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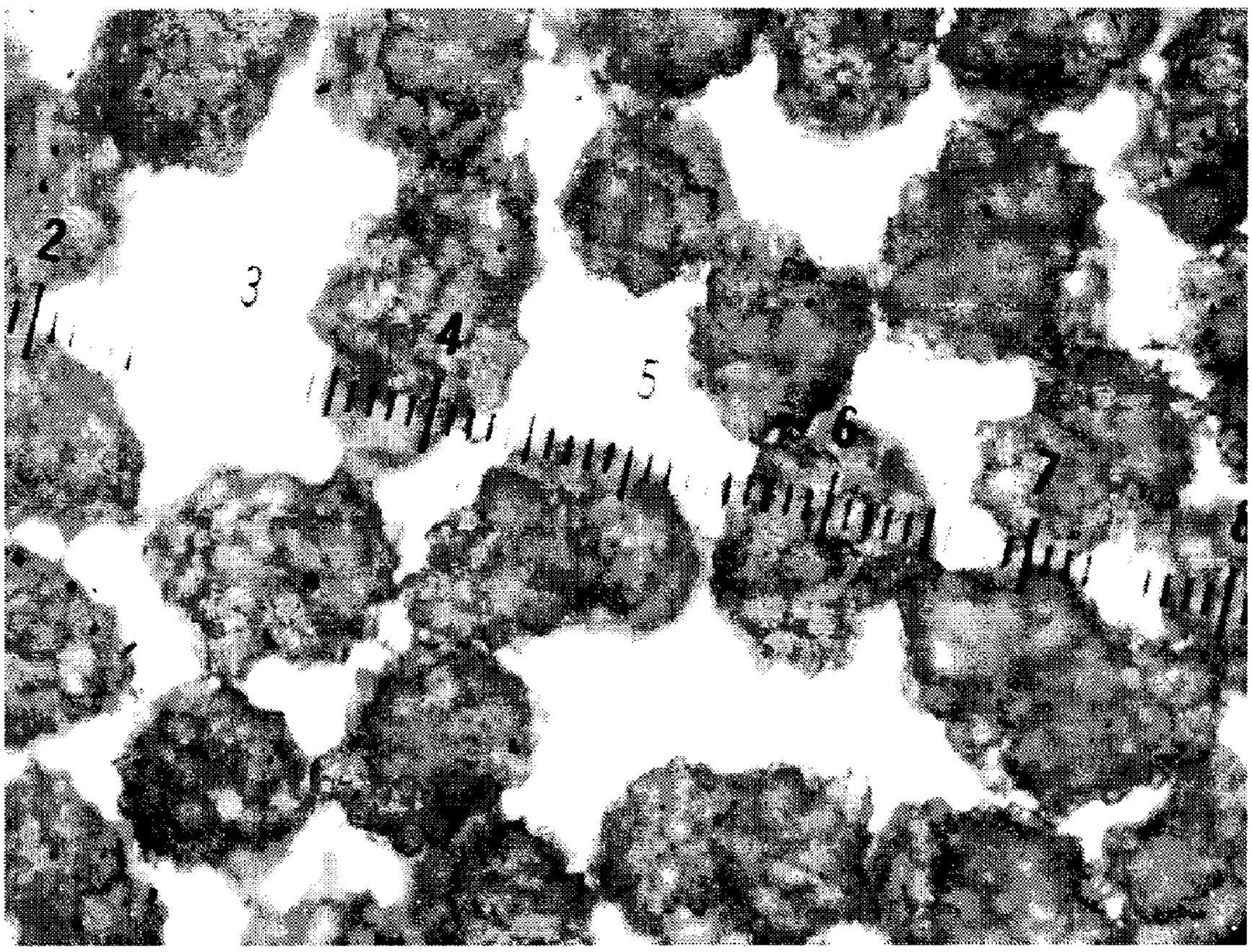
(54) Titre : CRISTALLISATION D'IODIXANOL PAR ULTRA-SONS
(54) Title: CRYSTALLIZATION OF IODIXANOL USING ULTRASOUND



Iodixanol agglomerates produced according to Example 1. Scale: 1 unit = 120 μm.

(57) Abrégé/Abstract:
This invention relates to the manufacture of iodixanol (1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane), more specifically to the purification of iodixanol by crystallization by using ultrasound.

ABSTRACT

This invention relates to the manufacture of iodixanol (1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane), more specifically to the purification of iodixanol by crystallization by using ultrasound.

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Crystallization of iodixanol using ultrasound

TECHNICAL FIELD

This invention relates to the manufacture of iodixanol (1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane), more specifically to the purification of iodixanol by crystallization.

BACKGROUND OF THE INVENTION

Iodixanol is the non-proprietory name of the chemical drug substance of a non-ionic X-ray contrast agent marketed under the trade name Visipaque™. Visipaque™ is one of the most used agents in diagnostic X-ray procedures and is manufactured in large quantities.

The manufacture of such non-ionic X-ray contrast agents involves the production of the chemical drug substance (referred to as primary production) followed by formulation into the drug product (referred to as secondary production). Primary production of iodixanol involves a multi step chemical synthesis and a thorough purification process. For a commercial drug product it is important for the primary production to be efficient and economical and to provide a drug substance fulfilling the specifications, e.g. as expressed in the US Pharmacopeia.

A number of methods are known for the preparation of iodixanol. These are all multi step chemical synthetic processes and the cost of the final formulated product thus mainly depends on these processes. It is therefore important to optimize the processes both for economic and environmental reasons.

Three main chemical synthetic processes are known for the preparation of iodixanol, all of which start with 5-nitroisophthalic acid. In the first process described in EP 108638,

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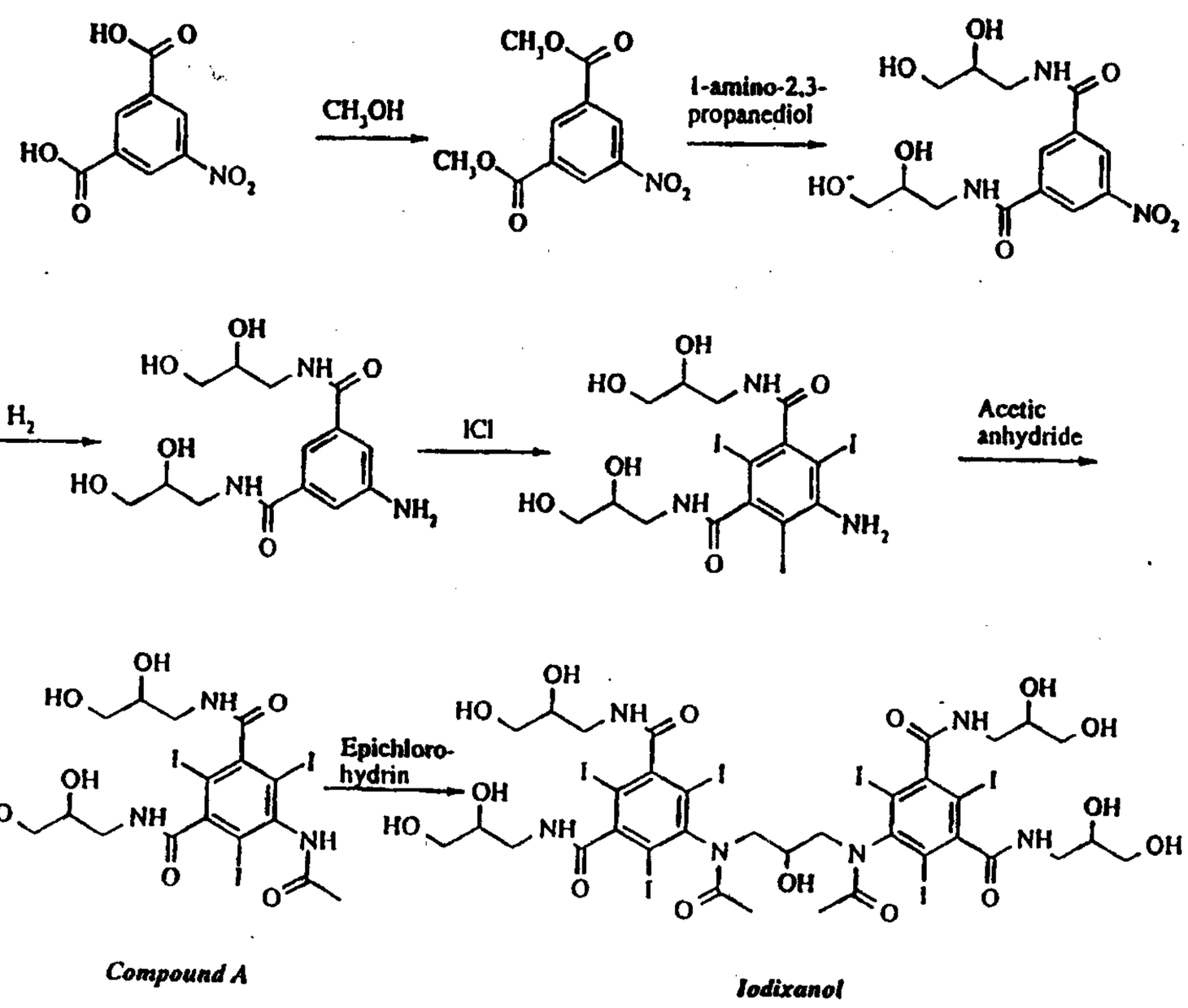
the final intermediate 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide (hereinafter "Compound A") is reacted with a dimerisation agent such as epichlorohydrin to yield the drug substance, see Scheme I.



Scheme I

The overall yield in this process is relatively low and the purification of the end product iodixanol is expensive and time consuming. The purification process described in EP patent 108638 involves purification by preparative liquid chromatography. The use of preparative liquid chromatography is a serious disadvantage in industrial processes in particular due to the high costs involved.

Several attempts have been made to find alternative manufacturing processes. Attempts to increase the yield of the chemical synthesis is published by Priebe et.al. (Acta Radiol. 36 (1995), Suppl. 399, 21-31). This publication describes another route which avoids the difficult last step of the process of Scheme I. However, the route involves eight reaction steps from 5-nitroisophthalic acid, which is undesirable, and one of the steps includes chlorination with

thionyl chloride, which is extremely corrosive. Also, the introduction of the iodine atoms takes place very early in the sequence, which is disadvantageous as iodine is the most expensive reagent in the process. The yield and final purification method for this route have not been reported.

The third route to iodixanol involves the synthesis of 5-amino-2,4,6-triiodoisophthalic acid (WO 96/37458) and then its dichloride (WO 96/37459), followed by conversion into Compound A (US 5705692) and finally dimerisation as in the process of Scheme I. This method thus has the same disadvantages as the first process, and also uses an undesirable acid chlorination step.

A common system for purification of the crude product in the final step of the primary production process, avoiding the liquid chromatography method, has been purification by crystallisation. To achieve the desired purity, the crude iodixanol produced by the synthetic chemical process is crystallized twice. The process is time consuming and takes about 3 days for the first crystallization and about 2 days for the second one. Hence, the crystallisation process is very demanding in terms of time and equipment size, it will take several days to perform and is often a bottleneck in industrial scale processes.

WO 99/18054 describes a process for the crystallization of i.a. iodixanol where the crystallization is effected with high thermal energy, specifically under elevated pressure and at a temperature above the boiling point of the solution at atmospheric pressure.

WO 00/47549 describes a process for the preparation of iodixanol where unreacted Compound A is precipitated from the reaction mixture and recovered for reuse in a later batch.

It is hence a desire to shorten the crystallization time and also improve the crystallization step in order to increase the purity of the final product.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows agglomerates of iodixanol produced in a crystallization step according to prior art. Scale: 1 unit = 120 µm.

FIG. 2 shows iodixanol particles produced in a crystallization step according to the present invention. Scale: 1 unit = 60 µm.

SUMMARY OF THE INVENTION

The present invention provides improvements to the crystallization of iodixanol.

Thus viewed from one aspect the invention provides a process for the purification of a crude product comprising iodixanol by crystallization, wherein the crystallization solution is exposed to ultrasound.

The process according to the present invention reduces the process time for the crystallization steps and improves the washing and hence the purity of the final product.

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In one aspect, this invention relates to an improved process for the purification of a crude reaction mixture resulting from the dimerization of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophtalamide (compound A) comprising iodixanol, 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophtalamide (compound A), iohexol and impurities having longer retention times than iodixanol in reversed phase HPLC, comprising the step of treating said crude reaction mixture with ultrasound during the crystallization process of said crude reaction mixture to reduce the agglomeration of iodixanol crystals.

DETAILED DESCRIPTION OF THE INVENTION

The processing time for the first crystallization is substantially longer than for the second one because of the high concentration of impurities at this stage of the process. Due to the slow kinetics, both crystallizations are run at high initial supersaturation and during the crystallization process it is formed large agglomerates, often of more than 100 µm in diameter. These agglomerates are shown in Figure 1. Agglomeration significantly reduces the available total surface area for crystal growth and therefore prolongs the process time to achieve the desired yield.

It has now surprisingly been found that it is possible to perform deagglomeration during the crystallization process by using ultrasound.

Thus viewed from one aspect, the invention provides a process for the purification of a crude product comprising iodixanol by crystallization, wherein the crystallization solution is deagglomerated by exposing said solution to ultrasound.

The use of ultrasound will significantly reduce the agglomeration of iodixanol crystals and by this reduce the process time for the crystallization steps. In cases where two crystallization steps are performed, the use of ultrasound will be able to reduce the process time from about three days to less than two days for the first crystallization and from about two days to less than 1 day for the second crystallization.

Further, the use of ultrasound in the crystallization step will also improve the purity of the final product. The purification process is finalized by filtering the precipitated iodixanol, preferably as unagglomerated crystals, from the solvents and finally washing the crystals with an alcohol such as methanol. The agglomerates of iodixanol crystals will also entrap mother liquor that needs to be removed by washing. By significantly reducing the agglomeration and hence the inclusion of mother liquor, a more effective washing of the crystals is achieved and also improved purity of the final product.

Figure 1 shows agglomerates produced during a crystallization process according to prior art. It can be seen that the agglomerates have a mean size in the area of about 120 µm. Figure 2 on the other hand shows particles produced under a process according to the present invention, and it can be seen that the particles are single crystals or very small agglomerates. The size of these particles is less then about 60 µm.

Any kind of ultrasound probes can be used, as a single probe or a battery of probes.

The ultrasound probe(s) can be mounted into the crystallizer or in-line to the crystallizer. When mounted in-line to the crystallizer the crystallization solution is circulated between the crystallizer and the ultrasound probe(s).

The crystallization solution can be continuously exposed to ultrasound throughout the crystallization, but normally a certain period at the start of the crystallization is sufficient to achieve the desired results.

The crude product referred to in the present invention can be obtained from the processes known from the state of the art, e.g. from the dimerisation process illustrated in Scheme I

above. The dimerisation step itself may be carried out as described in European patent 108638 and WO 98/23296, for example using epichlorohydrin, 1,3-dichloro-2-hydroxypropane or 1,3-dibromo – 2-hydroxypropane as the dimerisation agent, with epichlorohydrin being most preferred. The reaction is usually carried out in a solvent such as 2-methoxyethanol, methanol, 1-methoxy-2-propanol or a mixture of 2-methoxyethanol or 1-methoxy-2-propanol and water, and generally results in the conversion of 40 to 60% of Compound A to iodixanol.

Hence, in a second aspect of the invention it is provided a process for the manufacture of iodixanol comprising the steps of:

a) reacting 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide with a dimerisation agent in the presence of a solvent;
b) purifying the reaction product from step a) in a crystallization procedure;
c) deagglomerating the crystallization solution in the crystallization procedure by exposing said solution to ultrasound;
d) filtering and washing the product from step c).

The crude product from the dimerisation and following work-up steps is preferably in aqueous solution with small traces of organic solvent. The crude product normally contains about 75-90 weight% iodixanol, 3-10 weight% iohexol, 0-7 weight% Compound A, and also minor amounts of other impurities. The most important impurities in the reaction with regard to work-up consequences are the so-called backpeaks. This term refers to retention times in reversed phase HPLC, where the backpeaks have slightly longer retention times than iodixanol itself. Most of the backpeaks are either trimers or O-alkylated dimers. This crude product is preferably the starting material for the further purification by crystallization according to the present invention.

The invention is illustrated further by the following examples that are not to be construed as limiting the invention in scope to the specific procedures or products described in them.

Example 1 shows a conventional crystallization process according to prior art without the use of ultrasound. Figure 1 shows agglomerates of iodixanol produced (1 unit = 120 µm). After 12 hours the process reaches a yield of 2%. From the comparative example 2 showing the same process with the use of ultrasound, it can be seen that a yield of 25% is reached after the same period of time. Figure 2 shows iodixanol particles produced (1 unit = 60 µm).

EXAMPLES

EXAMPLE 1

305 g of crude product containing 253 g iodixanol and 17.8 g Compound A, 22.5 g iohexol and 5.1 g backpeaks was dissolved in a mixture of water and 1-methoxy-2-propanol (PM) in a 1 liter vessel equipped with a stirrer (with a magnet driven shaft), condenser and heating jacket. The amount of water and PM in the solution was 105 g and 442 g respectively. The solution was heated to reflux at atmospheric pressure and seeded with 2.4 g seed particles of iodixanol. The yield of iodixanol at 12 hours after seeding was 2%. Figure 1 shows iodixanol agglomerates produced.

EXAMPLE 2

305 g of crude product containing 253 g iodixanol and 17.8 g Compound A, 22.5 g iohexol and 5.1 g backpeaks was dissolved in a mixture of water and 1-mehtoxy-2-propanol (PM) in a 1 liter vessel equipped with a stirrer (with a magnet driven shaft), condenser, ultrasound probe and heating jacket. The amount of water and PM in the solution was 105 g and 442 g respectively. The solution was heated to reflux at atmospheric pressure and seeded with 2.4 g seed particles of iodixanol. The yield of iodixanol at 12 hours after seeding was 25%. Figure 2 shows iodixanol particles produced.

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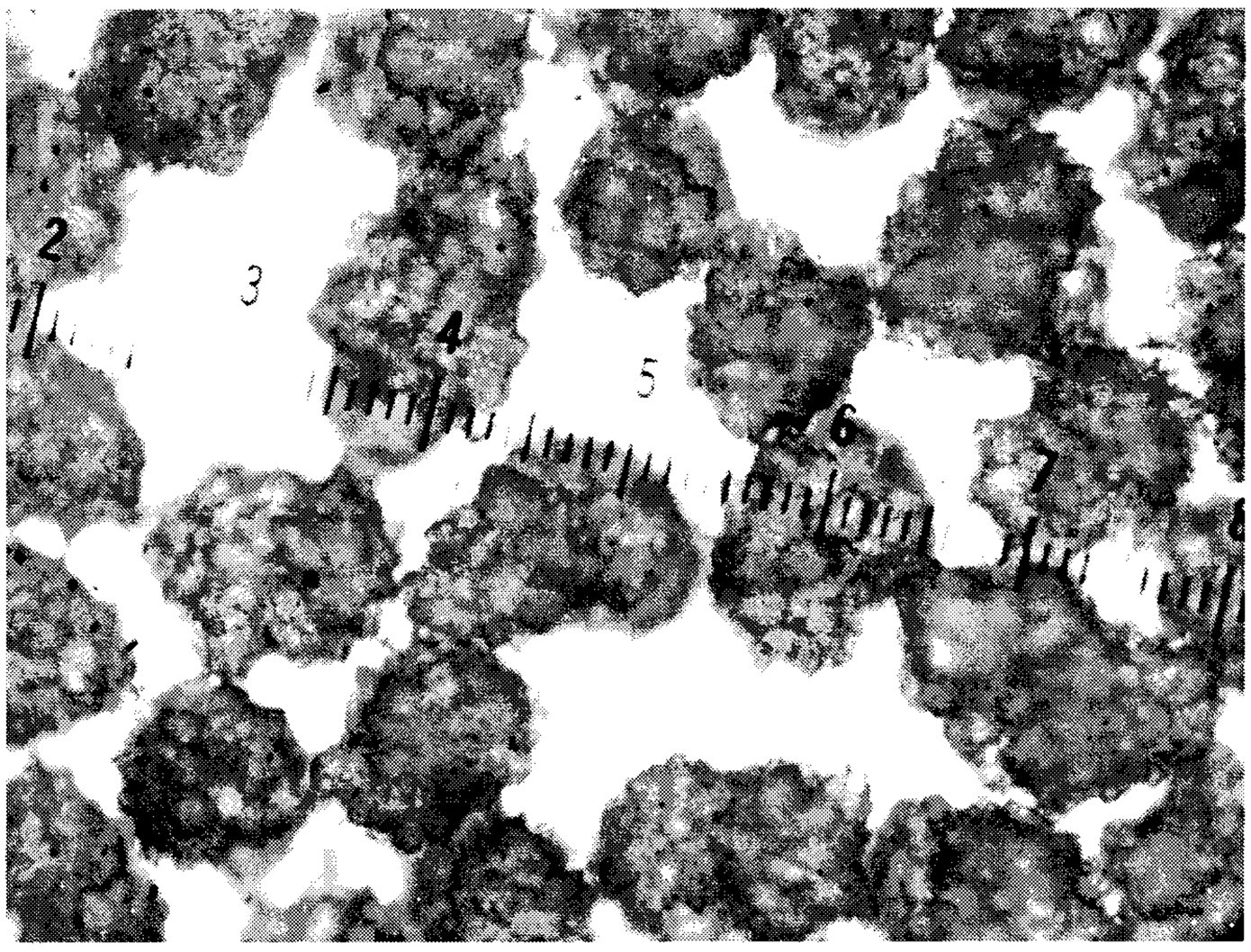
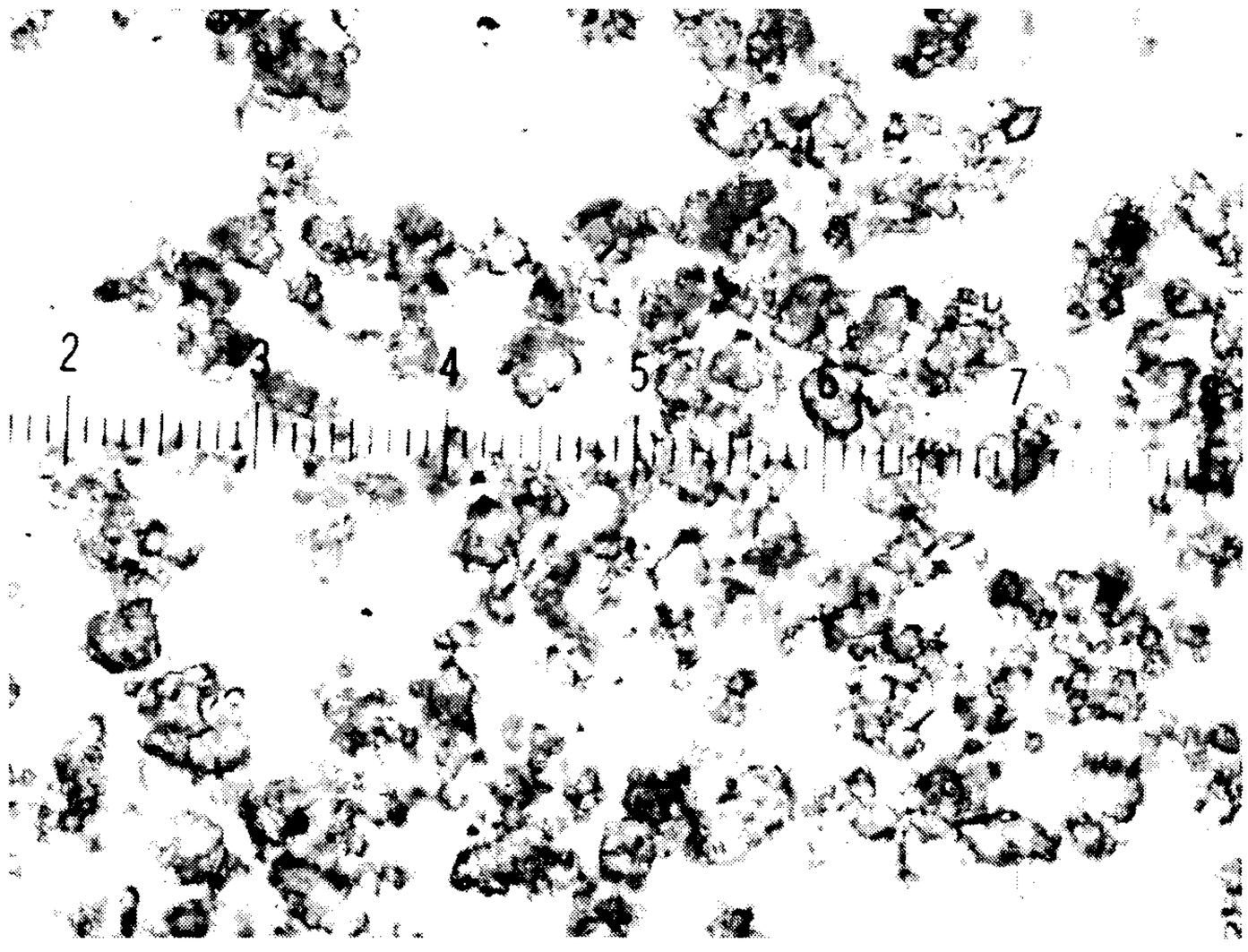
CLAIMS:

1. An improved process for the purification of a crude reaction mixture resulting from the dimerization of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophtalamide (compound A) comprising iodixanol, 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophtalamide (compound A), iohexol and impurities having longer retention times than iodixanol in reversed phase HPLC, comprising the step of treating said crude reaction mixture with ultrasound during the crystallization process of said crude reaction mixture to reduce the agglomeration of iodixanol crystals.



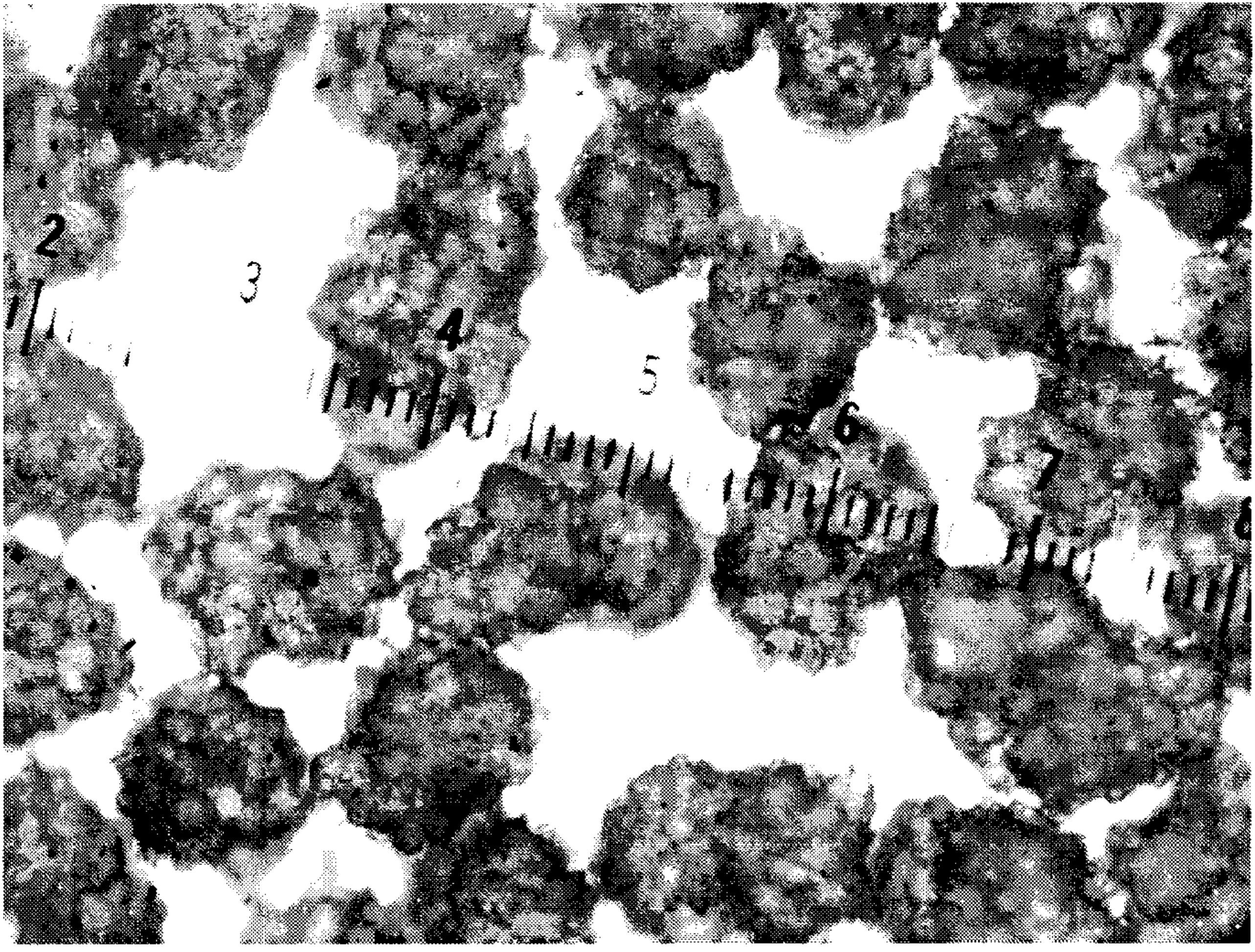
Iodixanol agglomerates produced according to Example 1. Scale: 1 unit = 120 μm.

FIG.1



Iodixanol particles produced according to Example 2. Scale: 1 unit = 60 μm.

FIG.2



Iodixanol agglomerates produced according to Example 1. Scale: 1 unit = 120 μm.