



(22) Date de dépôt/Filing Date: 2000/05/26

(41) Mise à la disp. pub./Open to Public Insp.: 2001/11/26

(51) Cl.Int.⁷/Int.Cl.⁷ C08F 120/06, C08F 120/54, C08J 3/24,
C08F 228/02

(71) Demandeur/Applicant:
GUILLET, JAMES E., CA

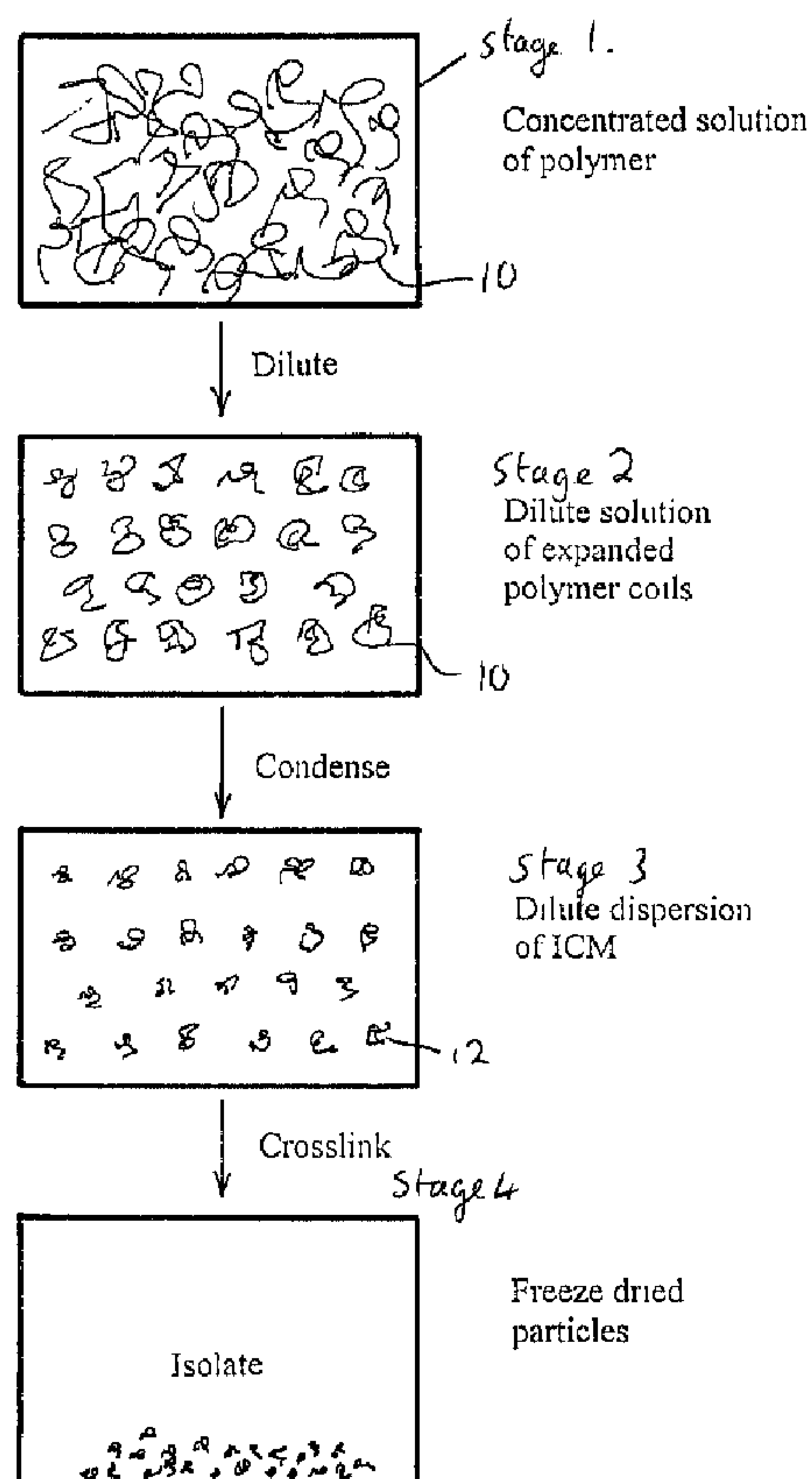
(72) Inventeur/Inventor:
GUILLET, JAMES E., CA

(74) Agent: RIDOUT & MAYBEE

(54) Titre : **MACROMOLECULES A RETICULATION INTERNE**

(54) Title: **INTERNALLY CROSS-LINKED MACROMOLECULES**

Synthesis of ICM



(57) Abrégé/Abstract:

There are provided internally cross-linked, stable polymeric materials, in the form of substantially spherical particles, each particle consisting essentially of a single macromolecule. They have the unusual property of being soluble or dispersible in a

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

liquid medium without significantly increasing the viscosity of the medium, rendering them potentially useful in imaging applications such as ink jet printers. They can be prepared by dissolving polymeric material in a solvent system to form a solution of the polymeric material at a concentration therein of less than the critical concentration for the polymer, causing the polymeric material to contract into an approximately spheroidal conformation in solution, cross-linking the polymeric material in solution in said spheroidal conformation so assumed, and recovering stable, cross-linked approximately spheroidal polymeric particles from the solution.

ABSTRACT OF THE DISCLOSURE

There are provided internally cross-linked, stable polymeric materials, in the form of substantially spherical particles, each particle consisting essentially of a single macromolecule. They have the unusual property of being soluble or dispersible in a liquid medium without significantly increasing the viscosity of the medium, rendering them potentially useful in imaging applications such as ink jet printers. They can be prepared by dissolving polymeric material in a solvent system to form a solution of the polymeric material at a concentration therein of less than the critical concentration for the polymer, causing the polymeric material to contract into an approximately spheroidal conformation in solution, cross-linking the polymeric material in solution in said spheroidal conformation so assumed, and recovering stable, cross-linked approximately spheroidal polymeric particles from the solution.

15

INTERNALLY CROSS-LINKED MACROMOLECULES

Field of the Invention

5 This invention relates to polymers, and methods for producing polymers of novel structure. More particularly, it relates to a process for cross-linking polymers to produce cross-linked polymers stabilized into particularly useful, dense structures. It also relates to novel polymeric materials having unusual properties.

10

Background of the Invention

 It is known that cross-linking of polymers substantially alters the physical properties of the polymers. Cross-linking can change a thermoplastic
15 polymer to a thermoset polymer, can alter its solubility, density and other physical characteristics. Normally, cross-linking of a polymer is an irreversible process, so that the shape, configuration and density of a cross-linked polymer remain substantially permanent once the cross-linking process is complete.

20

 A variety of different methods of polymer cross-linking are known. One method is reaction with chemical cross-linking reagents. This is particularly applicable where the starting polymer is unsaturated (polybutadiene, polyisoprene, styrene-butadiene copolymers, EPDM etc.), so that the groups of unsaturation take part in the cross-linking. Other methods involve creation of reactive sites
25 such as free radicals on the polymer chains, e.g. by hydrogen abstraction using a free radical-generating initiator, by irradiation with γ -rays, X-rays, etc. Cross-linking can take place with the polymer in solution in a suitable solvent, in suspension or in bulk. Cross-linking is normally a random process, which may involve links between different polymer chains and links between points on the
30 same polymer chain, and permits only limited control over its course and extent. In solution and suspension, non-cross-linked polymers tend to adopt an extended, coiled conformation, which is altered in a generally uncontrollable manner during cross-linking. There is a need for stable, solid particulate polymers of

predetermined shape, size and density, for use for example in ink-jet printers, photocopiers and other imaging applications, where the achievement of fine definition and resolution of images depends upon the particle size and uniformity of the particles comprising the imaging medium, and on the viscosity of the
5 imaging medium.

Summary of the Invention

The present invention provides a process whereby polymers in
10 solution contract from the normal, random coil conformation to adopt an approximately spheroidal configuration. Then cross-linking conditions are applied to the solution, so that the dissolved polymer is internally cross-linked in its newly assumed, spheroidal configuration, to form independent particles cross-linked and stabilized in that conformation. In essence, the particles are single
15 macromolecules, independent of other, surrounding macromolecules.

By means of the present invention, dense, spherical particles of polymers can be made, having a high degree of uniformity as to particle size, shape and density. A solution of the polymer is first prepared using a solvent or
20 mixture of solvents in which the polymer fully dissolves, and at a concentration below the critical concentration, and caused to contract into a spheroidal conformation. Then the polymer is cross-linked.

The resulting polymeric materials are internally cross-linked
25 macromolecules, i.e. substantially all of the cross-links are between groups on the same polymer chain as opposed to cross-links between groups on different polymer chains to bond the polymer chains together in a network. These internally cross-linked polymers according to the invention have solution properties which are completely different from those of the same polymeric material either before
30 cross-linking or after cross-linking in bulk. High molecular weight polymers (100,000 and higher) have high viscosity in solution. If such a polymer is cross-linked in the bulk phase, the resulting polymer will not dissolve in any solvent, but

may swell when contacted with solvents. Internally cross-linked materials of the invention, in contrast, even with molecular weights in excess of 1,000,000 can be dispersed in a wide variety of solvents and non-solvents, but scarcely affect the viscosity of the solution or dispersion at all. This remarkable property makes these
5 new compositions of the invention of potential utility not only in imaging compositions as described above, but also in drug delivery applications.

Thus according to one aspect of the present invention, there is provided a process for preparing stable polymeric materials having substantially
10 spherical particulate form, which comprises:

dissolving a polymeric material in a solvent system to form a solution of the polymeric material at a concentration therein of less than the critical concentration for the polymer;
15

causing the polymeric material to contract into an approximately spheroidal conformation in solution;

cross-linking the polymeric material in solution in said spheroidal
20 conformation so assumed;

and recovering stable, cross-linked approximately spheroidal polymeric particles from the solution.

25 According to another aspect, the invention provides internally cross-linked particulate independent macromolecules having substantially spheroidal particle shapes, said particles having the ability to be dispersed in a liquid medium without significantly changing the viscosity of the medium.

30 Brief reference to the drawings.

FIGURE 1 of the accompanying drawings is a digrammatic

illustration of a preferred process according to the invention;

FIGURE 2 is an atomic force microscopy picture of one product of Example 1 below;

5

FIGURE 3 is an atomic force microscopy picture of another product of Example 1 below;

FIGURE 4 is an atomic force microscopy picture of the product of Example 3 below.

10

Description of the Preferred Embodiments

The process of the present invention is applicable to a wide variety of polymeric materials, natural and synthetic. The polymeric materials can be homopolymers or copolymers of two or more monomers, including block copolymers and graft copolymers. It is necessary that the chosen polymeric material be soluble to a substantial extent in at least one solvent system, so as to enable it to adopt a contracted spheroidal conformation in solution, as described below.

20

The chosen polymeric material is first dissolved in an appropriate solvent system. This may be water, an organic solvent or a mixture of two or more such solvents. The polymeric material is dissolved such that, in solution individual macromolecules thereof remain distinct, separated and non-entangled with one another. This can be achieved by arranging that the concentration of polymer in solution is below the "critical concentration," which is the concentration at which the individual polymer chains in the solution interpenetrate. The separated, non-interpenetrating macromolecules in solution can be condensed e.g. by changing the solution characteristics, and stabilized by internal cross-linking, to a particle size which, assuming spherical shape, can be calculated from the molecular weight of the polymer. The ability of the macromolecules to achieve a condensed

30

particle size largely in accordance with theoretical calculations, assuming spheroidal shape, acts as a check or test that the polymer in solution, prior to condensation and cross-linking, was indeed in the form of independent, separated, non-interpenetrated macromolecules for the initial stages of the process of the present invention.

Either as it dissolves (for example in the case of sodium styrene sulfonate-vinyl naphthalene copolymers and similar copolymers), or by reduction of the solvent power of the solution, for example by adding to it a precipitating non-solvent, or a salt which changes the ionization conditions of the solution, the polymer is caused to condense and to contract to dense spheroidal structures. Then it is internally cross-linked, using a system which is compatible with the chosen polymer and the chosen solvent system, for example by exposure to γ -radiation. When each polymer molecule contains 3 or more internal cross-links, it can no longer expand to form its normal random coil configuration in solution. Instead, it retains its spheroidal confirmation, the density of which increases with the degree of cross-linking.

A wide variety of polymers and copolymers can be used in the present invention, provided only that a suitable solvent system is available for them, and that the random coils can be condensed to denser spheroidal particles prior to cross-linking. Preferred polymers have ionic charges so that, in the preferred aqueous solvent systems, the macromolecules are mutually repellant and less likely to agglomerate prior to cross-linking.

Examples of useful polymers in the present invention include polymers and copolymers derived from such monomers as styrene, vinyl naphthalene, styrene sulphonate, vinyl naphthalene sulphonate, acrylic acid, methacrylic acid, methylacrylate, acrylamide, methacrylamide, acrylates, methacrylates, acrylonitrile, N-loweralkyl acrylamides and the like.

One preferred embodiment of the invention involves the use of

polymers having a critical solution temperature, i.e. a temperature below which they are soluble in water, and above which they are insoluble in water. Using the process of the present invention, such polymers can be dissolved in water, caused to assume a condensed, spheroidal conformation and internally cross-linked as described. They can then be used for delivery and controlled release of other organic compounds such as drugs. The drug can be dispersed in a suspension of the cross-linked polymer at a temperature above the critical solution temperature, at which the drug will be absorbed by the polymer in its collapsed-particulate form. When the temperature is reduced below the critical solution temperature, the polymer particle swells and slowly releases the drug. Polymers having critical solution temperatures include polymers of N-isopropylacrylamide (NIPAM), the critical solution temperature of which can be adjusted by copolymerization with other monomers.

Fig. 1 of the accompanying drawings diagrammatically illustrates a process according to an embodiment of the invention. At stage 1, the polymer exists in a concentrated solution, in which the macromolecule chains 10 are intertwined and interpenetrated, so that any attempt to cross-link them at this stage would cause inter-reaction between the polymer chains.

Upon dilution of the solution, stage 2, below the critical concentration, the polymer macromolecules 10 are spaced apart from one another, but still in their random coil configuration. Upon reducing the solvent power of the solvent system, e.g. by introducing a non-solvent or a salt, the macromolecules condense, stage 3, into generally spherical conformation 12, and can now be cross-linked, eg. by application of ionizing radiation, at stage 4, whereupon internal cross-linking, as opposed to inter-macromolecular cross-linking occurs, effectively locking the macromolecules into the configurations assumed in stage 3. Then the cross-linked, approximately spherical macromolecule particles can be recovered e.g. by freeze drying, for use in applications referred to above.

The invention is further described with reference to the following

specific illustrative examples.

Example 1 - Internally Cross-linked Polyacrylic Acid

5

The sodium salt of poly(acrylic) acid (Polysciences Inc. Cat#18755), of molecular weight of 1,300,000, was used in a cross-linking process according to the invention. 97 mg of polymer was dissolved in 100ml of distilled water. After solution was complete the pH was 8.2, and 98mg of sodium chloride was slowly
10 added to cause the polymer particles to contract. 5cc. of the solution was flushed with nitrogen, sealed in a glass vial, and irradiated with 10 megarad of Co^{60} γ radiation. After radiation the vial was opened and the solution dialysed against water for 5 days to remove the salt, and the polymer particles recovered by freeze drying under vacuum. The particles were studied by atomic force microscopy
15 (A.F.M) and shown to be perfectly spherical, with diameters of 6 to 10 nanometers (see Fig. 2). No such particles were observed in the uncross-linked control sample. The particles observed are close to the size calculated for a completely collapsed macromolecular chain of molecular weight one million. When dispersed in water at a concentration of 1%, the solution had a viscosity virtually the same
20 as pure water. At the same concentration a water solution of uncross-linked starting material was much more viscous.

The procedure was repeated with a polyacrylic acid (sodium salt) of molecular weight about 700,000, and the A.F.M. picture of this product is
25 presented as Fig. 3 hereto. The spherical shape of the particles is clearly apparent from this picture. The scale on the Figure is in millimicrons. The particles have a diameter of approximately 4 nanometers (0.4 millimicrons).

Example 2

30

The procedure of Example 1 was repeated except that before addition of the sodium chloride the pH of the solution was reduced to 3.2 by

addition of small amounts of 0.1 N hydrochloric acid. After addition of sodium chloride and cross-linking with 10 megarad of γ -rays, nanoparticles of the same size (6-10 nanometers) were observed as in Example 1 by A.F.M.

5 **Example 3**

Copolymers of sodium styrene sulfonate and vinyl naphthalene containing about equal quantities of each comonomer are known to form hypercoiled pseudomicellar conformations in water, i.e. they do not form
10 expanded random coils, but are collapsed into much smaller spherical structures with much higher coil density due to the hydrophobic interactions between the naphthalene groups and water. These particles are negatively charged due to the ionization of the styrene sulfonate groups in water. The polymers can also be internally cross-linked by the following procedure. A polymer containing 50% by
15 weight sodium styrene sulfonate and 50% of vinyl naphthalene was prepared in benzene solution AIBN as catalyst. After isolation and purification by dialysis against pure water it had a molecular weight M_w of 200,000.

100 mg of this polymer was dissolved in 100 ml distilled water and
20 after purging with oxygen-free nitrogen was irradiated with a dose of .40 megarad of Cobalt⁶⁰ γ -rays. A.F.M. analysis of the resulting particles showed spherical particles with an average diameter of 7.5 nanometers. The A.F.M. picture of the particles is presented as Fig. 3 hereof. A 1% solution of these particles in water showed very little increase over that of water itself.

25

Example 4

Internal cross-linking can be carried out by other means besides γ radiation. In some cases, irradiation of the aqueous dispersion with high intensity
30 U.V. laser light will cause internal cross-linking. A simpler procedure is to prepare a copolymer with a small number of double bonds which can be connected by vinyl polymerization. In this example a copolymer of 50% styrene sulfonate and 48%

vinyl naphthalene and 2% divinyl benzene was prepared as in Example 3. 100 mg of this polymer was dissolved in 100 ml of water to which was slowly added with stirring 1.0 cc of benzene containing 4 mg styrene and 1 mg of AIBN (azobis-isobutyryl nitrile). After purging with nitrogen 2 cc of this mixture was heated to 70°C for 5 hours with stirring. After isolation and purification by dialysis spherical nanoparticles were observed by A.F.M.

Example 5

10 An additional 2 cc of the solution prepared in Example 4 was shaken with a small amount of styrene monomer and allowed to separate. Excess styrene was removed and the polymer was internally cross-linked by exposure of the solution to near ultraviolet light ($\lambda = 313$ nm from the American Ultraviolet Irradiation System for 1 hour. After isolation and purification cross-linked
15 nanoparticles with the viscosity properties of the γ irradiated materials from Example 1 and 2 were produced.

Example 6

20 Poly N-isopropyl acrylamide (NIPAM) is an important polymer which is often used in drug delivery systems. It has a lower critical solution temperature (LCST) of 31°C. It is soluble in water below this temperature but precipitates sharply above this. This temperature can be lowered by copolymerization with hydrophobic monomers such as acrylonitrile and raised by hydrophilic monomers
25 such as acrylamide. These co-polymers can be internally cross-linked by any of the procedures described above. In a specific example 100 mg of polyNIPAM with a molecular weight of 200,000 g/mole was dissolved in 100 ml water at 20°C and was cross-linked with 10 megarads of γ radiation. After isolation and purification, the internally cross-linked 5-10 nm nanoparticles can be used for the controlled
30 delivery of other organic compounds. For example the drug can be absorbed by the collapsed particle in a water dispersion above LCST. After removal of the unabsorbed drug, the dispersion will remain stable until the temperature of the

water is reduced below LCST, at which point the particle swells and slowly releases the drug. Since the size of the internally cross-linked nanoparticle is extremely small (~10 nm) it can access almost any part of the human body including the smallest blood capillaries which makes it of interest in a variety of medical therapies. The delivery polymers can also be made sensitive to pH instead of temperature.

Example 7

10 Polymers such as NIPAM, polyacrylamide and polyethylene oxide, which do not contain ionized groups, are difficult to keep separate in water solution while the cross-linking process is taking place. This reduces the yield and purify of the desired internally cross-linked nanoparticles. Cleaner products and higher conversions can be achieved by including an ionizable comonomer. A copolymer
15 of 2% acrylic acid and 98% NIPAM was prepared. At a pH of about 8-9 in water most of the acrylic acid units will be ionized, thus giving a strong negative charge to each polymer molecule. At high dilution, this prevents the agglomeration of individual chains to form larger particles. 100 mg of this polymer was internally cross-linked by the procedure of Example 6. A.F.M. studies of the internally cross-
20 linked particles showed a much lower concentration of larger agglomerated particles than those prepared in Example 6.

Example 8

25 A solution of sodium polyacrylate was prepared as in Example 1, and after the addition of sodium chloride, 4 mg of 4,4'-diazidostilbene-2,2' sodium sulfite dissolved in 1 cc benzene was added slowly with continuous stirring. After flushing with nitrogen, the ampoule was sealed and irradiated for 1 hour with 313 nm U.V. light in the American Ultraviolet Irradiation system. After irradiation the
30 product was isolated by freeze drying and purified by dialysis as in Example 1. A.F.M. measurements showed particles similar to those found in Example 1.

5 The particles produced from the internally cross-linked polymers having ionic functional groups, for example sodium polyacrylic acid made by the procedures of Examples 1, 2 and 8 above, can be modified by a number of simple processes. For example, by dissolving them in water containing a large excess of ferrous ions, the sodium ions can be replaced by ferrous ions. After removal of the sodium ions, the particles can be heated in air or oxygen to above 200-300°C. The polymer content is removed leaving extremely small particles of iron oxide
10 with very large surface area and important electrical and catalytic properties. If the process is carried out in a reducing atmosphere, high surface metal particles can be obtained. Other metal salts can be used to produce finely divided metal particles useful in catalysis.

15 In another modification, ionic groups on internally cross-linked polymers of the present invention, for example the sodium acrylate groups in the particles made in examples 1, 2 and 8 above, can easily be converted to other useful functional groups. Sodium acrylate groups for example can be converted to acrylic acid groups by treatment with excess hydrochloric acid, and isolated by
20 dialysis and freeze drying. Some or all of these groups can be converted to the corresponding acid chloride by treatment with thionyl chloride. Dye molecules containing reactive hydroxyl or amino groups can then be permanently bound to both the surface and the interior of the particles giving rise to products useful in imaging applications such as in ink-jet printing.

25

30

Synthesis of ICM

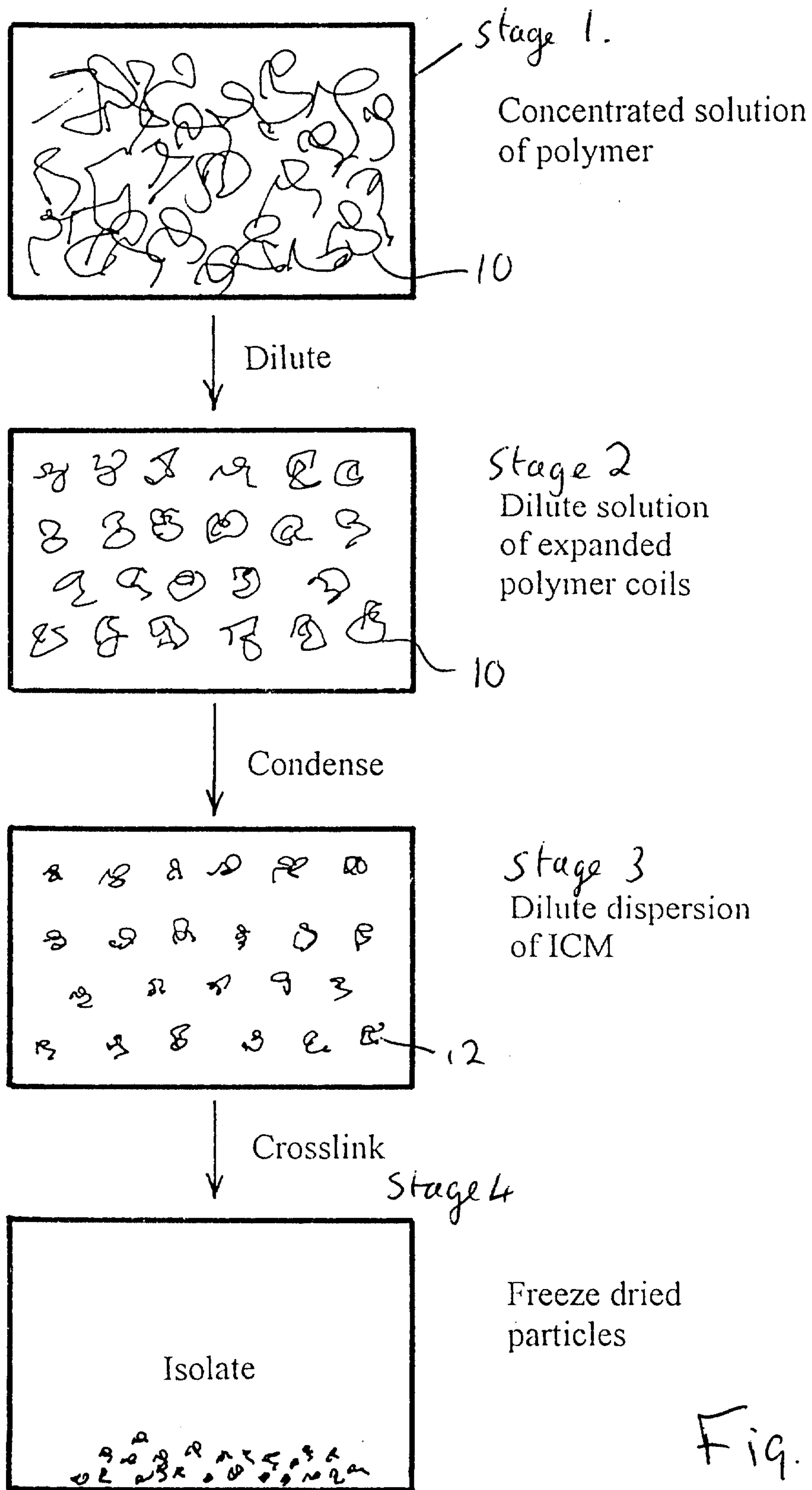
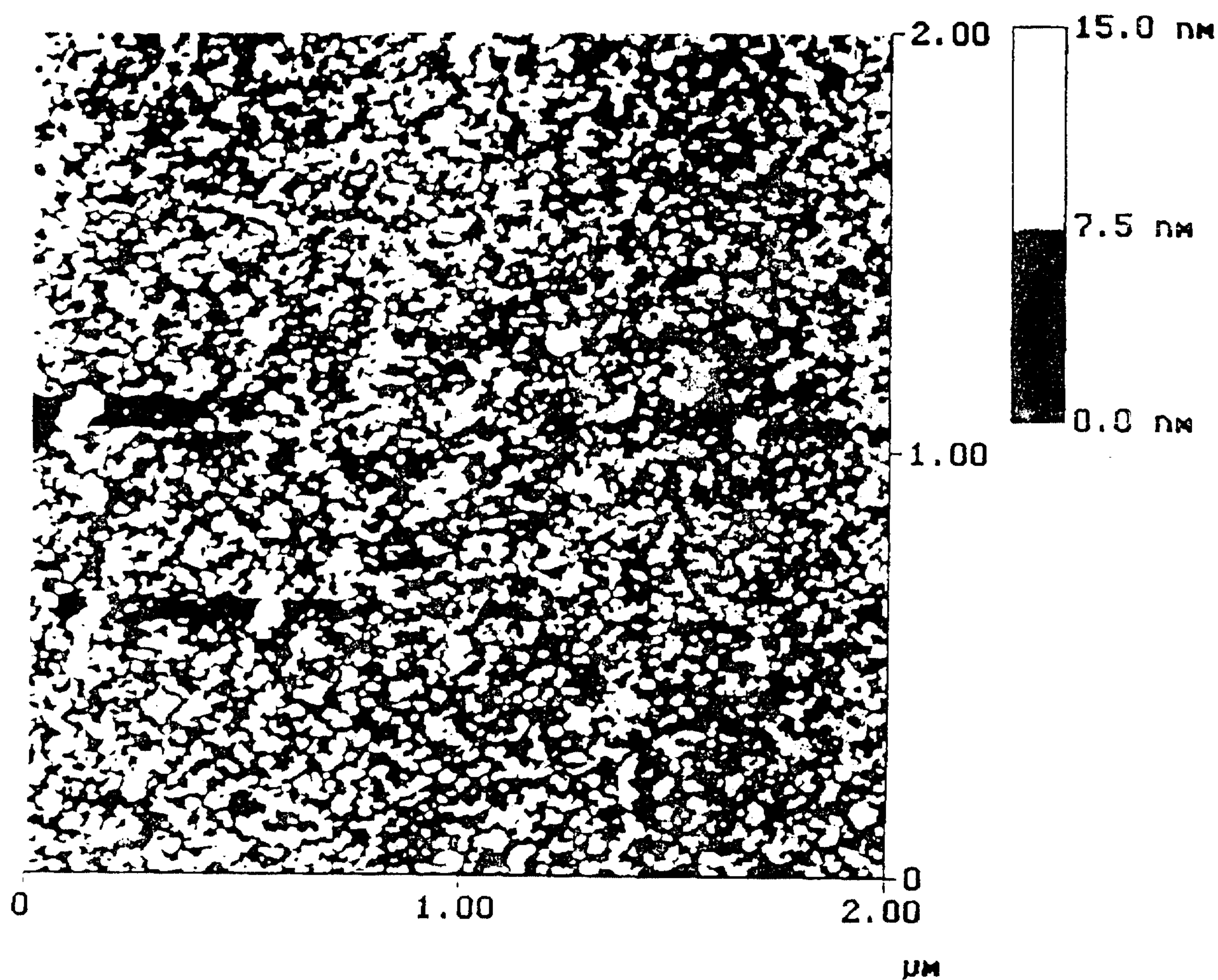


Fig. 1.

FIG 2

PAA 10 MR



Film cast onto mica
Tapping mode AFM height image

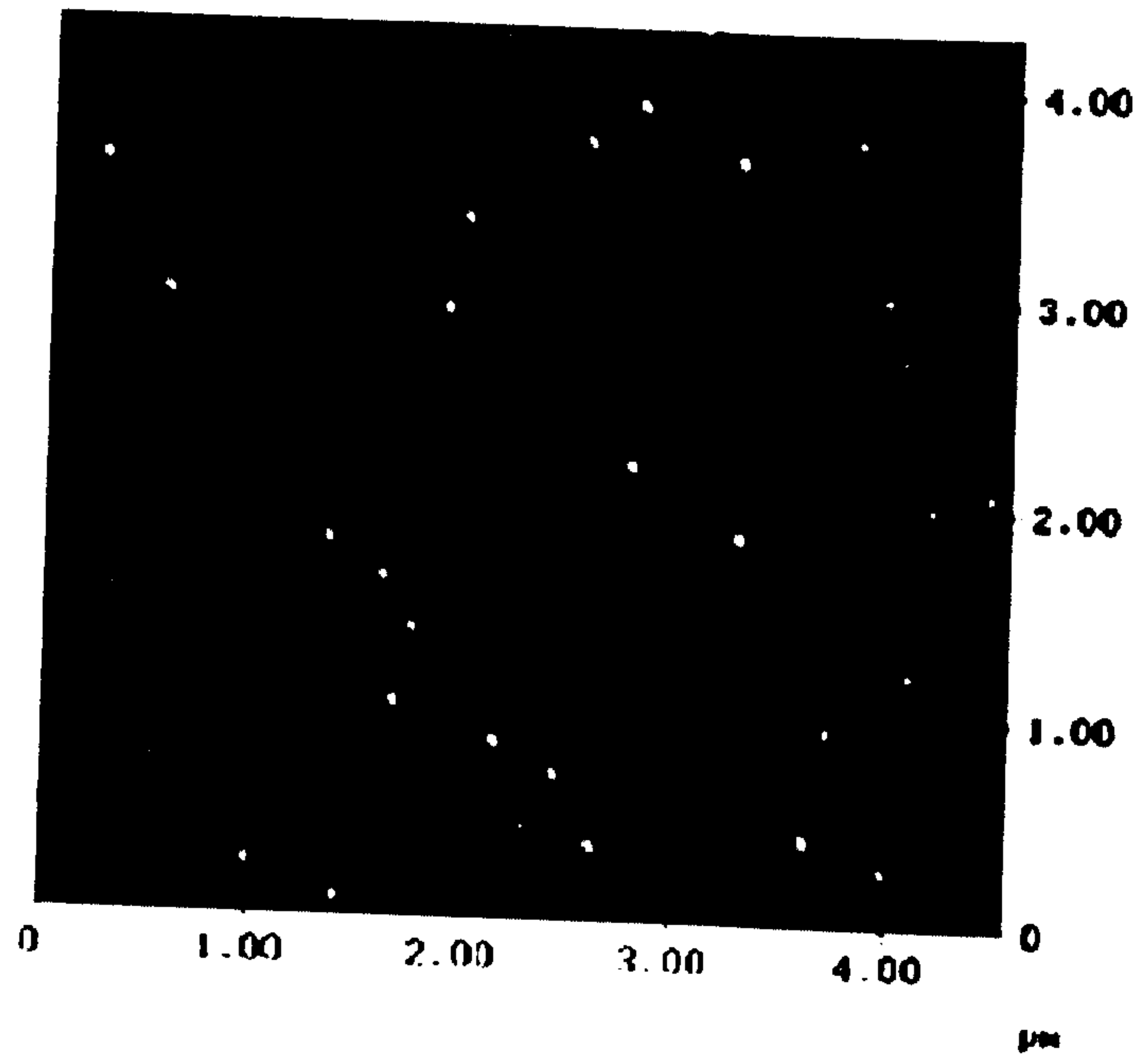
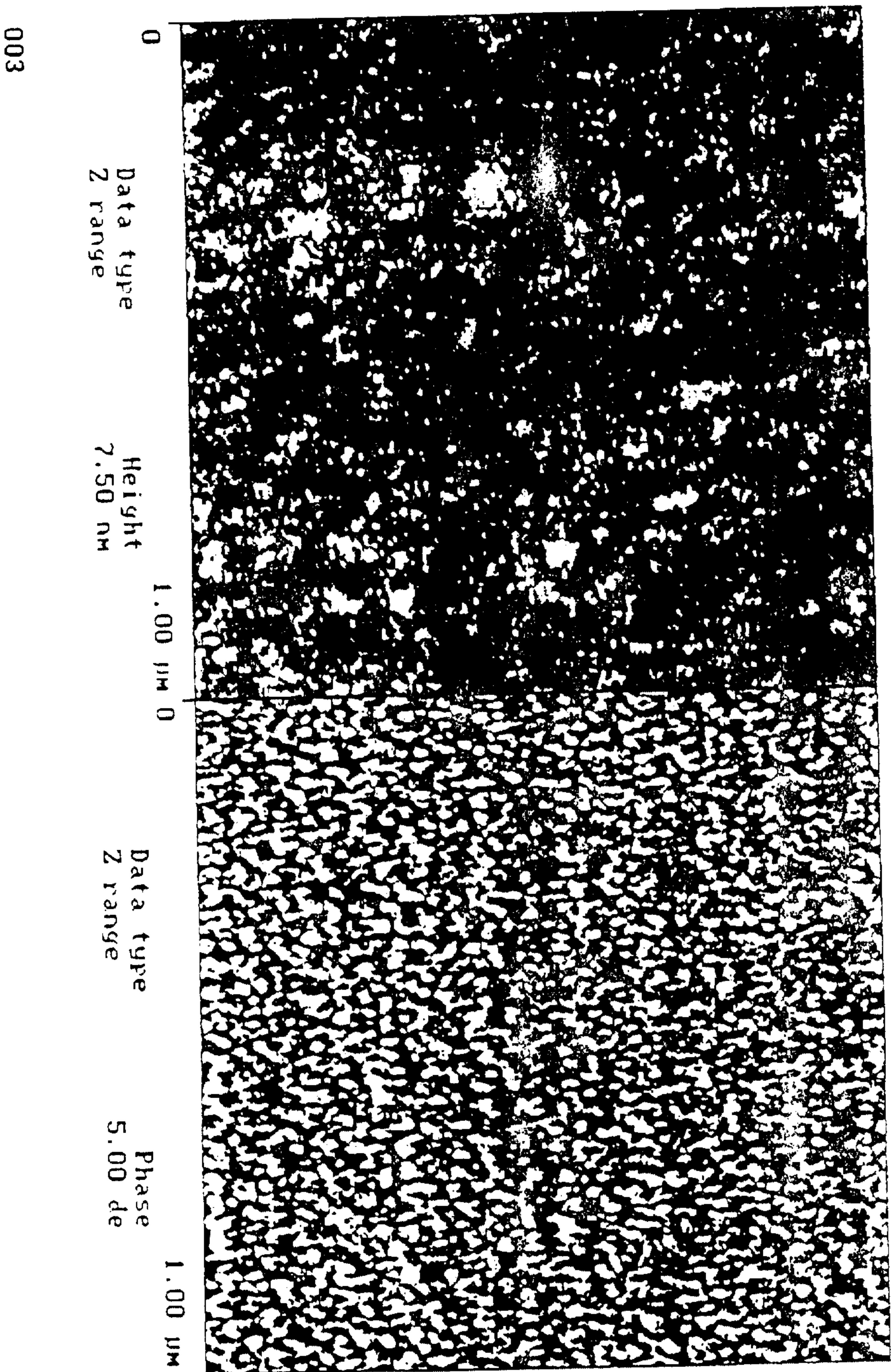


Fig. 3

sample 6

FIG 4. PSSSVN



Synthesis of ICM

