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MANUFACTURING OF CONCENTRATES OF FAT-SOLUBLE ACTIVE SUBSTANCES, ESPECIALLY VITAMINES

Felix Grandel and Hans Neumann, Emmerich/Rhein, Germany; vested in the Alien Property Custodian

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The subject matter of this invention is the manufacturing of concentrates of fat-soluble active substances, especially vitamines, from fats and oils of vitamine content or vitamine pre-concentrates, through alcoholysis of same by means of low monovalent alcohols, distilling off the newly formed low-boiling esters by vacuum and, if necessary, purifying the residual vitamine concentrate by re-dissolving them in monovalent alcohols and extraction of the stearines from the solutions by freezing.

It is known to make concentrates of fat-soluble vitamines and active substances by saponifying fats of vitamine content with alcalis, separating the unsaponifiable and therefrom obtaining vitamine high concentrates through re-dissolving and re-crystallizing. This method is largely applied in technics nowadays, although it entails many drawbacks. F. i. in saponifying there arise considerable losses of the neutral fat portion, the majority of biologically important by-products of the vitamines are destructed and the output of vitamine concentrates leaves much to be desired. Besides, the vitamine concentrates produced by saponification mostly are of a rather bad durability, as they no longer contain any concomitant materials of stabilising effect.

It is further known to prepare vitamines by high vacuum distillation. In this or similar methods (short-way distillation) the natural connection of the vitamines and by-products is destructed. One invariably gets "vitamine fractions," but never the totality of fat-soluble active matter. This will account for the fact that the very acidy concentrates retained through high vacuum distillation equally show poor stability. The neutral oil liberated of the vitamines that result by high vacuum distillation is of inferior quaitly from a biological point of view and nearly always show an odour and flavour of fish and train-oil. Even after the application of refining methods, it is hardly serviceable as edible oil and has to be used in the soap industry. This method also requires costly apparatus, whose efficiency is but limited. In many cases, the yield of vitamines is far from being sufficient.

Moreover, it has been suggested to obtain concentrates of fat-soluble vitamines and active substances from vitaminous fats and oils through extraction (perforation) by solvents, particularly monovalent alcohols; by this method, however, vitamine concentrates of mean concentration (pre-concentrates) only will be the result.

Concentrates of fat-soluble active substances are likewise obtainable by applying chromatographic adsorption or absorption methods. But for the most part, the concentrates to be got in this way are acidy and must undergo additional treatment previous to their utilisation; besides, one does not extract the whole amount of fat-soluble active matter, but only fractional portions enriched with vitamine, as in the high vacuum distillation.

Other processes hitherto known for the manufacture of concentrates of fat-soluble active substances are without importance, since they could not succeed in practice.

Contrary to this process, in the method according to the invention, concentrates of fat-soluble active substances are produces from fats or oils of vitamine content or from pre-concentrates without applying any saponification, high vacuum distillation or chromatography. These pre-concentrates can be made f. i. by dissolving the vitaminous fats and oils in organic solvents which are little, if at all, soluble in aqueous monovalent alcohols, and then f. i. by shawing or perforation with aqueous monovalent alcohols (see patent application Serial No. 379,550).

The new method is based upon the understanding that through alcoholysis by low monovalent alcohols, the boiling-point of vitaminous fats and oils or their pre-concentrates can be brought down, thus making it possible by mere vacuum distillation and without high vacuum distillation, to separate the low-boiling esters so far as newly produced by alcoholysis, from the higher boiling fat-soluble active materials. It is most striking that neither in the alcoholysis nor distillation there appear any losses of biological active substances.

The vitaminous fats and oils or pre-concentrates made therefrom are f. i. alcoholysed by ethyl- or methylic alcohol in the manner already known, the liberated glycerine removed and the resultant esters of the monovalent alcohols by vacuum distillation separated from the residual fat-soluble active matter. The alcoholysis can be effected under normal or increased pressure, at normal or increased temperature with the aid of catalysers such as gaseous chlorhydric acid, sulphuric acid, β-naphthaline-sulpho-acid, sodium alcoholate etc. The glycerine nascent with the alcoholysis may be removed by washing with water, unless it separates down immediately. By vacuum distillation, it is easily possible to sever the low-boiling esters of the monovalent alcohols produced by alcoholysis, from the higher-boiling fat-soluble vitamines. The resultant con-

centrates of the fat-soluble active substances can be further purified by re-dissolving in monovalent alcohols, when stearines will be retained as by-product. The purified vitamine concentrate is absolutely acid-free and contains the entire amount of biological active substances as included in the raw oil, in unchanged form. Hence, these concentrates show good stability and optimal therapeutic efficiency.

One may equally proceed in such a way as to alcoholyse the vitaminous fats and oils only partially by monovalent alcohols, remove the liberted glycerine and separate the low-boiling esters by means of distillation. According to the extent to which the alcoholysis has been carried through, an oil more or less enriched with vitamines will be received.

The by-products such as methyl ester, glycerine and stearine, accumulating in the preparation of concentrates, represent valuable raw materials. Methylic esters and glycerine are products in brisk demand for the explosive, paper, soap- and pharmaceutical industries and the stearines constitute a highgrade starting material for the synthetical preparation of vitamine-D and hormons (corpus luteum).

In a technical view, the method according to this invention shows considerable advantages as compared with the processes already known. So, it is possible to manufacture big quantities of concentrates with relatively simple and generally known apparatus in common use.

Examples

(1) 100 kgs. wheat germ oil with a vitamine-E-content of 0,5% $\alpha+\beta$ tocopherol are heated with 400 g. of 100% methylic alcohol and 1 gramme sodium alcoholate in the autoclave under carbon dioxide at a temperature of 200° for five hours. The converted product is, after due cooling, thrice shaken with 200 ccm. of water to remove the glycerine, the watery extracts united and the glycerine therefrom extracted. The vitaminous methylic esters solved in the methanol are liberated of methanol and heated till boiling in 5 mm. vacuum. The limpid methylic esters of a slight yellowish tint distill over at 200–230°, yielding about 350 grammes methylic ester with an acid number of 0,2 and a vitamine-E-content of 0,005% $\alpha+\beta$ tocopherol. The residue liberated of methylic esters is severed from impurities through re-dissolution. The final product retained will be about 40 grammes of a dark red oil with an acid value 5,9 and a vitamine-E-content of 4,3% $\alpha+\beta$ tocopherol.

(2) 400 grammes of a vitamine-E-concentrate from maize germ oil (see patent application Serial No. 379,550) with an efficiency of 1,2% $\alpha+\beta$ tocopherol are heated in the autoclave with 400 grammes of 98% gaseous muriatic acid containing ethyl alcohol for five hours to 200°. After alcoholysis, the glycerine is removed by means of shaking with water and the vitaminous ethyl esters subjected to distillation in 3 mm. vacuum. At a temperature of 190–220°, the ethyl esters distill over, yielding about 350 grammes of ethyl ester with a slight vitamine-E-content. The residue to be again dissolved in ethyl alcohol and the solution cooled down in order to free it from stearines. The resultant oil of a dark red colour (about 40 grammes) shows a vitamine-E-content of 10,3% $\alpha+\beta$ tocopherol.

(3) 400 grammes cod liver oil with a vitamine-E-content of 3000 I. E. and a vitamine-D-content of 500 I. E. per gramme are alcoholysed with 800 ccm. methanol with admixture of 6 grammes sodium alcoholate and 1000 ccm. benzole by means of heating for 60 hours on the water-bath under reflux-condenser. On removal of the liberated glycerine, the vitaminous methylic esters are distilled off by vacuum at 1 mm. Hg. The methylic esters contain only small proportions of vitamine-A, whereas the residue (about 30 grammes), after re-dissolving in methanol will show a vitamine-A-content of 20,000 I. E. and a vitamine-D-content of 5000 I. E.

(4) 50 kgs. wheat germ oil with a vitamine-E-content of 0,213% $\alpha+\beta$ tocopherol and an acid value of 15,3 are heated with 50 kgs. methanol and 0,5 kgs. of concentrated sulphuric acid under backflow-condenser. After 20 hours the alcoholysis is interrupted and the liberated glycerine, the main proportion of methanol not converted and the sulphuric acid methylic esters separated by washing with water. Thereupon the methylic esters are distilled off by vacuum of 3 mm. Hg. at 200–230°, 29 kgs. methylic ester distilling over. As residue will be retained 21 kgs. wheat germ oil with a tocopherol content of 0,485% and an acid number 1,2. The final product can be conveniently used in veterinary as a germ oil enriched with vitamine-E for injections to combat sterility and Bang infection (caused by bacillus abortus).

FELIX GRANDEL.
HANS NEUMANN.