro, JP
 (73) Propriétaires/Owners:
 Hata, Kazuhiko, JP;
 Noda, Hideo, JP;
 Makuta, Masahiro, JP;
 Nippon Suisan Kaisha, Ltd., JP;
 KANSAI CHEMICAL ENGINEERING CO., LTD., JP
 (74) Agent: SWABEY OGILVY RENAULT

(54) Titre : METHODE DE PREPARATION DE L'ACIDE ICOSAPENTENOIQUE OU D'UN ESTER DE CE DERNIER
 (54) Title: METHOD OF PRODUCING EICOSAPENTAENOIC ACID OR THE ESTER DERIVATIVE THEREOF



(57) Abrégé/Abstract:

The present invention provides a continuous method of purifying eicosapentaenoic acid and esters of eicosapentaenoic acid, comprising (a) fractionally distilling a starting mixture containing eicosapentaenoic acid or esters of eicosapentaenoic acid using

(57) **Abrégé(suite)/Abstract(continued):**

a system of at least three distillation columns connected in flow arrangement to separate a fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids from a fraction containing lower-number carbon fatty acids and from a fraction containing higher-number carbon fatty acids, and (b) continuously collecting the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid. The pressure in the distillation columns is maintained at 10 Torr or below and the bottom temperature of the distillation columns is maintained at 210°C or below.

**METHOD OF PRODUCING EICOSAPENTAENOIC ACID OR THE ESTER
DERIVATIVE THEREOF**

ABSTRACT

The present invention provides a continuous method of purifying eicosapentaenoic acid and esters of eicosapentaenoic acid, comprising (a) fractionally distilling a starting mixture containing eicosapentaenoic acid or esters of eicosapentaenoic acid using a system of at least three distillation columns connected in flow arrangement to separate a fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids from a fraction containing lower-number carbon fatty acids and from a fraction containing higher-number carbon fatty acids, and (b) continuously collecting the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid. The pressure in the distillation columns is maintained at 10 Torr or below and the bottom temperature of the distillation columns is maintained at 210°C or below.

METHOD OF PRODUCING EICOSAPENTAENOIC ACID OR THE ESTER
DERIVATIVE THEREOF

[FIELD OF THE INVENTION]

The present invention relates to a method for producing high-concentration eicosapentaenoic acid or the ester derivative thereof, more specifically to a new method of producing, at high efficiency, high-concentration form of eicosapentaenoic acid (EPA) or the ester derivative thereof effective as prescription medicine for prevention of thrombosis and the medical treatment and prevention of thrombus-induced diseases.

[PRIOR ARTS]

Eicosapentaenoic acid (EPA) or the ester, amid or other derivatives thereof have been conventionally known as effective as prescription medicine for the prevention of thrombosis and for the medical treatment of thrombus-induced diseases.

It is known that these eicosapentaenoic acid (EPA) or the derivatives thereof are contained per se or in the form of the glyceride and other derivatives thereof, in natural fats and oils, particularly in fats and oils of mackerel, sardine, cod and other marine products. Studies have been made concerning the methods for taking out eicosapentaenoic acid from these fish oils.

However, an overwhelming quantity of fatty acids having less than 19 carbon atoms and more than 21 carbon atoms, other than eicosapentaenoic acid, an unsaturated fatty acid having 20 carbon atoms, are mixed in the natural fats and oils which consist of these fish oils. This makes it exceedingly difficult to

efficiently and selectively take out eicosapentaenoic acid alone as high-concentration (high purity) product.

For example, a method has been proposed in which fatty acid mixtures from natural fats and oils are esterified, and put to precision fraction under reduced pressures and the resultant fraction is purified with a urea addition method to provide eicosapentaenoic acid from natural fats and oils (Patent Provisional Publication No. 149400/82).

By this method by which fatty acid mixtures from natural fats and oils are subjected to precision fraction under a reduced pressures of 10 mmHg; preferably of 0.1 to 0.01 mmHg at a single rectifying column filled with rings and the resulting products are rectified by the urea addition method, eicosapentaenoic acid with a concentration of some 80% can be obtained. By this method, however, a mere 30% of eicosapentaenoic acid ester exists in the C₂₀ fraction obtained by the rectification, and also it is necessary to adopt complicated trouble-some treatment processes, such as the treatment of urea adduct and the subsequent distillation under reduced pressures. Even with these processes, it is exceedingly difficult to improve the concentration of eicosapentaenoic acid ester to 85% or higher. By the foregoing method publicly known, large quantities and multiplicity of treatments with urea become

practically required, placing great limitations on the reduction of manufacturing cost as well as the improvement of production efficiency. There has been a serious limitation to putting it into practical application.

Almost concurrently with this publicly known method, a method was proposed by the applicant of the present invention wherein two distillation columns are employed to subject fatty acid mixtures from natural fats and oils to continuous distillation to provide approximately 50% eicosapentaenoic acid as C_{20} fraction, then the product is subjected to urea addition treatment and purification through column chromatography (Patent Provisional Publication No. 8037/1983). This improved method has substantially enhanced the efficiency of distillation purification process and the whole process, but eicosapentaenoic acid and the ester derivative thereof with a concentration (or purity) as high as 80% or more cannot be produced without the subsequent urea addition treatments. Even with the urea addition process, the method still remains unsuccessful in producing eicosapentaenoic acid and the ester derivative thereof with a concentration as high as 85% or higher. For this reason, there has been a limit to the rationalization of production process and the improvement of production efficiency.

In order to use eicosapentaenoic acid and the ester derivative thereof, effective as medical prescription medicine, to studies applied for clinical purposes or in much wider kind of diseases, it is strongly desired to produce them with a

concentration of 80% or more, furthermore, 85% or more in large quantities and at high efficiency. Yet, under the aforestated circumstances, such demand has been unable to be met.

[SUMMARY OF THE INVENTION]

The present invention has been made considering the aforestated circumstances, and it is designed to provide a method which makes it possible to overcome the shortcomings of the conventional production and purification methods and provide eicosapentaenoic acid and the ester derivative thereof with a concentration higher than 85% in a convenient fashion, at high efficiency and low costs.

In order to overcome the foregoing problems, the present invention provides a method of producing eicosapentaenoic acid and the ester derivative thereof in a concentration as high as 80% or more, characterized by placing fatty acids or the ester mixtures thereof obtained from the natural fats and oils including eicosapentaenoic acid and the ester derivative thereof to continuous distillation under a reduced pressure of 10 Torr or below and a bottom temperature of 210°C or less.

The method comprises fractionally distilling a starting mixture containing eicosapentaenoic acid or esters of eicosapentaenoic acid using a system of at least three distillation columns connected in flow arrangement to separate a fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids from a fraction containing lower-number carbon fatty acids and from a fraction containing higher-number carbon fatty acids, and continuously collecting the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid. The pressure in the distillation columns is maintained at 10

Torr or below and the bottom temperature of the distillation columns is maintained at 210°C or below.

In the method according to the present invention, it is preferred to send the condensate of the top fraction obtained from the pre-stage or first distillation column to the rectifying or second column for the collection of the initial fraction containing the lower-number carbon containing fatty acids and to establish a rectifying or third column for collecting the main fraction which contains eicosapentaenoic acid and the ester derivative thereof and for collecting the fraction containing higher-number carbon fatty acids independently for continuous distillation.

The present invention also provides a method of producing eicosapentaenoic acid and the ester derivative thereof by placing fatty acids or the ester mixtures thereof obtained from the natural fats and oils including eicosapentaenoic acid and the ester derivative thereof to continuous distillation under a reduced pressure of 10 Torr or below and a bottom temperature of 210°C or less, by means of the foregoing method, further including steps of bringing the main fraction containing the resultant eicosapentaenoic acid and the ester derivative thereof into contact with a solution urea in methanol to give urea adduct, putting the same to a drainage treatment with non-polar solvent and removing the non-polar solvent to provide eicosapentaenoic acid and the ester derivative thereof in a concentration as high as 85% or more.

[BRIEF DESCRIPTION OF DRAWINGS]

FIG. 1 is a system construction drawing illustrating one embodiment of a method of producing eicosapentaenoic acid and the ester derivative thereof through continuous distillation.

FIG. 2 is a system construction drawing illustrating urea-

addition treatment processes following the continuous distillation.

FIG. 3 is a system construction drawing illustrating a purification process following the urea addition.

FIG. 4 is a system construction drawing depicting the conventional two-column distillation method.

[DETAILED DESCRIPTION OF THE INVENTION]

Eicosapentaenoic acids and other long-chain high-degree unsaturated fatty acids contain so many double bonds in the molecules thereof that they are apt to be subjected to degradation, polymerization and other thermal denaturation due to heating in distillation, rendering condensation through distillation exceedingly difficult.

On the other hand, the natural fats and oils containing eicosapentaenoic acids contain various kinds of fatty acids other than eicosapentaenoic acids, which have boiling points closer to each other, and hence they cannot be separated unless a distillation column is made fairly high and the amount of reflux is increased. However, this causes thermal denaturation due to rises in the bottom pressure and the resultant temperature rise, making distillation purification exceedingly difficult.

For these reasons, by the conventional methods, distillation condensation is controlled to a low level and it is forced to purify the fatty acids to a high degree through urea addition and other processes at the subsequent stage.

Inevitably, the load on the processes at the subsequent stages become larger.

The method according to the present invention provides eicosapentaenoic acid or the ester derivative thereof with a purity as high as 80% or 85% without causing any problem, in a simple operation requiring only distillation purification, and at high efficiency. It also becomes possible to purify the resultant eicosapentaenoic acid or the ester derivative thereof to a product with a concentration as high as 90% at extremely high efficiency by the subsequent urea addition processes.

As the fatty acid mixtures applicable to the method according to the present invention, any substances obtainable from the natural fats and oils which contain quantities of eicosapentaenoic acid or the glycerid derivative thereof can be used. For instance, fatty acid mixtures from sardine, mackerel, herring, saury and other fish, and Antarctic euphausian, and other animal marine plankton.

These fatty acid mixtures are esterified for continuous distillation as desired.

As the continuous distillation method according to the present invention, filling spring, column plate and other various systems can be employed, and more preferably, a mesh plate can be used with a theoretical number of plates being more than 5.

Continuous distillation using 3 or more distillation columns according to the present invention is accomplished under a reduced pressure of approximately 0.1Torr and at 210°C or

below, or more preferably, at a bottom temperature of 195°C or less.

The construction of this three-or-more column distillation columns is such that in any cases, one of them is made independent as a rectifying column for the collection of initial fraction. For instance, in case of such three-column construction, the columns are divided as follows:

- (I) First distillation column;
- (II) Second distillation column (rectifying column for initial fraction);
- (III) Third distillation column (rectifying column for main fraction and residual fraction).

In case of four-column construction, the columns are divided as follows:

- (I) First distillation column;
- (II) Second distillation column (rectifying column for initial fraction);
- (III) Third distillation column (rectifying column for residual fraction); and,
- (IV) Fourth distillation column (rectifying column for main fraction).

Furthermore, in the case of three-column construction, the columns can be able divided as follows:

- (I) First distillation column (rectifying column for initial fraction);
- (II) Second distillation column (rectifying column for residual fraction); and,

(III) Third distillation column (rectifying column for main fraction).

Needless to say, the construction of the rectifying columns can be further divided.

In any of the above cases, in the method according to the present invention, it is essential that the bottom liquid of the rectifying column for initial fraction be returned as reflux liquid to the first distillation column as in the above example. It is also preferable to condensate the top fraction of the first distillation column, then send it as condensate to the rectifying column for initial fraction.

The main fraction of C₂₀ obtainable through continuous distillation, i.e., the one containing eicosapentaenoic acid or the ester derivative is then subjected to urea treatment to provide urea adduct. Then, the urea adduct is dissolved in methanol, ethanol and other highly soluble solvent to be used as urea adduct solution. Normally, the concentration of urea adduct is to be 5 to 20%.

Mixing the main fraction with this urea adduct solution is accomplished at a ratio of 0.5 to 10 part to 1 part by weight of main fraction. The mixture is subjected to forced cooling to room temperature or below, more preferably to 15°C or less. Such treatment permits C₂₀ fatty acids having lower degree of unsaturation, for example, 1 to 4 unsaturated bond to be separated as a compound material with urea.

Then, in the method according to the present invention, non-polar solvents, for instance, hexane and isooctane are added

to a reaction mixture, the urea adduct and remaining urea are caused to shift to methanol layer, and the fatty acids to hexane layer for extraction and separation.

Then, in order to remove coloring matter, oxides and other impurities as needed, the resulting substances are subjected to adsorption treatment via an adsorption column.

As the adsorption column, silica gel, activated clay, alumina and activated carbon can be used, but silica gel is the most preferred. Thereafter, the aforesaid solvents are removed through distillation.

While referring to the drawings attached, more detailed descriptions will be given to the method according to the present invention.

(Continuous distillation)

FIG. 1 shows an example in which four distillation columns are used.

For instance, as indicated in this FIG.1, the fatty acid mixture (A) is subjected to continuous distillation using four distillation columns (1), (2), (3) and (4).

At each of the distillation columns (1) (2) (3) and (4), vacuum systems (5) (6) (7) and (8), the condensate systems (9) (10) (11) and (12) and the reboilers (13) (14) (15) and (16) are also provided.

These distillation columns (1) (2) (3) and (4) are strictly controlled to a reduced pressure of 10Torr or below, and at a bottom temperature of 210°C or lower. The degree of vacuum is closely associated with temperature, and it is

preferred but not essential that the vacuum systems (5) (6) (7) and (8) are made independent from one another. It is permissible to construct these vacuum systems arbitrarily in accordance with the capability and control systems of the vacuum pumps.

Under the aforesaid construction, raw material (A) is introduced into the first distillation column (1), for instance, in the vicinity of the top thereof, the top fraction is condensed at the condensate system (9) and is introduced in liquid form into a rectifying column as the second distillation column (2), for example, at the bottom thereof. Such introduction of the top fraction in liquid form is one of the important factors in the method according to the present invention.

In the second distillation column (2), the initial fraction (B) consisting of fatty acids having lower carbon number ($< C_{19}$) as the top fraction thereof is collected. Some of the bottom liquid is refluxed to the vicinity of the top of the first distillation column (1). This is also a very important factor to the method of the present invention. The bottom condensate of the first distillation column (1) is heated with a reboiler (13) and returned to the bottom thereof, and at the same time, introduced in liquid form to the vicinity of the top of the third distillation column (3).

The top fraction of the third distillation column (3) is supplied to the bottom of the fourth distillation column (4) as condensate through a condensation system (11). The bottom

condensate is heated with a reboiler (15) and returned to the bottom thereof, and concurrently the remaining fraction (C) consisting primarily of C₂₁ or greater fatty acids with longer chains than eicosapentaenoic acid or the ester derivative.

At the fourth distillation column (4) into which condensate has been introduced from the top of the third distillation column (3), the fraction from the top is condensed at the condensation system (12), some of them being refluxed to the vicinity of the top and the main fraction (D) consisting primarily of eicosapentaenoic acid or the ester derivative. On the other hand, the bottom condensate is heated with a reboiler (16) and returned to the bottom, and concurrently some of them is refluxed to the vicinity of the third distillation column (3).

Raw material (A) is treated at a flash tank (17) maintained at a reduced pressure prior to the introduction thereof into the first distillation column (1), removing air, water content and other impurities. It is advantageous to use a falling film evaporation type reboilers as reboilers (13) (14) (15) and (16). This can effectively prevent thermal degradation. (Continuous distillation and urea addition treatment)

FIG. 2 illustrates the treatment process of the formation of urea adduct. The main fraction (D) containing eicosapentaenoic acid or the ester derivative with a concentration of 80% or higher is obtained by the foregoing continuous distillation.

As shown in FIG. 2, the main fraction (D) is sent to a column in contact with a solution of urea, and, for instance, a solution of urea in methanol is guided

from a tank (22) to be brought into contact with the column. At this time, the solution of urea in methanol is introduced at a temperature of 35 to 45°C, and is subjected to forced cooling at the column in contact therewith so that it is at or below room temperatures.

Then, the treatment liquid is fed through a tank (23) to a product extraction column (24) using non-polar solvent, e.g., n-hexane. The product solvent layer (E) which separates the solution of urea in methanol and the urea adduct is sent to the next process. The solution of urea in methanol and the urea adduct are fed to a tank (25), and after being subjected to thermal decomposition, they are put to another cycle of extraction treatment at a residue extracting column (25') to separate a residue solvent layer (G). The non-polar solvent is either cooled or heated at a cooling column (26) or a heating column (27) and fed to the extracting columns (24) (25'). The solvent layers (E) (G) are taken out of decanters (28) (29).

Then, the product solvent layer (E) is fed to a methanol rectifying column (32) through a tank (31) as indicated in FIG. 3. By the operation at the methanol rectifying column (32) in which a rectifying condenser (33) and a methanol evaporator (34) are provided, a product extracting solvent layer which is subjected to a treatment of removing methanol is obtained, and filtering the same removes the remaining urea.

Then, this substance is led to adsorption columns (36) (37) through a tank (35), removing coloring matter, oxides and other impurities. Next, solvent, e.g., n-hexane, is removed using an evaporator (38).

An n-hexane condenser (39) is provided for this evaporator.

In this way, a product (F) can be obtained. The final concentration of the product (F) is increased to 85% or higher.

Then, specific examples of production by the production method of the present invention will be given using the systems as indicated from FIGs. 1 to 3. (Production example 1)

The ethylester in a fatty acid mixture (60% for C₁₉, 23% for C₂₀ and 17% for C₂₁) obtained from fish oil was treated at a flash tank (17) which is kept at a vacuum of 1 Torr, then supplied to the first distillation column (1) with a column diameter of 300 mm and a height of approx. 7 m and maintained at a vacuum of 0.1 Torr at a rate of 15 to 20 ℓ /hr.

At this first distillation column (1), the bottom temperature was controlled at 194 to 195°C, and the top temperature at 124 to 125°C. Inside it, a 4 mm-mesh plate was provided, with the theoretical number of plates set at 4. Since fatty acid ester mixtures greater than C₂₀ are collected at the bottom of this first distillation column (1), it becomes difficult to control the degree of vacuum and temperature at the bottom thereof. Accordingly, the quantity of packing into the first distillation column was less than that into the second distillation column (2).

The top condensate of the first distillation column (1) was introduced into the bottom of the second distillation column (2). The bottom temperature of this second column was set at 184 to 185°C, while the top temperature at 100 to 111°C, with the column operated under a reduced pressure of 0.1Torr. The theoretical number of column plates was set at 6. The top fraction was refluxed at a reflux ratio of 1:2, some of them being collected as the initial fraction (B).

The composition of the initial fraction was, as indicated in Table 1, 99% for C₁₉ or lower fatty acids, 1% for C₂₀ eicosapentaenoic acid ester and others and 0% for C₂₁ or greater fatty acids.

The second distillation column (2) was controlled so that the bottom condensate thereof was constant as level, and said condensate was returned to the vicinity of the top of the first distillation column (1). In other words, the bottom condensate was returned as reflux liquid to the first distillation column (1).

The bottom liquid of the first distillation column (1) was fed to the vicinity of the top of the third distillation column (3). The pressure of the third distillation column (3) was a reduced pressure of 0.1Torr, while the bottom temperature was 194 to 195°C and the top temperature at 124 to 125°C. The theoretical number of column plates was 4.

As the bottom liquid of the third distillation column (3), the residual fraction (C) was collected. The residual fraction

was, as indicated in Table 1, composed of 0.1% for C_{18} or lower fatty acids, 20% for C_{20} eicosapentaenoic acid ester and others and 79.9% for C_{21} or greater fatty acids.

The top fraction of this third distillation column (3) was supplied to the fourth distillation column (4) as condensate. The fourth distillation column (4) with a theoretical number of column plates being 6 was operated under a reduced pressure of 0.1 Torr, at a bottom temperature of 194 to 195°C and a top temperature of 110 to 111°C.

The bottom liquid was returned as reflux liquid to the top of the third distillation column (3). The level of the bottom liquid of the fourth distillation column was kept constant.

The top condensate was refluxed at a reflux ratio of 1 to 2, and at the same time, the main fraction (D) was collected.

The residual fraction was, as indicated in Table 1, composed of 0.1% for C_{19} or lower fatty acids, 0% for C_{21} or greater fatty acids and 99.9% for C_{20} eicosapentaenoic acid ester and others.

The concentration of eicosapentaenoic acid ethylester in the C_{20} fraction was 88%.

(Comparative example)

For comparison, attempts were made to perform continuous distillation under reduced pressure using a two-column distillation column system (41) (42) (a theoretical number of column plates being 10) as shown in FIG. 4.

Again in this case, each of the distillation columns (41) (42) was provided with independent vacuum systems (43) (44) and

condensation systems (45) (46), and also with reboilers (47) (48).

The system was so designed that the initial fraction (B') be collected from the top of the first distillation column (41), the main fraction (D') from the top of the second distillation column (42) and the residual fraction (C') from the bottom thereof. Each of the distillation columns (41) (42) was under a reduced pressure of 0.1 Torr. In spite of the attempts to control the bottom temperature of the first distillation column (41) to 195°C or lower, it was difficult to control temperatures; the bottom temperature could rise to 210°C or higher.

The compositions of the initial fraction, main fraction and residual fraction was as indicated in Table 2. The efficiency of separation/purification of C₂₀ fraction by this example proved to be by far inferior to the method of the present invention, making it exceedingly difficult to control distillation operation. Only 76% of the eicosapentaenoic acid ethylester of the main fraction which was collected as C₂₀ fraction was collected. Even though the bottom temperature of the first distillation column (41) was controlled to 195°C or lower, as is evident from Table 2, fatty acids with lower carbon number, particularly C₁₈ fatty acids, were inevitably included, rendering the resultant product incompletely unsatisfactory.

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Table 1

Composition	Row Material (A)	Initial Fraction (B)	Residual Fraction (C)	Main Fraction (product) (D)
<C ₁₉	60	99	0.1	0.1
C ₂₀	23	1	20	99.9
C ₂₁ <	17	0	79.9	0

Table 2

Composition	Row Material (A)	Initial Fraction (B')	Residual Fraction (C')	Main Fraction (product) (D')
<C ₁₉	60	80	5.1	10.1
C ₂₀	23	20	20.0	89.9
C ₂₁ <	17	0	74.9	0

(Production example 2)

The main fraction (D) which contains 99.9% C₂₀ ethylester and 88% eicosapentaenoic acid ethylester, both obtained from Example 1, was brought into contact with 15% solution of urea in methanol at a contact column (21). The temperature of this solution was 42°C, and it was subjected to forced cooling down to 10°C in the contact column (21).

Using the n-hexane cooled to 10°C, the product was put to drainage treatment in an extraction column (24).

The product solvent layer (E) obtained was removed of methanol in a methanol-removing column (32), and further urea was filtered. The product solvent layer (E) contained the following components, but the methanol and urea were completely removed.

Fatty acid ester	12 to 13%
Methanol	5%
Hexane	82 to 83%
Trace amount of urea	

The treatment liquid was then guided to silica gel adsorption columns (36) (37), coloring matter, oxides and other impurities were removed, and hexane was removed in an evaporator (38), providing eicosapentaenoic acid ethylester product (F). The concentration thereof was 93%.

As has been described in detail, the method of the present invention can provide eicosapentaenoic acid or the ester derivative thereof having a concentration (purity) of 85% or higher, and further 90% or higher. It can also produce the

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product at high efficiency.

The embodiments of the invention, in which an exclusive property or privilege is claimed are defined as follows:

1. A method of purifying eicosapentaenoic acid and esters of eicosapentaenoic acid, comprising the steps of:

a) fractionally distilling a mixture containing eicosapentaenoic acid or esters of eicosapentaenoic acid using a system of at least three distillation columns connected in flow arrangement to separate a fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids from a fraction containing lower-number carbon fatty acids and from a fraction containing higher-number carbon fatty acids, wherein the pressure in the distillation columns is maintained at 10 Torr or below and the bottom temperature of the distillation columns is maintained at 210° C or below, and

b) collecting the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid.

2. A method according to claim 1, wherein said fractional distillation step comprises feeding the mixture to a first distillation column, fractionally distilling the mixture to obtain a top fraction, condensing the top fraction, feeding the condensed top fraction to a second distillation column, fractionally distilling the condensed top fraction in the second

column to obtain a top fraction, the top fraction in the second column being the fraction containing the lower-number carbon fatty acids, and removing the top fraction from the second column, thereby separating the fraction containing the lower-number carbon fatty acids from the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid.

3. A method according to claim 1, wherein said fractional distillation step comprises feeding the mixture to a first distillation column, fractionally distilling the mixture to obtain a top fraction, condensing the top fraction, feeding the condensed top fraction to a second distillation column, fractionally distilling the condensed top fraction in the second column to obtain a bottom liquid fraction, and recycling the bottom liquid fraction in the second column to the top of the first distillation column.

4. A method according to claim 1, wherein said fractional distillation step comprises feeding the mixture to a first distillation column, fractionally distilling the mixture to obtain a bottom liquid fraction, feeding the bottom liquid fraction to a third column, and fractionally distilling the bottom liquid fraction in the third column to obtain a top fraction containing the eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids and a bottom liquid fraction containing the higher-number carbon fatty acids.

5. A method according to claim 4, wherein the top fraction containing the eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids obtained in the third column is fed to a fourth distillation column and further distilled to obtain a top fraction in the fourth column containing a more purified concentration of eicosapentaenoic acid or esters of eicosapentaenoic acid.

6. A method according to claim 1, wherein each of the distillation columns is equipped with an independent vacuum system and condenser system.

7. A continuous method of purifying eicosapentaenoic acid and esters of eicosapentaenoic acid, comprising the steps of:

a) feeding a starting mixture of eicosapentaenoic acid or esters of eicosapentaenoic acid to a first distillation column,

b) fractionally distilling the mixture using the first distillation column to obtain a bottom liquid fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and higher-number carbon fatty acids and a top fraction containing lower-number carbon fatty acids,

c) condensing the top fraction and feeding it to a second distillation column, then fractionally distilling the condensed top fraction in the second column to obtain a top fraction containing the lower-number carbon fatty acids and a bottom liquid fraction, removing the top fraction from the second column to separate the fraction containing the lower-

number carbon fatty acids from the system, and recycling the bottom liquid fraction in the second column to the first distillation column, while simultaneously feeding the bottom liquid fraction obtained in the first column to a third column, fractionally distilling the bottom liquid fraction in the third column to obtain a top fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and a bottom liquid fraction containing the higher-number carbon fatty acids, removing the bottom liquid fraction from the third column to separate the fraction containing the higher-carbon number fatty acids from the system,

d) feeding the top fraction obtained in the third column to a fourth column, fractionally distilling the top fraction in the fourth column to obtain a top fraction containing purified eicosapentaenoic acid or esters of eicosapentaenoic acid,

e) collecting the top fraction containing purified eicosapentaenoic acid or esters of eicosapentaenoic acid, and

f) repeating steps (a) through (e), wherein the pressure in the distillation columns is maintained at 10 Torr or below and the bottom temperature of the distillation columns is maintained at 210°C or below.

8. A method of purifying eicosapentaenoic acid and esters of eicosapentaenoic acid, comprising the steps of:

a) fractionally distilling a mixture containing eicosapentaenoic acid or esters of eicosapentaenoic acid using a system of at least three distillation columns connected in flow arrangement to separate a fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids from a fraction containing lower-number carbon fatty acids and from a fraction containing higher-number carbon fatty acids, wherein the pressure in the distillation columns is maintained at 10 Torr or below and the bottom temperature of the distillation columns is maintained at 210°C or below,

b) collecting the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid,

c) treating the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid with a solution of urea and a non-polar solvent to obtain a urea adduct, and

d) removing the solvent by distillation to obtain a fraction containing concentrated eicosapentaenoic acid or esters of eicosapentaenoic acid.

9. A method according to claim 8, wherein said fractional distillation step comprises feeding the mixture to a first distillation column, fractionally distilling the mixture to obtain a top fraction, condensing the top fraction, feeding the condensed top fraction to a second distillation column, fractionally distilling the condensed top fraction in the second

column to obtain a top fraction containing the lower-number carbon fatty acids, and removing the top fraction from the second column, thereby separating the fraction containing the lower-number carbon fatty acids from the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid.

10. A method according to claim 8, wherein said fractional distillation step comprises feeding the mixture to a first distillation column, fractionally distilling the mixture to obtain a top fraction, condensing the top fraction, feeding the condensed top fraction to a second distillation column, fractionally distilling the condensed top fraction in the second column to obtain a bottom liquid fraction, and recycling the bottom liquid fraction in the second column to the first distillation column.

11. A method according to claim 8, wherein said fractional distillation step comprises feeding the mixture to a first distillation column, fractionally distilling the mixture to obtain a bottom liquid fraction, feeding the bottom liquid fraction to a third column, fractionally distilling the bottom liquid fraction in the third column to obtain a top fraction containing the eicosapentaenoic acid or esters of eicosapentaenoic acid and other C₂₀ fatty acids and a bottom liquid fraction containing the higher-number carbon fatty acids.

12. A method according to claim 11, wherein the top fraction containing the eicosapentaenoic acid or

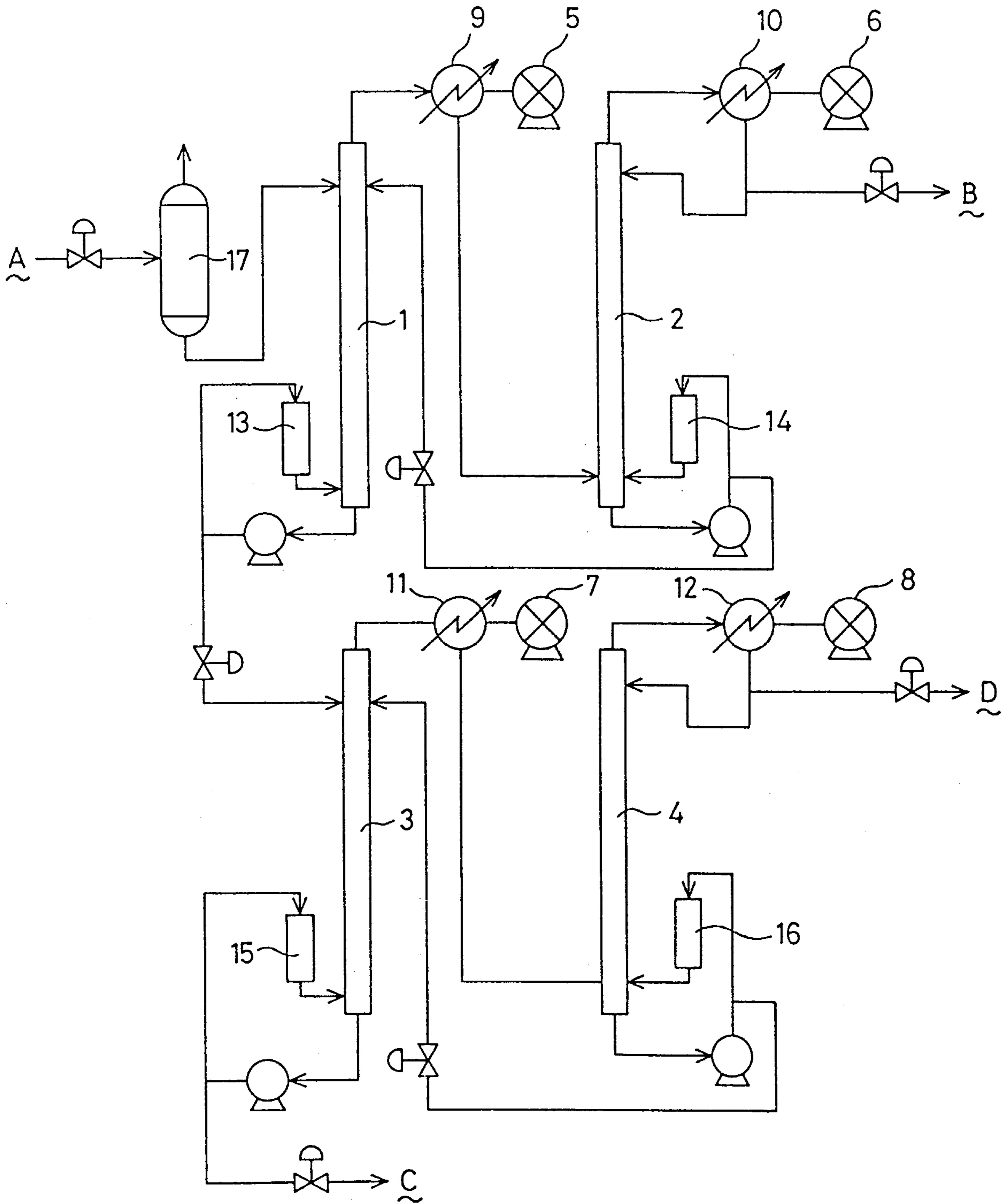
esters of eicosapentaenoic acid and other C₂₀ fatty acids obtained in the third column is fed to a fourth column and further distilled to obtain a top fraction containing a more purified concentration of eicosapentaenoic acid or esters of eicosapentaenoic acid.

13. A method according to claim 8, wherein each of the distillation columns is equipped with an independent vacuum system and condenser system.

14. A method according to claim 8, wherein the fraction containing eicosapentaenoic acid or esters of eicosapentaenoic acid is treated with a solution of urea in methanol at a temperature lower than room temperature.

15. A method according to claim 8, wherein the non-polar solvent is hexane.

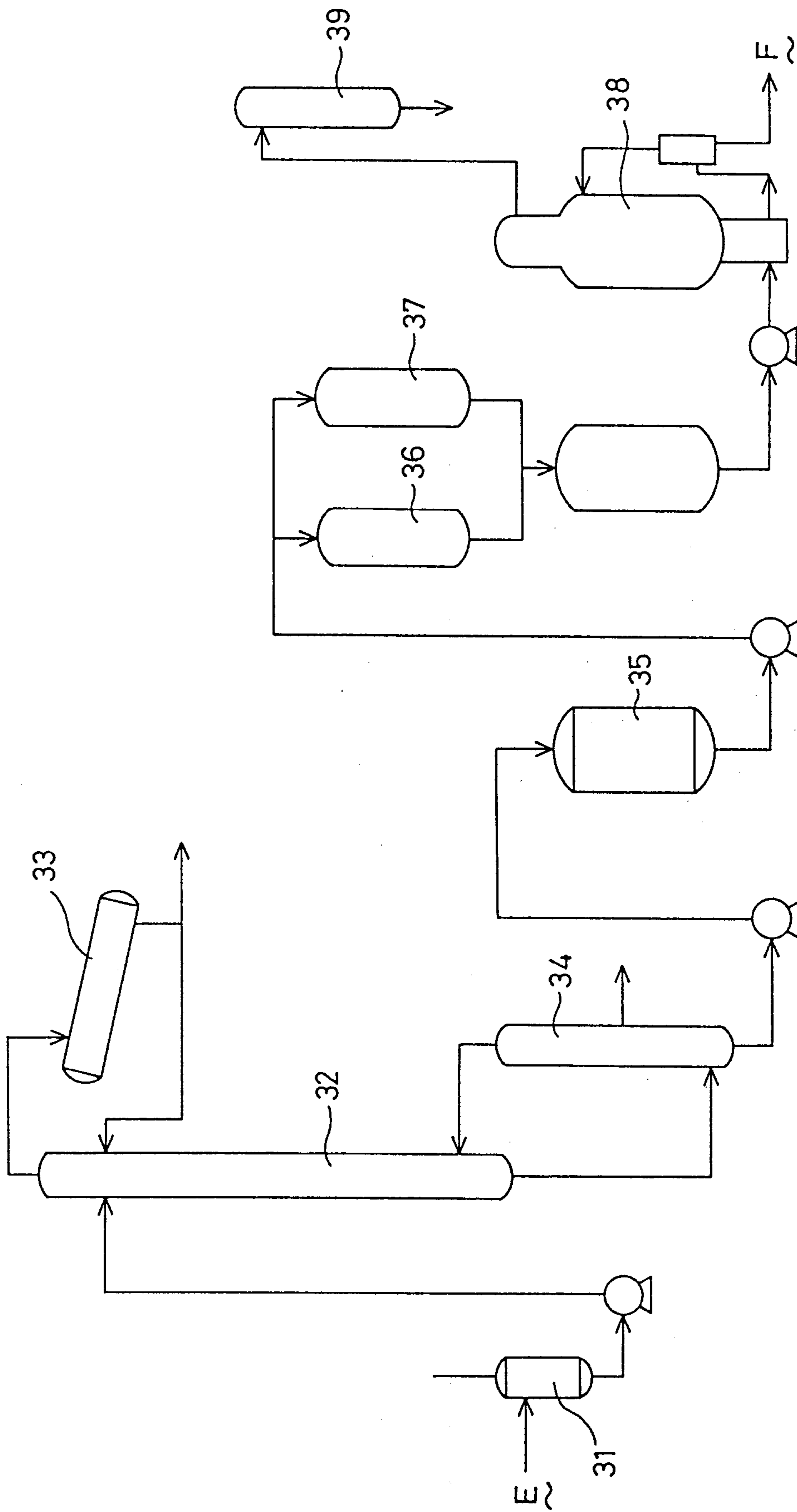
FIG. 1



PATENT AGENTS

Swabeys Ogilvy Renault

FIG. 3



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PATENT AGENTS

Aurhey Ogilvy Renault

FIG. 4
PRIOR ART

