



- (51) **International Patent Classification:**  
*C08B 37/00* (2006.01)
- (21) **International Application Number:**  
PCT/IB2012/052144
- (22) **International Filing Date:**  
30 April 2012 (30.04.2012)
- (25) **Filing Language:** Italian
- (26) **Publication Language:** English
- (30) **Priority Data:**  
TO2011A000372 28 April 2011 (28.04.2011) IT
- (71) **Applicant (for all designated States except US):** **UNIVERSITA' DEGLI STUDI DI TORINO** [IT/IT]; Via Verdi, 8, Torino (IT).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** **TROTTA, Francesco** [IT/IT]; c/o UNIVERSITA' DEGLI STUDI DI TORINO, Via Verdi, 8, I-10124 Torino (IT). **SHENDE, Pravin** [IN/IT]; c/o UNIVERSITA' DEGLI STUDI DI TORINO, Via Verdi, 8, I-10124 Torino (IT). **BIASIZZO, Miriam** [IT/IT]; c/o UNIVERSITA' DEGLI STUDI DI TORINO, Via Verdi, 8, I-10124 Torino (IT).
- (74) **Agents:** **JORIO, Paolo** et al.; STUDIO TORTA S.p.A., Via Viotti, 9, I-10121 Torino (IT).

- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) **Title:** METHOD FOR PREPARING DEXTRIN NANOSPONGES

(57) **Abstract:** The present invention regards a method for preparing dextrin nanospheres comprising the steps of dissolving at least one dextrin in a basic aqueous solution having a pH higher than or equal to 10 to form a dextrin solution, dissolving a polyfunctional cross-linking agent in a water-immiscible organic solvent to obtain a solution of cross-linking agent, and setting the dextrin solution in close contact with the solution of cross-linking agent to precipitate the nanosphere. Moreover provided is a nanosphere that can be obtained by means of the method according to the present invention.



WO 2012/147069 A1

**"METHOD FOR PREPARING DEXTRIN NANOSPONGES"**TECHNICAL FIELD

The present invention relates to a method for preparing  
5 dextrin nanosponges by means of interfacial cross-linking.

BACKGROUND ART

Dextrin nanosponges are polymers of dextrans, in particular  
cyclodextrins, obtained by means of cross-linking with  
appropriate cross-linking agents.

10 Cyclodextrins (CD) are non-reducing cyclic oligosaccharides  
constituted by 6-8 glucose molecules linked with a 1,4- $\alpha$ -  
glucosidic bond, which have a characteristic frustoconical  
structure. The arrangement of the functional groups of glucose  
15 molecules is such that the surface of the molecule is polar,  
whereas the internal cavity is relatively lipophilic.

The lipophilic cavity bestows on cyclodextrins the capacity  
for forming stable inclusion complexes even in solution with  
20 organic molecules of a suitable polarity and dimension.

For this reason, cyclodextrins have already been studied and  
have numerous applications in various fields of chemistry in  
which the characteristics of inclusion compounds are  
exploited.

25 The documents Nos. WO03/085002, WO06/002814, and WO09/003656  
describe cyclodextrin-based polymers obtained by cross-linking  
with cross-linking agents and used as drug carriers or for  
removal of pollutant agents from water. Said polymers are by  
30 now commonly known as "nanosponges".

These polymers have moreover shown interesting properties of  
application also in controlled-release systems in the  
pharmaceutical field.

35 Currently known are various methods for preparing dextrin

nanosponges, which envisage use of anhydrous dextrans, high temperatures, and high-boiling solvents that are difficult to remove. In addition, said methods enable preparation of nanosponges in the form of solid blocks that then require  
5 further treatments to enable use thereof, for example, washing, Soxhlet extraction, and grinding.

Consequently, there is felt the need to identify new methods for preparing dextrin nanosponges that are extremely fast and  
10 will not require the use of complex laboratory apparatuses.

#### DISCLOSURE OF THE INVENTION

The aim of the present invention is consequently to provide a new method for preparing dextrin nanosponges that will be free  
15 from the disadvantages of the methods according to the known art.

The above aim is achieved by the present invention in so far as it relates to a method for preparing dextrin nanosponges according to Claim 1 and to a nanosponge according to Claim  
20 12.

#### Definitions

By the term "polyfunctional cross-linking agent" is meant a  
25 molecule having at least two reactive functional groups capable of creating a bond with different dextrin molecules.

By the term "water-immiscible organic solvent" is understood an organic solvent having a certain difference of polarity as compared to water. In particular, given that the index of  
30 polarity of water is equal to 9, all the organic solvents having a difference of index of polarity with respect to that of water of at least 5.0 are considered water-immiscible. Moreover considered water-immiscible are solvents with a  
35 miscibility number higher than 17.

By the term "reactive carbonyl group" is meant a functional group characterized by a carbon atom linked with a double bond to an oxygen atom and with two simple bonds to activating groups such as halogens, imidazole, electronegative atoms.

By the term "nanosponge" is meant a highly cross-linked porous polymer obtained by polymerization of dextrans.

#### BRIEF DESCRIPTION OF THE DRAWINGS

For a better understanding of the present invention, there now follows a description also with reference to the attached drawings, wherein:

- Figure 1a illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-cyclodextrin with carbonyl diimidazole in a ratio 1:8 according to the methods known to the art;

- Figure 1b illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-cyclodextrin with carbonyl diimidazole in a ratio 1:8 according to the method of the present invention;

- Figure 2a illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:4 according to the methods known to the art;

- Figure 2b illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:4 according to the method of the present invention;

- Figure 3a illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:8 according to the methods known to the art;

- Figure 3b illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-

cyclodextrin with hexamethylene diisocyanate in a ratio 1:8 according to the method of the present invention;

- Figure 4 illustrates the results of the DSC thermal analysis for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:2 according to the method of the present invention and not obtainable according to the methods known to the art;

- Figure 5a illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with carbonyl diimidazole in a ratio 1:8 according to the methods known to the art;

- Figure 5b illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with carbonyl diimidazole in a ratio 1:8 according to the method of the present invention;

- Figure 6a illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:8 according to the methods known to the art;

- Figure 6b illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:8 according to the method of the present invention;

- Figure 7a illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:4 according to the methods known to the art;

- Figure 7b illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:4 according to the method of the present invention;

- Figure 8 illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:2 according to the method of the present invention;

- Figure 9a illustrates the IR spectrum for a nanosponge obtained by cross-linking of beta-cyclodextrin with carbonyl diimidazole in a ratio 1:8 according to the methods known to the art;

5 - Figure 9b illustrates the IR spectrum for a nanosponge obtained by cross-linking of beta-cyclodextrin with carbonyl diimidazole in a ratio 1:8 according to the method of the present invention;

10 - Figure 10a illustrates the results of the thermogravimetric analysis (TGA) for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:8 according to the methods known to the art;

15 - Figure 10b illustrates the IR spectrum for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:8 according to the method of the present invention;

20 - Figure 11a illustrates the IR spectrum for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:4 according to the methods known to the art;

- Figure 11b illustrates the IR spectrum for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:4 according to the method of the present invention;

25 - Figure 12 illustrates the IR spectrum for a nanosponge obtained by cross-linking of beta-cyclodextrin with hexamethylene diisocyanate in a ratio 1:2 according to the method of the present invention; and

30 - Figure 13 illustrates a Raman spectrum of a nanosponge obtained by means of the method of the present invention as compared with that of a nanosponge obtained by means of the methods known to the art.

#### DETAILED DESCRIPTION OF THE INVENTION

35 The method of the present invention is a method of interfacial

polymerization in which the nanosponge is produced by precipitation at the interface between an organic phase and an aqueous phase that are immiscible with one another.

5 According to the present invention, the aqueous phase is constituted by an aqueous solution of a dextrin having a pH equal to or higher than 10, in particular comprised between 12 and 13.

10 The aqueous solution is a solution of a strong inorganic base, in particular a base of alkali metals or of alkaline-earth metals. The base preferably used is potassium hydroxide.

To obtain the present method of preparation both linear  
15 dextrins and cyclodextrins can be used, in particular, natural cyclodextrins and their derivatives, and more in particular, beta-cyclodextrins.

The organic phase is, instead, constituted by an organic  
20 solution obtained by dissolving a cross-linking agent in an organic solvent, in particular chosen in the group constituted by methylene chloride, butanone, hexane, methyl isobutyl ketone, cyclohexane, carbon tetrachloride, methyl t-butyl ether, 1,2-dichloroethane, ethyl acetate, and chloroform.

25 The polyfunctional cross-linking agent is a compound comprising a compound chosen in the group constituted by compounds comprising at least one reactive carbonyl group and epichlorohydrin, and in particular selected in the group  
30 constituted by carbonyl diimidazole, triphosgene, diphenyl carbonate, pyromellitic anhydride, epichlorohydrin, di- and polyisocyanates, and chlorides of carboxylic acids, more in particular carbonyl diimidazole and hexamethylene diisocyanate.

35

Once prepared, the aqueous dextrin solution and the organic solution of cross-linking agent are set in close contact and possibly stirred so as to increase the surface of contact also through the use of ultrasound.

5

Up to now interfacial polymerization has found application only in the preparation of polymers of selected monomers. Its limited application is due also to the difficult recovery of the polymer from the reaction environment.

10

More widely used is, instead, emulsion polymerization, conducted in the presence of surfactants in so far as it leads to better results.

15 Unlike the emulsion-polymerization methods known to the art and used for preparing polymers such as polycarbonates and polyamides, the method of the present invention does not require the use of a surfactant in solution.

20 Advantageously, the method according to the invention, unlike the methods known to the art for preparing dextrin nanosponges, does not require the use of anhydrous dextrans and of extractions for a subsequent purification. This method moreover enables nanoparticles to be obtained without the use  
25 of processes of a mechanical type, enables a reduction in the amount of solvents used, a reduction in the energy used, and is very fast.

The thermogravimetric analysis (TGA) and the differential-scanning-calorimetry (DSC) analysis conducted on the  
30 nanosponges obtained by applying the method according to the invention have shown how these products present profiles different from those obtained from the corresponding nanosponges obtained with the methods currently known to the  
35 art. Said nanosponges consequently prove to be structurally

different. This is evident from a comparison of the spectra appearing in Figures 1b-3b and 5b-7b with those of Figures 1a-3a and 5a-7a.

5 The analysis of the infrared spectra of the nanosponges obtained (see Figures 9-12) has moreover revealed how the nanosponges obtained with the method according to the invention show characteristic peaks not present in the dextrin nanosponges obtained with known methods, which indicates the  
10 fact that a new type of products has been obtained, which show excellent chemical and thermal stability and also a higher inclusion capacity.

Consequently, according to a further aspect of the invention,  
15 a nanosponge is provided, which can be obtained with the method described above.

In accordance with the data present in the relevant literature, for interfacial polymerizations the  
20 cyclodextrin/cross-linking agent ratio (D/CL) appears to be a factor that is less determining, if indeed of no effect, for obtaining nanosponges, affecting, rather, the global process yield.

25 Further characteristics of the present invention will emerge from the ensuing description of some examples provided merely by way of non-limiting illustration.

#### Examples

30

##### Example 1

##### Preparation of a nanosponge of beta-cyclodextrin cross-linked with N,N carbonyl diimidazole (CDI)

35 1.135 grams of beta-cyclodextrin were dissolved completely in

20 mL of an 0.1-M aqueous solution of potassium hydroxide under magnetic agitation or by means of a sonicator.

1.297 grams of CDI were dissolved in 20 ml of methylene chloride to obtain an organic CDI solution (CDI/CD molar ratio = 8.0).

The dextrin solution was added to the CDI solution under continuous agitation for 30 minutes. The precipitate was washed with distilled water and centrifuged at 3000 rpm for 15 minutes. The filtrate was filtered in vacuum conditions with distilled water and then with pure ethanol to remove the material that had possibly not reacted. The filtrate was collected and dried in vacuum conditions to obtain the nanosponge.

#### Examples 2-23

Following the method illustrated, nanosponges were prepared also with alpha-cyclodextrin and gamma-cyclodextrin, according to what appears in Table 1.

Table 1

| Ex. No. | Aqueous phase | Organic phase                   | Dextrin (D) | Cross-linking agent (CL) | D/CL molar ratio |
|---------|---------------|---------------------------------|-------------|--------------------------|------------------|
| 2       | 0.1 M KOH     | CH <sub>2</sub> Cl <sub>2</sub> | β-CD        | CDI                      | 1:8              |
| 3       | 0.1 M KOH     | CH <sub>2</sub> Cl <sub>2</sub> | β-CD        | CDI                      | 1:8              |
| 4       | 0.1 M KOH     | methyl isobutyl ketone          | β-CD        | CDI                      | 1:8              |
| 5       | 0.1 M NaOH    | CH <sub>2</sub> Cl <sub>2</sub> | β-CD        | CDI                      | 1:8              |
| 6       | 0.1 M KOH     | hexane                          | β-CD        | PMDA                     | 1:8              |
| 7       | 0.1 M KOH     | CH <sub>2</sub> Cl <sub>2</sub> | β-CD        | TPh                      | 1:2              |
| 8       | 0.1 M KOH     | CH <sub>2</sub> Cl <sub>2</sub> | β-CD        | TPh                      | 1:4              |
| 9       | 0.1 M KOH     | DMC                             | β-CD        | DMC                      | 1:8              |
| 10      | 0.1 M KOH     | CH <sub>2</sub> Cl <sub>2</sub> | α-CD        | CDI                      | 1:8              |

|    |               |                                 |      |                 |     |
|----|---------------|---------------------------------|------|-----------------|-----|
| 11 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | γ-CD | CDI             | 1:8 |
| 12 | 0.1 M<br>LiOH | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | CDI             | 1:8 |
| 13 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | DPC             | 1:8 |
| 14 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | α-CD | CDI             | 1:8 |
| 15 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | γ-CD | CDI             | 1:8 |
| 16 | 0.1 M<br>KOH  | hexane                          | β-CD | PMDA            | 1:8 |
| 17 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | TPh             | 1:2 |
| 18 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | TDI             | 1:8 |
| 19 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | HDI             | 1:8 |
| 20 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | SSC             | 1:8 |
| 21 | 1 M<br>KOH    | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | CDI             | 1:8 |
| 22 | 0.1 M<br>KOH  | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | epichlorohydrin | 1:8 |
| 23 | 1 M<br>KOH    | CH <sub>2</sub> Cl <sub>2</sub> | β-CD | epichlorohydrin | 1:8 |

PMDA: pyromellitic anhydride, TPh: triphosgene, CDI: carbonyl diimidazole, SSC: sebacoyl chloride, DCM: dichloromethane, DPC: diphenyl carbonate, CD: cyclodextrin, TDI: toluene diisocyanate, DMC: dimethyl carbonate, HDI: hexamethylene diisocyanate.

The reaction of interfacial polymerization for the production of cross-linked cyclodextrin polymers hence appears generally applicable.

#### Example 24

#### Solubility of the nanosponges

The solubility in various solvents of some of the nanosponges appearing in Table 1 was measured. The results obtained are given in Table 2.

Table 2

| Nanosponge | Diethyl ether | DMF | Ethanol | Petroleum ether | DMSO | Water |
|------------|---------------|-----|---------|-----------------|------|-------|
| β-NS-CDI   | -             | -   | -       | -               | -    | -     |

|                  |   |   |   |   |   |   |
|------------------|---|---|---|---|---|---|
| $\alpha$ -NS-CDI | - | - | - | - | - | - |
| $\gamma$ -NS-CDI | - | - | - | - | - | - |
| $\beta$ -NS-HDI  | - | - | - | - | - | - |
| $\beta$ -NS-TPh  | - | - | - | - | - | - |
| $\alpha$ -NS-HDI | - | - | - | - | - | - |
| $\beta$ -NS-SSC  | - | - | - | - | - | - |

$\beta$ -NS-CDI: nanosponge obtained by cross-linking of  $\beta$ -cyclodextrin and CDI;  $\alpha$ -NS-CDI: nanosponge obtained by cross-linking of  $\alpha$ -cyclodextrin and CDI;  $\gamma$ -NS-CDI: nanosponge obtained by cross-linking of  $\gamma$ -cyclodextrin and CDI;  $\beta$ -NS-HDI: nanosponge obtained by cross-linking of  $\beta$ -cyclodextrin and HDI (hexamethylene diisocyanate);  $\beta$ -NS-TPh: nanosponge obtained by cross-linking of  $\beta$ -cyclodextrin and TPh;  $\alpha$ -NS-HDI: nanosponge obtained by cross-linking of  $\alpha$ -cyclodextrin and HDI;  $\beta$ -NS-SSC: nanosponge obtained by cross-linking of  $\beta$ -cyclodextrin and sebacoyl chloride.

The insolubility observed of the products obtained in solvents with different polarity is in accordance with the formation of a cross-link in the synthesis of nanosponges.

#### Example 25

##### Charging of 4-nitrophenol in nanosponges

100 mg of nanosponges were set in contact with 2 ml of a solution of 4-nitrophenol (molecular weight 139.11). The nanosponge samples thus obtained were analysed under the UV spectrophotometer after 30 minutes and after 1 day. The results of the encapsulation appear in Table 3.

Table 3

| Nanosponge                     | Weight (mg) | Vol. (ml) | Absorbance (415 nm) | mg/100ml | Encaps. effectiveness |
|--------------------------------|-------------|-----------|---------------------|----------|-----------------------|
| $\alpha$ -NS-HDI<br>30 minutes | 100         | 2         | 0.72                | 0.0706   | 0.9294                |
| $\alpha$ -NS-HDI<br>1 day      | 100         | 2         | 0.62                | 0.0608   | 0.9392                |
| $\beta$ -NS-HDI                | 100         | 2         | 0.65                | 0.0637   | 0.9363                |

|                               |     |   |       |        |        |
|-------------------------------|-----|---|-------|--------|--------|
| 30 minutes                    |     |   |       |        |        |
| $\beta$ -NS-HDI<br>1 day      | 100 | 2 | 0.5   | 0.049  | 0.951  |
| $\beta$ -NS-CDI<br>30 minutes | 100 | 2 | 0.77  | 0.0755 | 0.9245 |
| $\beta$ -NS-CDI<br>1 day      | 100 | 2 | 0.61  | 0.0598 | 0.9402 |
| $\beta$ -NS-SSC<br>30 minutes | 100 | 2 | 0.725 | 0.0711 | 0.9289 |
| $\beta$ -NS-SSC<br>1 day      | 100 | 2 | 0.48  | 0.0471 | 0.9529 |
| $\beta$ -NS-TPh<br>30 minutes | 100 | 2 | 0.71  | 0.0696 | 0.9304 |
| $\beta$ -NS-TPh<br>1 day      | 100 | 2 | 0.59  | 0.0578 | 0.9422 |

It should be noted that the majority of nitrophenol is encapsulated in a few minutes.

#### 5 Example 26

The nanosponges obtained by means of the method according to the invention with reactive carbonyl groups were subjected to IR analysis after prior formation of tablets with KBr: all the analyses show a peak at  $1752\text{ cm}^{-1}$ , which is characteristic of the carbonyl group present in the bond between the molecules of cyclodextrin as illustrated in Figures 9-12. From said figures it is also evident that the peak around  $1700\text{ cm}^{-1}$  typical of cross-linked cyclodextrins is absent in the IR spectrum of the native cyclodextrins.

15

As a whole, the FTIRs show small differences in the signals, whereby it may be stated that the main bonds are the same in the nanosponges obtained with interfacial polymerization and those obtained with the methods known to the art. However, the fine structure appears significantly different, as a demonstration of the different interactions present and as a confirmation of what was already observed with the thermal analyses.

20

In addition, the so-called Boson Peak in the Raman spectra (Figure 13) is located at approximately  $28\text{-}29\text{ cm}^{-1}$  in the nanosponges obtained with the method according to the invention, a value that is a little higher than the average  
5 value of  $26\text{ cm}^{-1}$  obtained for nanosponges synthesized according to the methods known to the art. Also this experimental observation shows the peculiar and different molecular structure of the nanosponges according to the invention as compared to those already known.

## CLAIMS

1.- A method for preparing dextrin nanosponges comprising the steps of:

- 5 - dissolving at least one dextrin in an aqueous solution having a pH higher than or equal to 10 to form a dextrin solution;
- dissolving a polyfunctional cross-linking agent in a water-immiscible organic solvent to obtain a solution of cross-
- 10 linking agent; and
- setting in close contact in the absence of a surfactant said dextrin solution with said solution of cross-linking agent to precipitate said nanosponge.

15 2.- The method according to Claim 1, characterized in that said basic aqueous solution has a pH of between 12 and 13.

3.- The method according to Claim 1, characterized in that said basic aqueous solution is a solution of a base selected

20 in the group constituted by bases of alkali metals and bases of alkaline-earth metals.

4.- The method according to Claim 3, characterized in that said basic solution is a solution of potassium hydroxide.

25 5.- The method according to any one of the preceding claims, characterized in that said dextrin is selected in the group constituted by linear dextrans and cyclodextrans.

30 6.- The method according to Claim 5, characterized in that said cyclodextrans are selected in the group constituted by natural cyclodextrans and their derivatives.

35 7.- The method according to Claim 6, characterized in that said cyclodextrans are beta-cyclodextrans.

8.- The method according to any one of the preceding claims, characterized in that said polyfunctional cross-linking agent is a compound chosen in the group constituted by compounds comprising at least one reactive carbonyl group and epichlorohydrin.

9.- The method according to Claim 8, characterized in that said polyfunctional cross-linking agent is selected in the group constituted by carbonyl diimidazole, triphosgene, diphenyl carbonate, pyromellitic anhydride, epichlorohydrin, di- and polyisocyanates, and chlorides of dicarboxylic acids.

10.- The method according to Claim 9, characterized in that said polyfunctional cross-linking agent is selected in the group constituted by carbonyl diimidazole and hexamethylene diisocyanate.

11.- The method according to any one of the preceding claims, characterized in that said water-immiscible organic solvent is selected in the group constituted by methylene chloride, butanone, hexane, methyl isobutyl ketone, cyclohexane, carbon tetrachloride, methyl t-butyl ether, 1,2-dichloroethane, ethyl acetate, and chloroform.

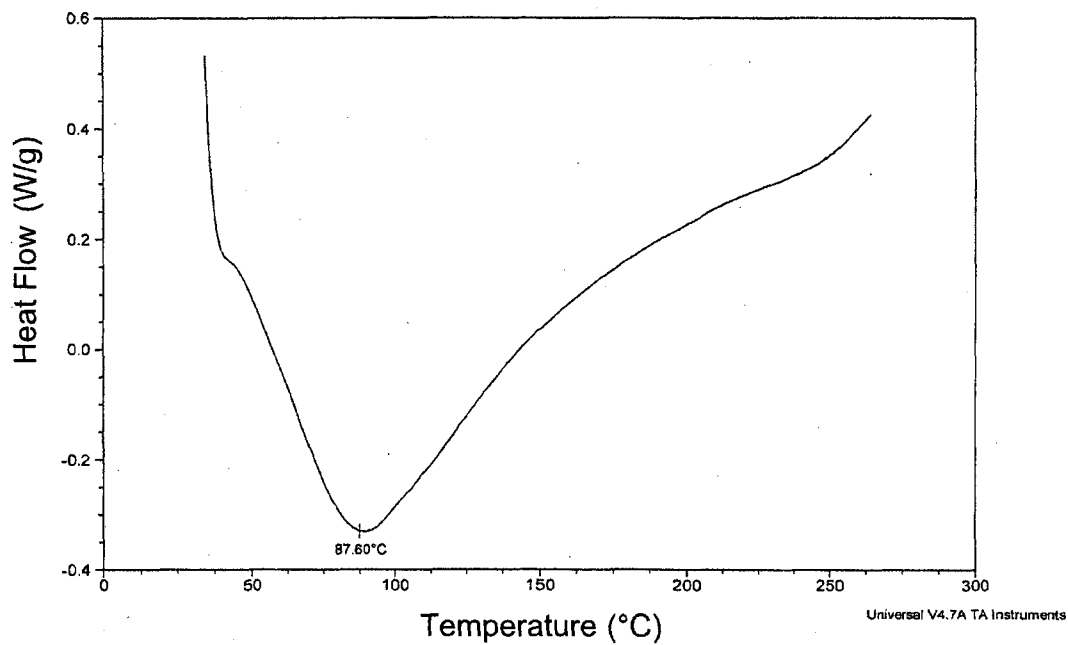
12.- A dextrin nanosponge that can be obtained by means of a method according to any one of Claims 1 to 11.

13.- The nanosponge according to Claim 12, characterized in that the cross-linking agent is chosen in the group constituted by carbonyl diimidazole and hexamethylene diisocyanate.

1 / 13

DSC

a)



DSC

b)

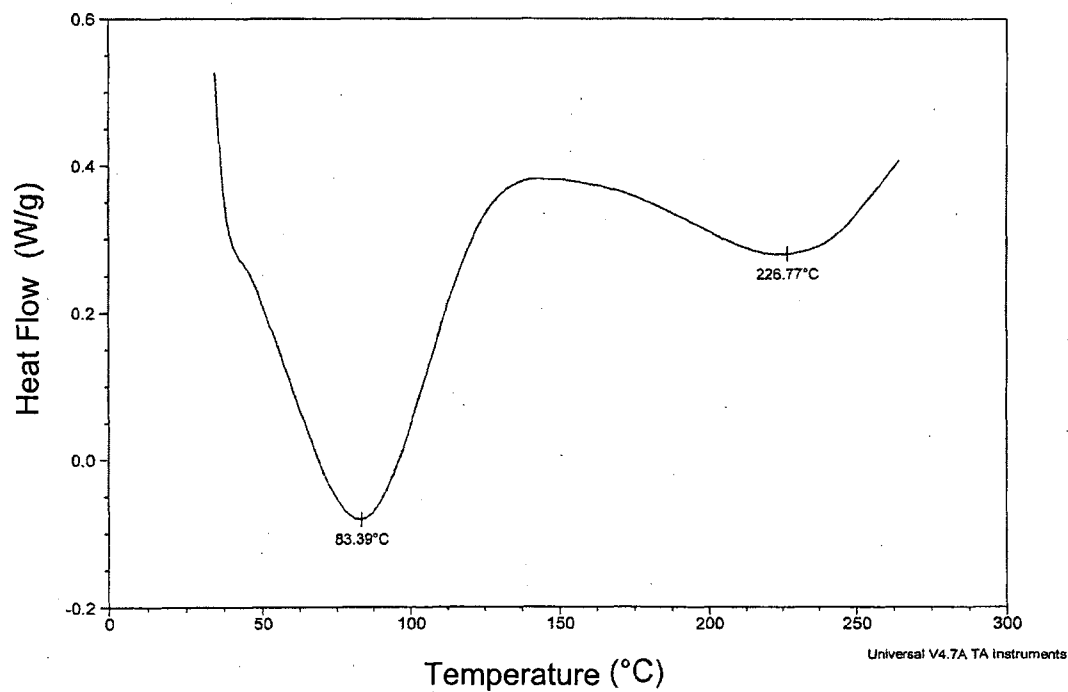


FIG. 1

2 / 13

DSC

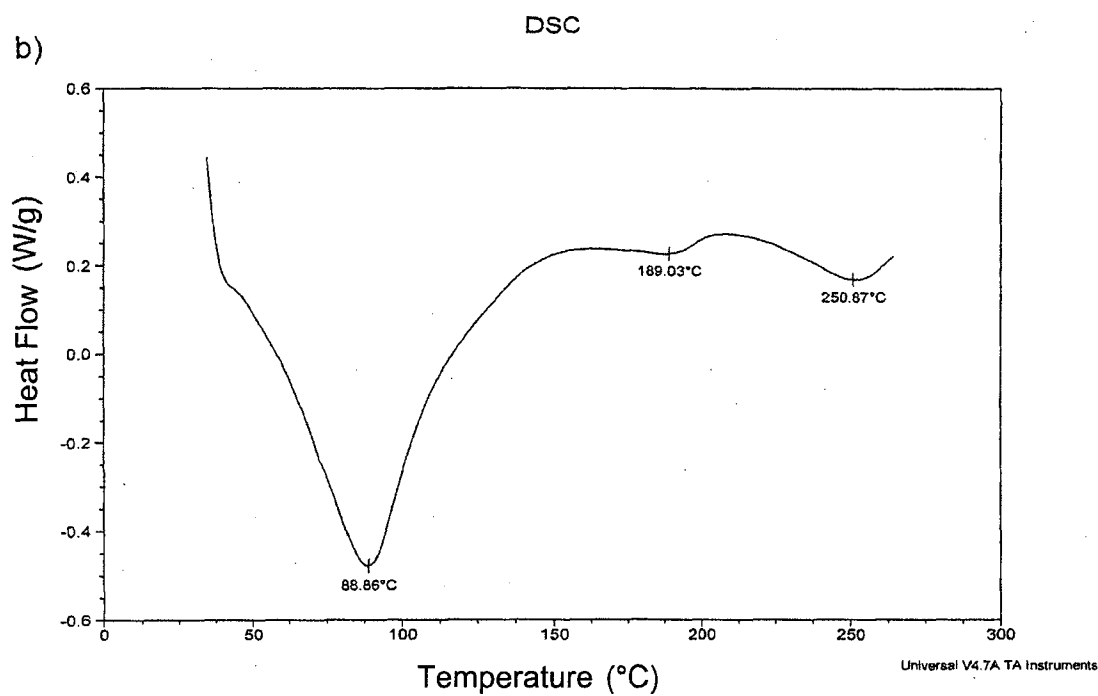
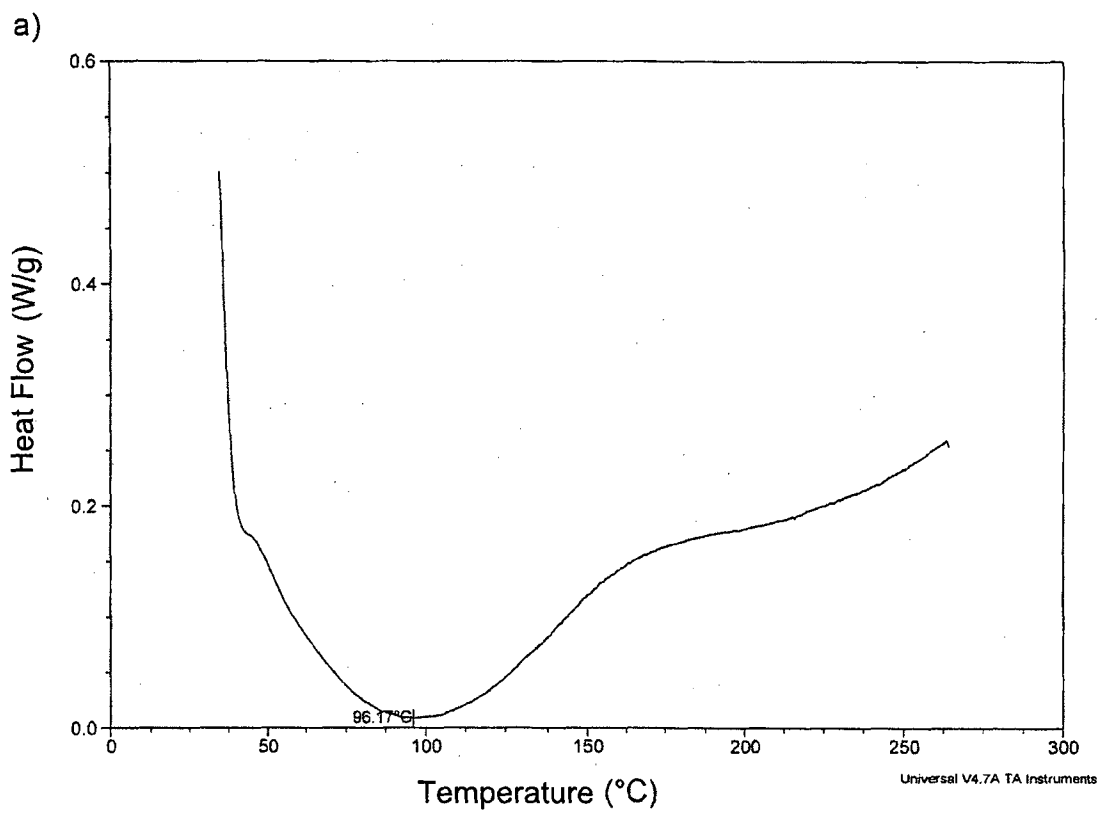


FIG. 2

3 / 13

DSC

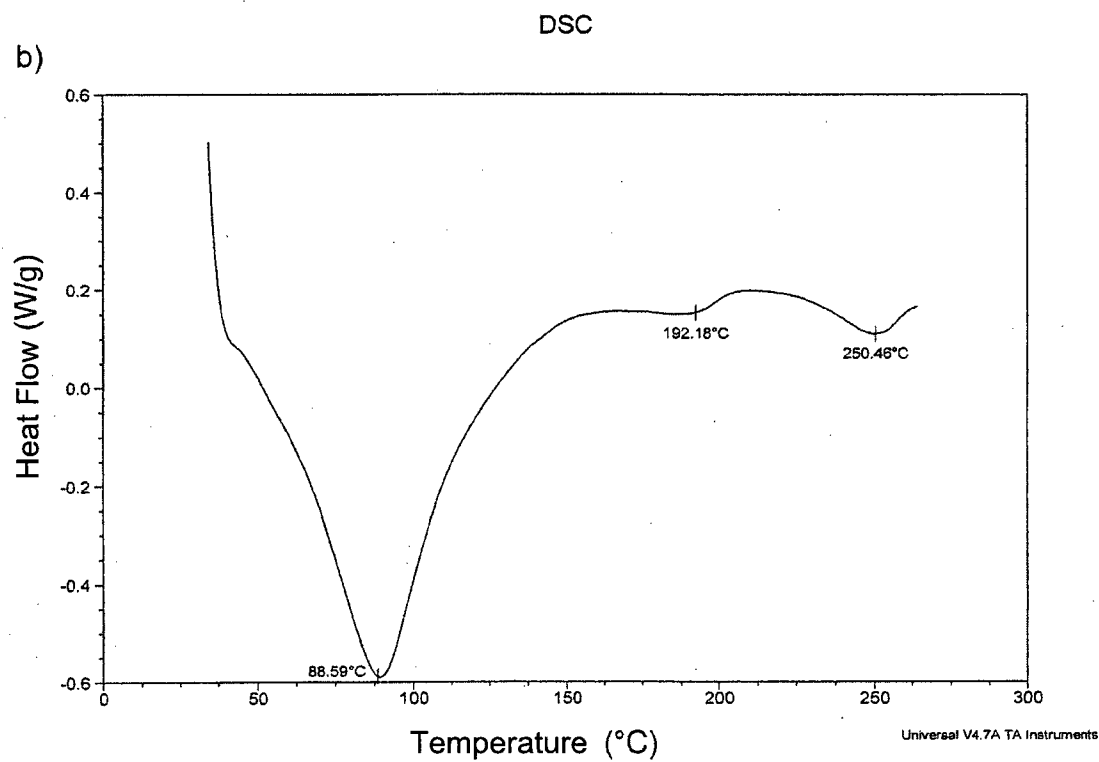
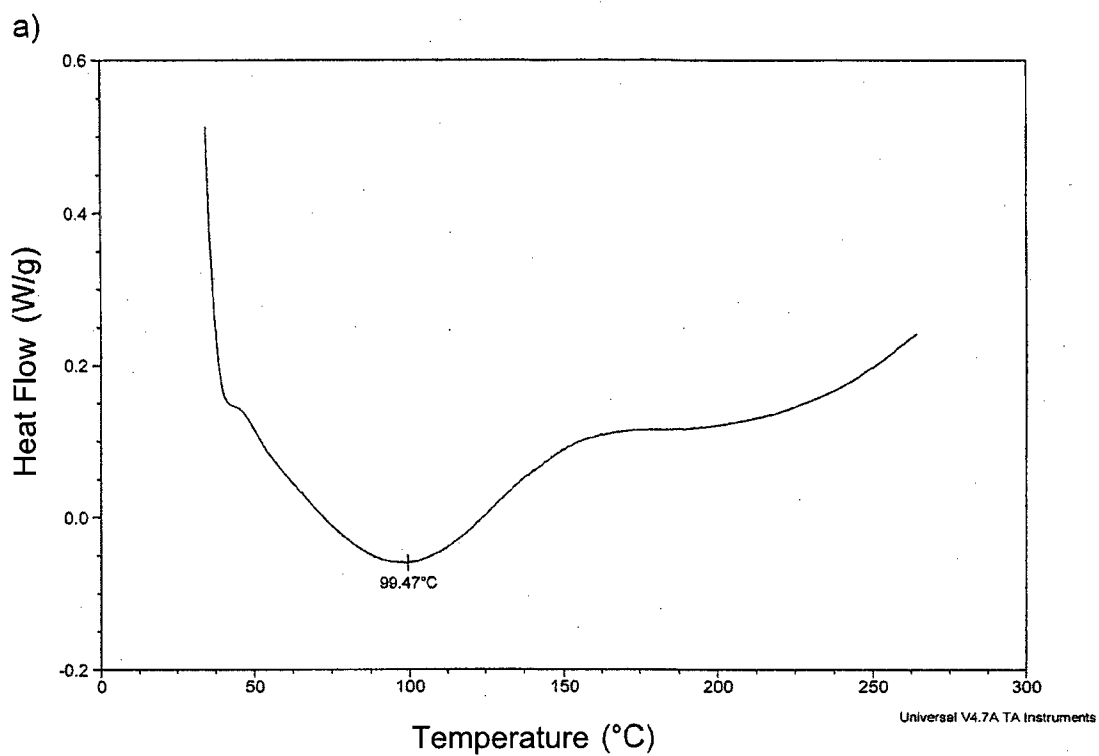


FIG. 3

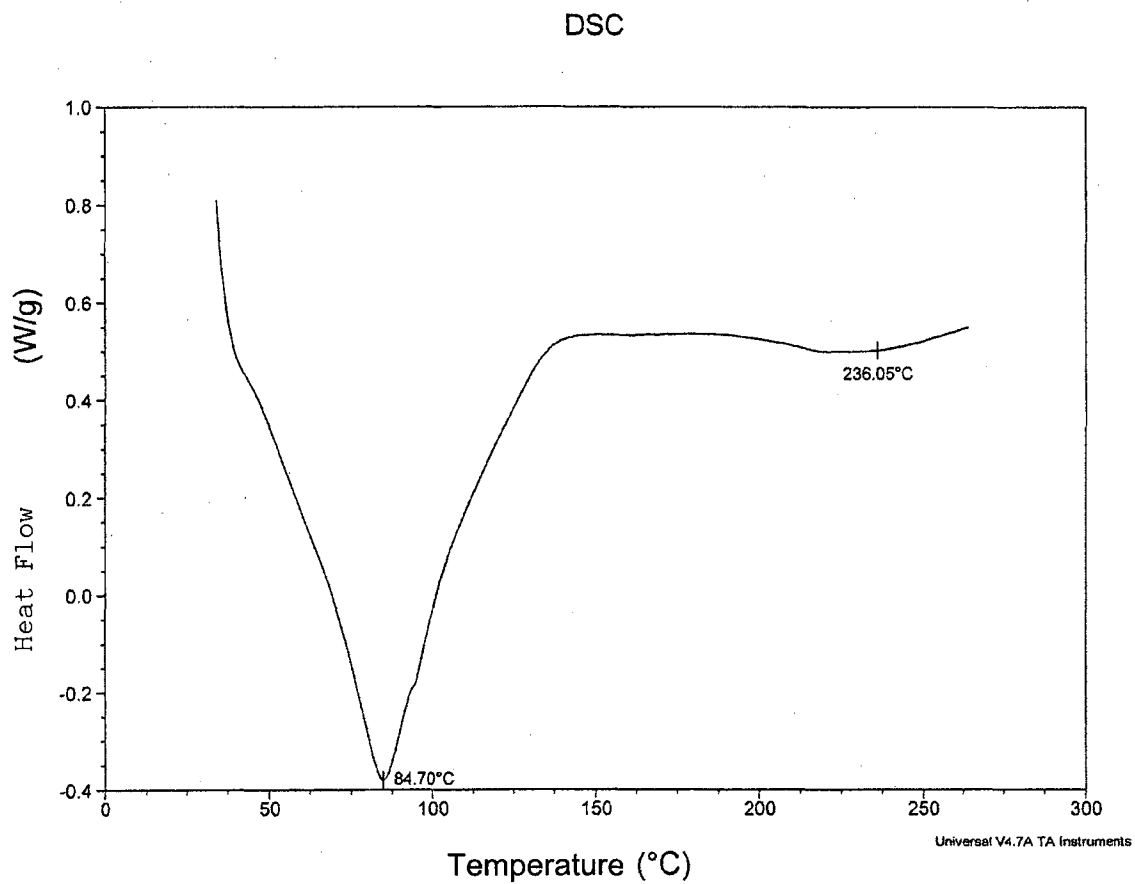
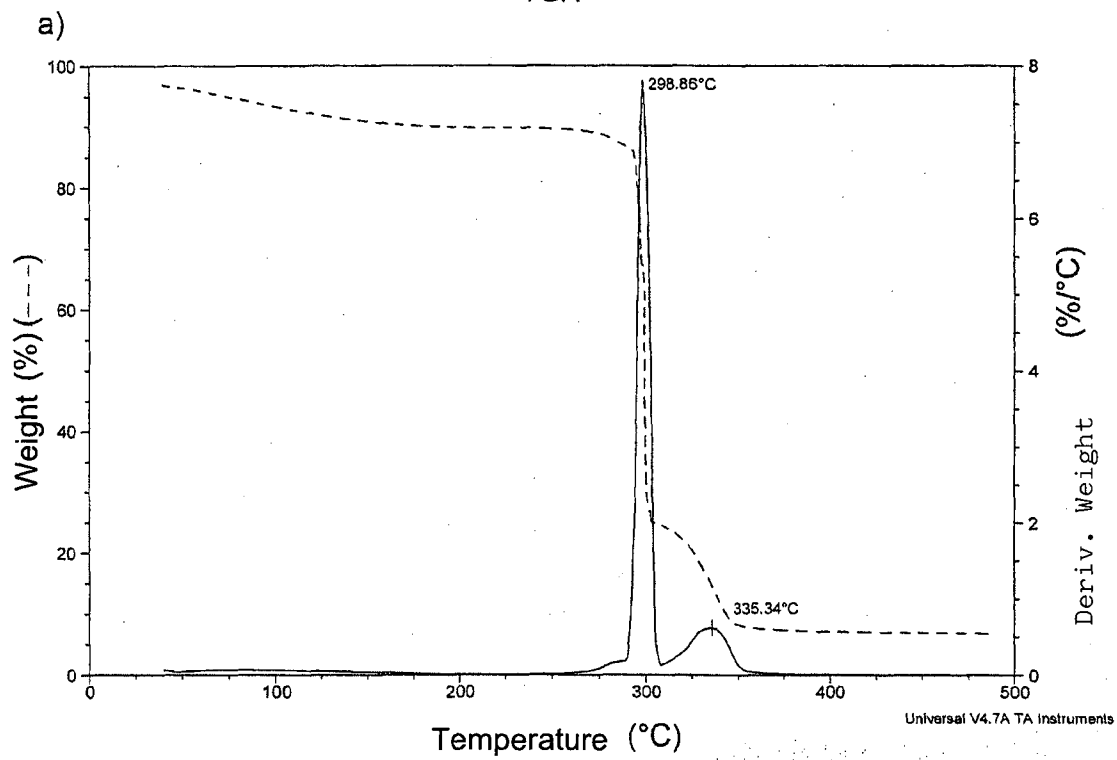


FIG. 4

5 / 13

TGA



TGA

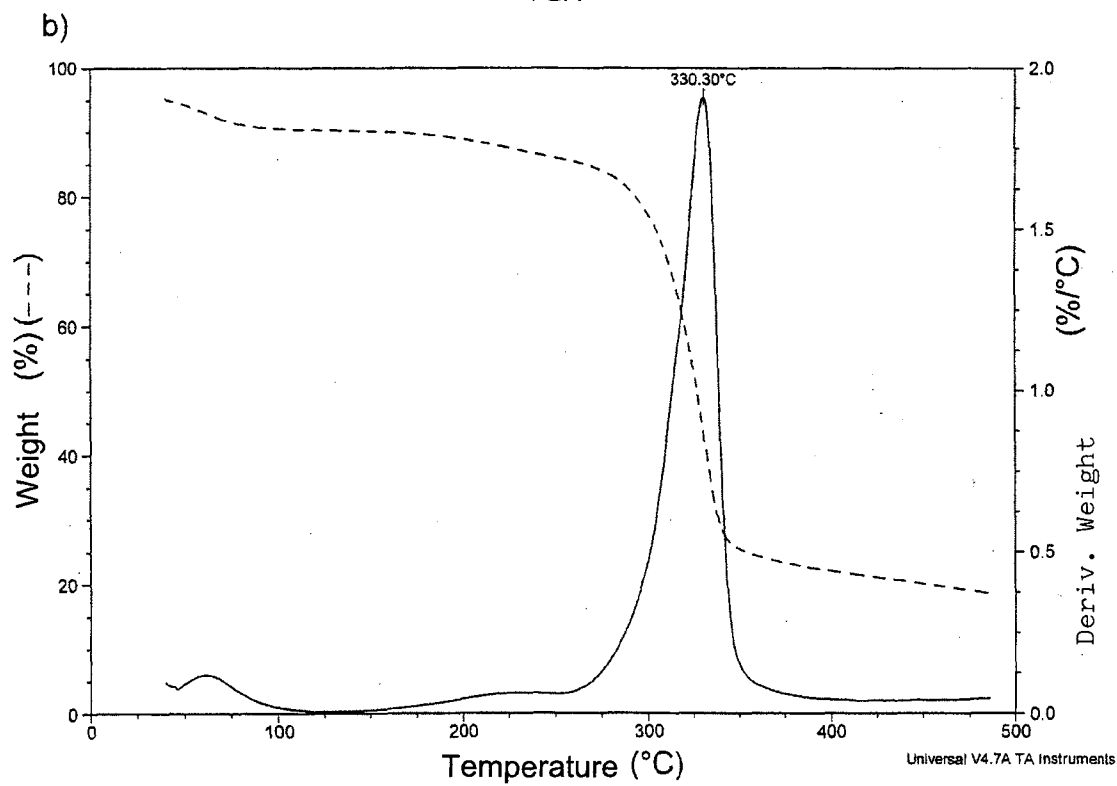


FIG. 5

6 / 13

TGA

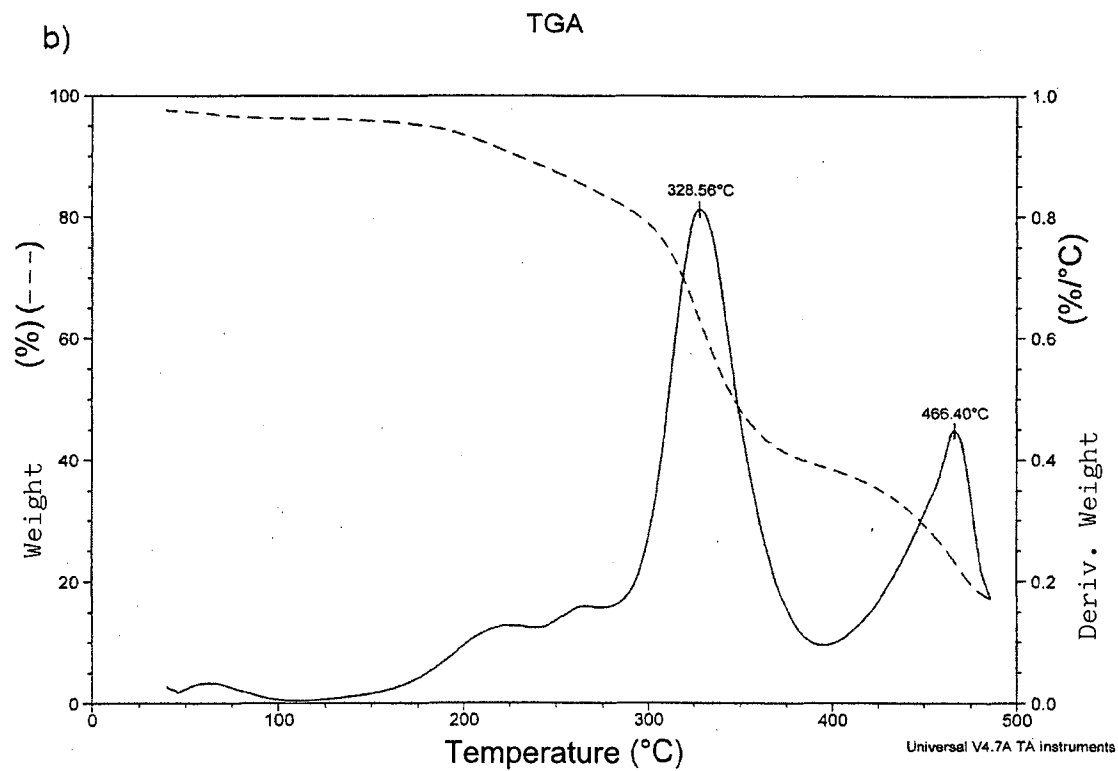
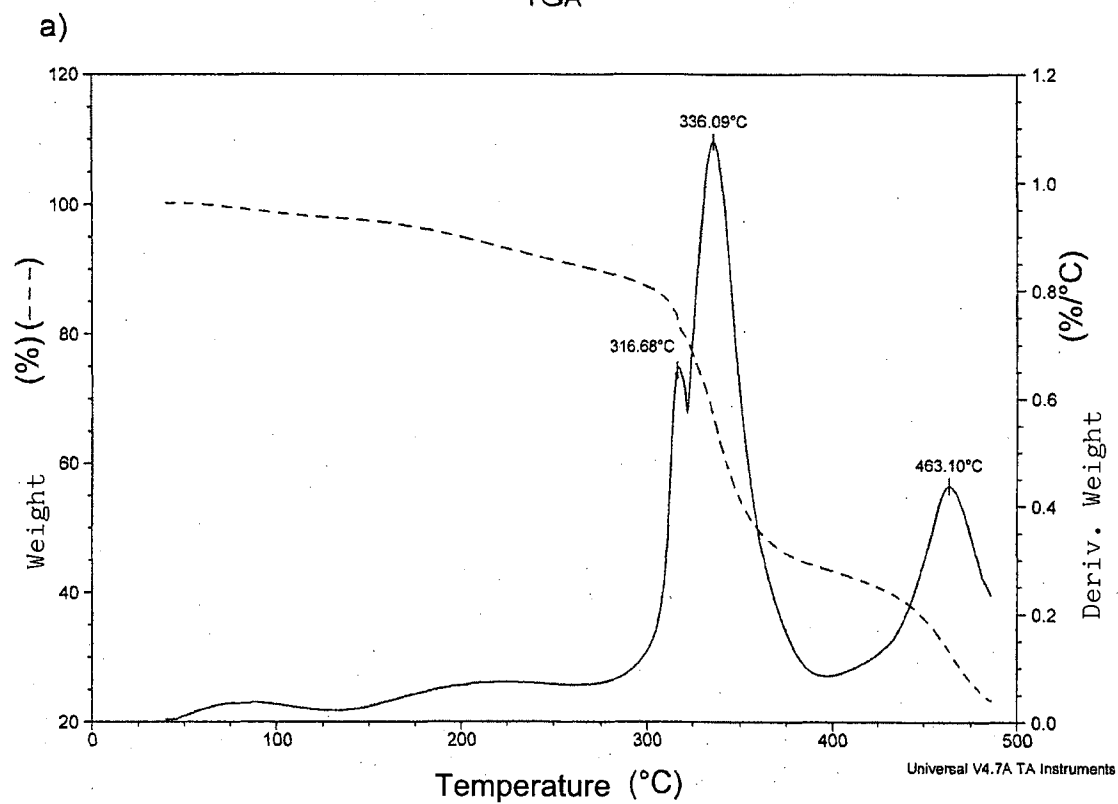


FIG. 6

7 / 13

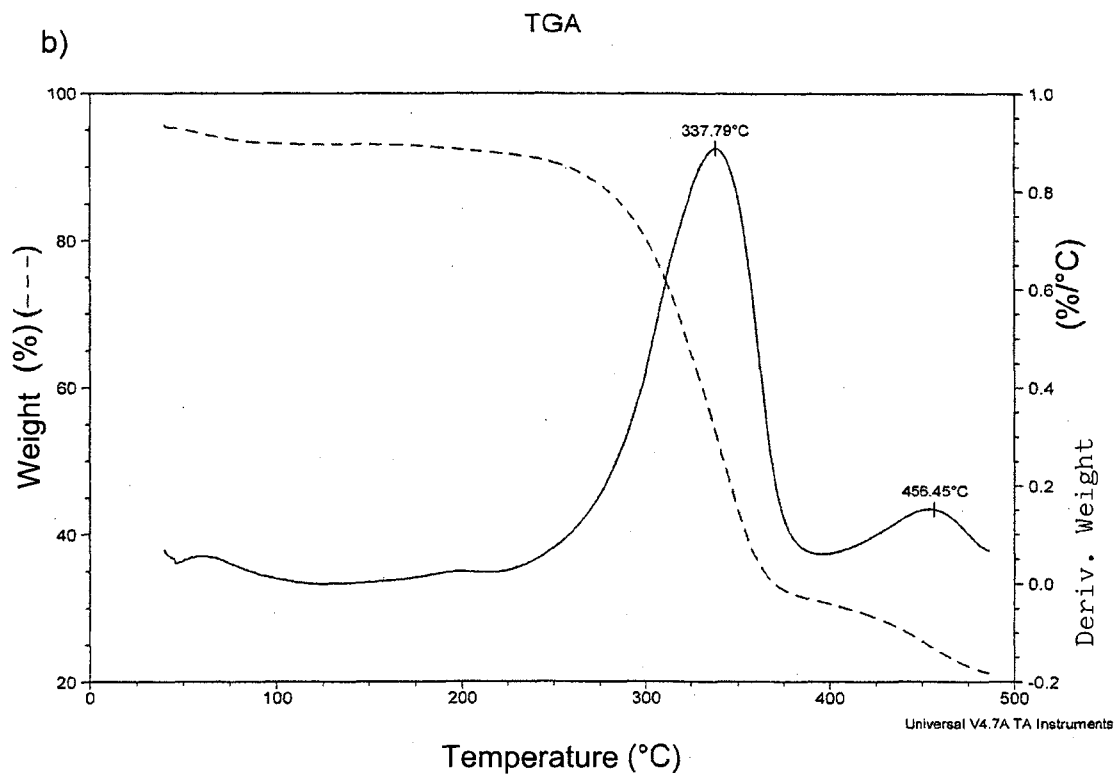
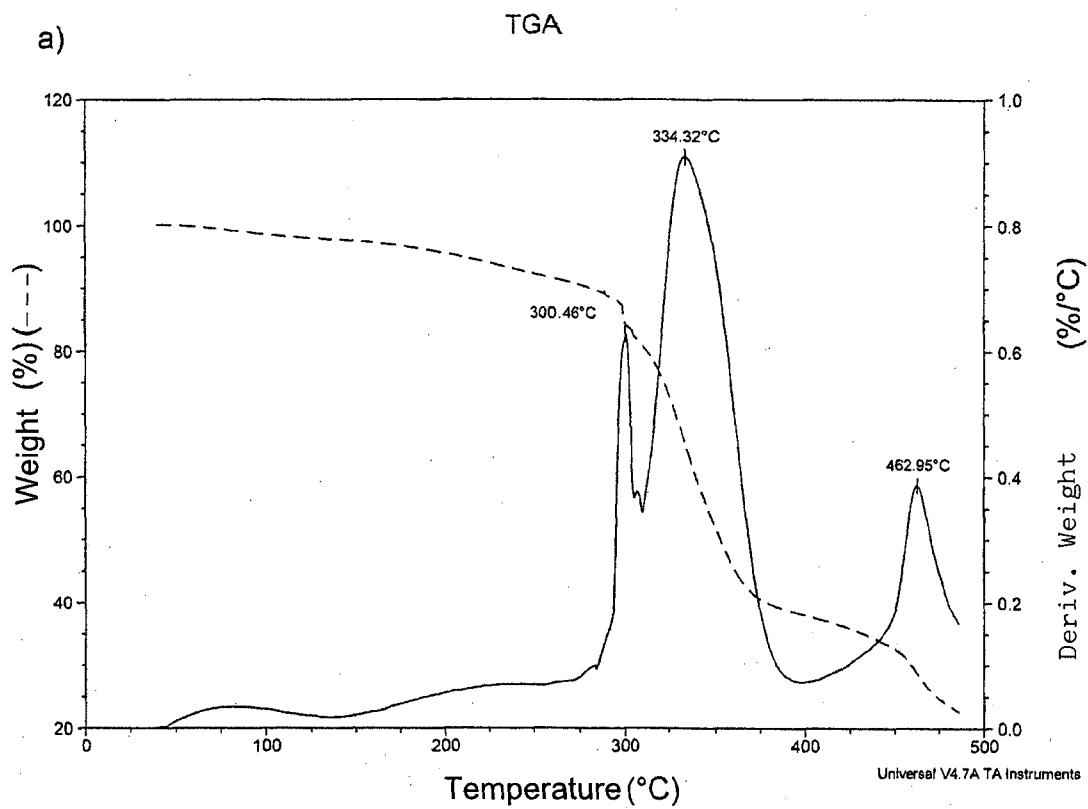


FIG. 7

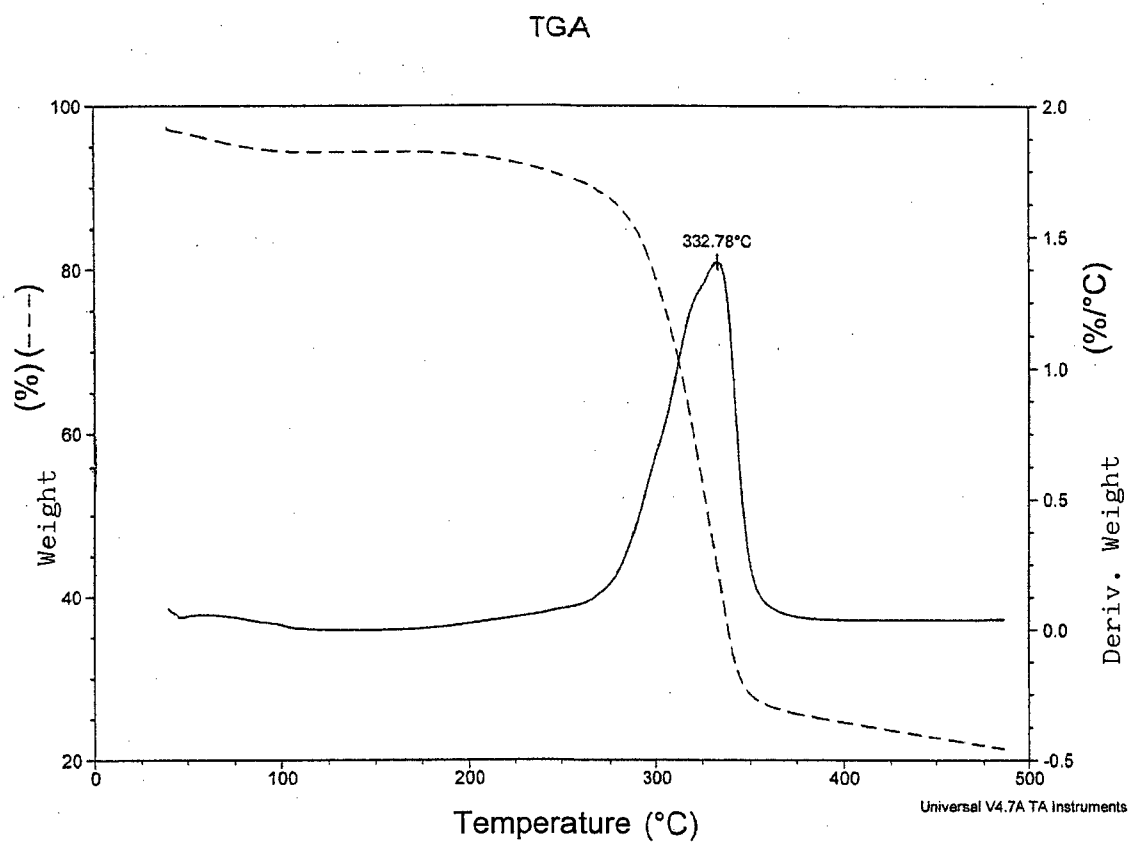


FIG. 8

9 / 13

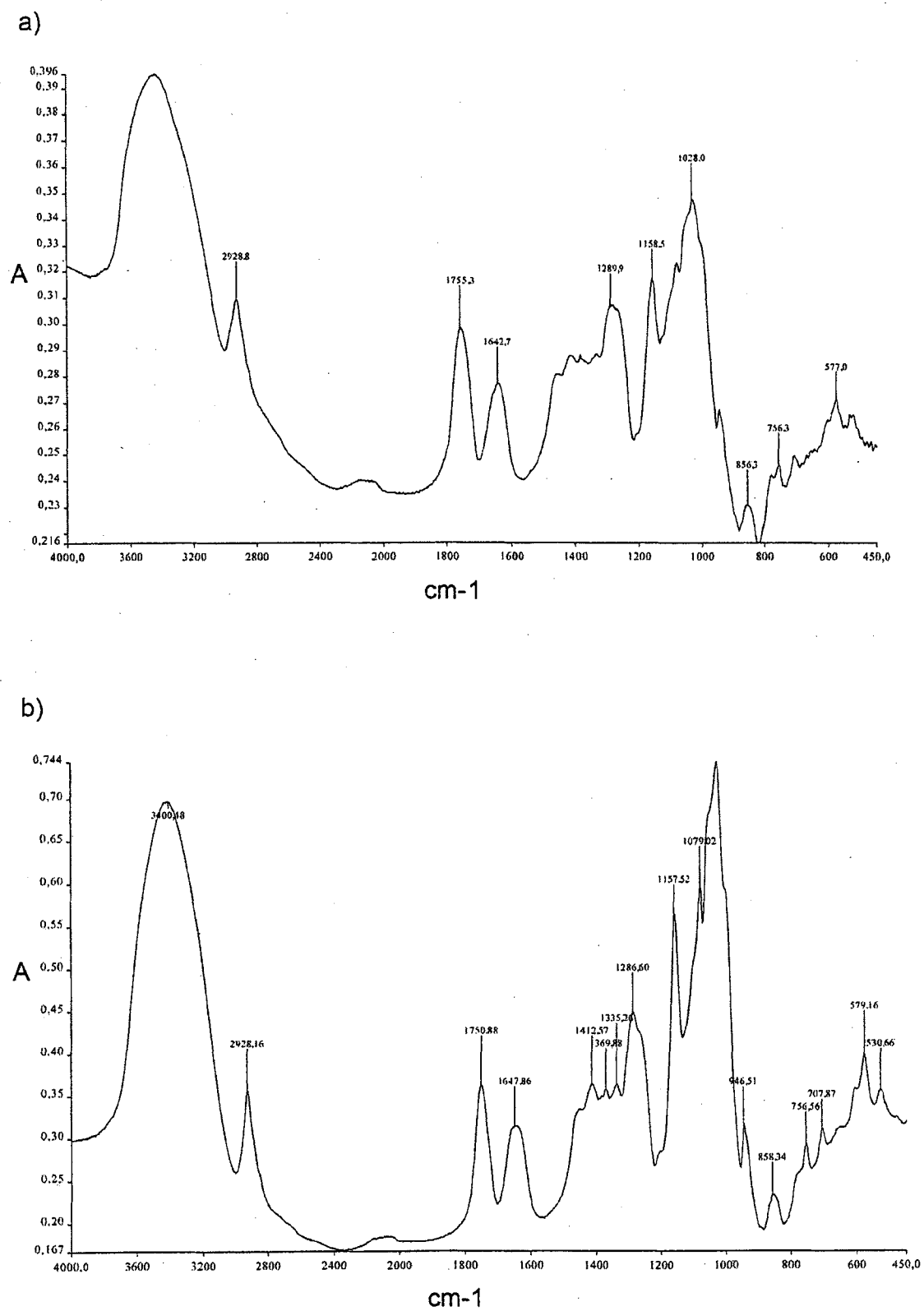


FIG. 9

10 / 13

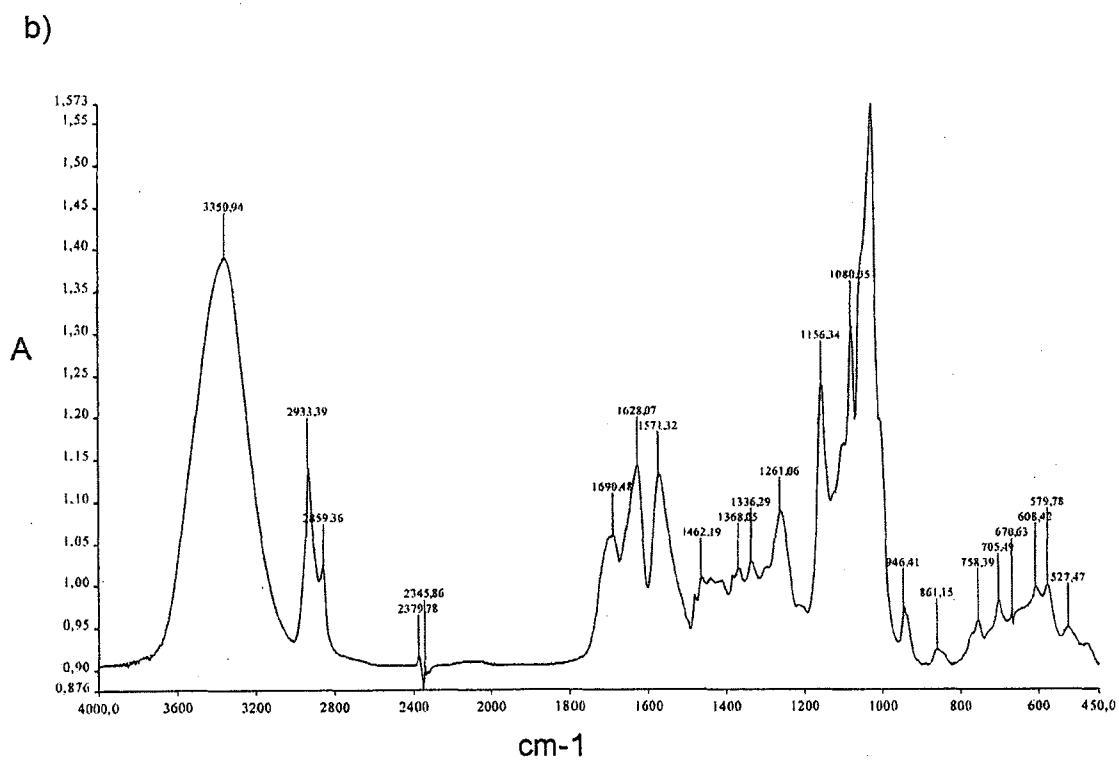
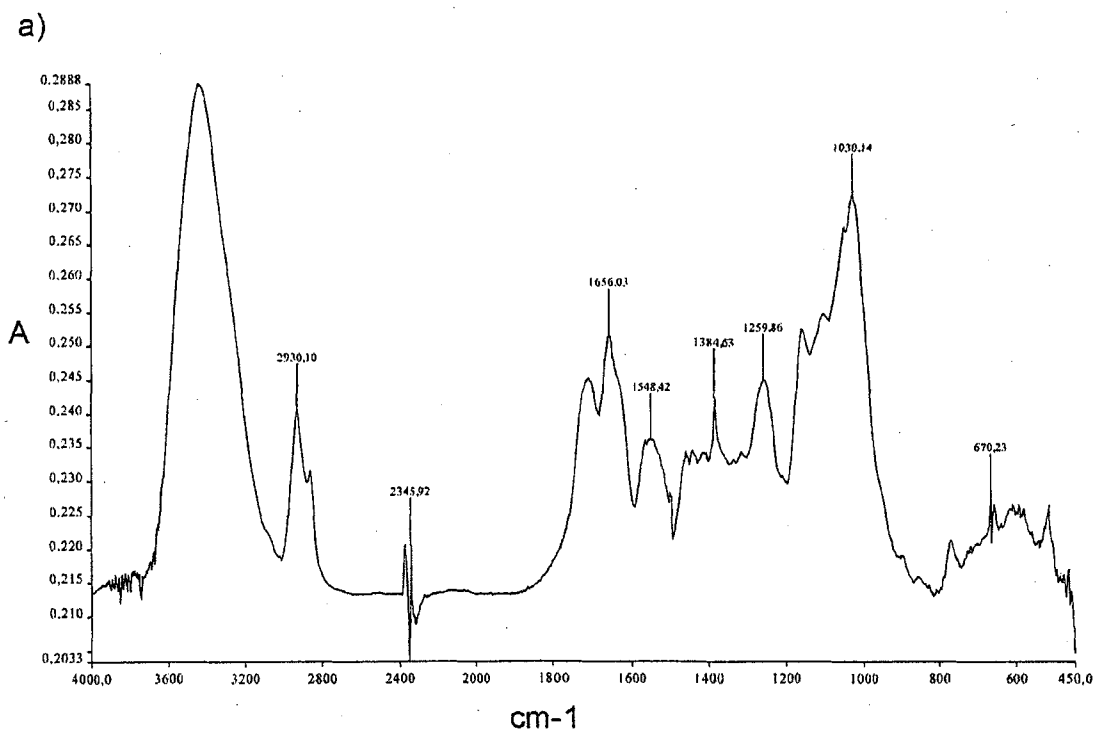


FIG. 10

11 / 13

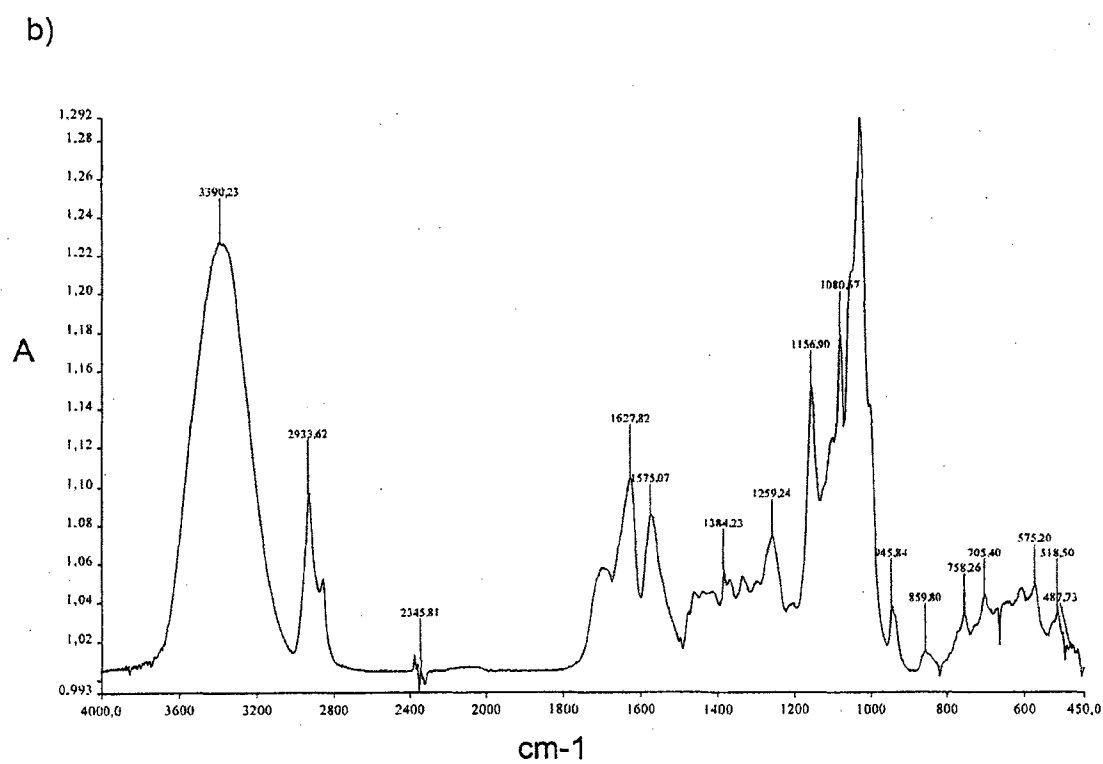
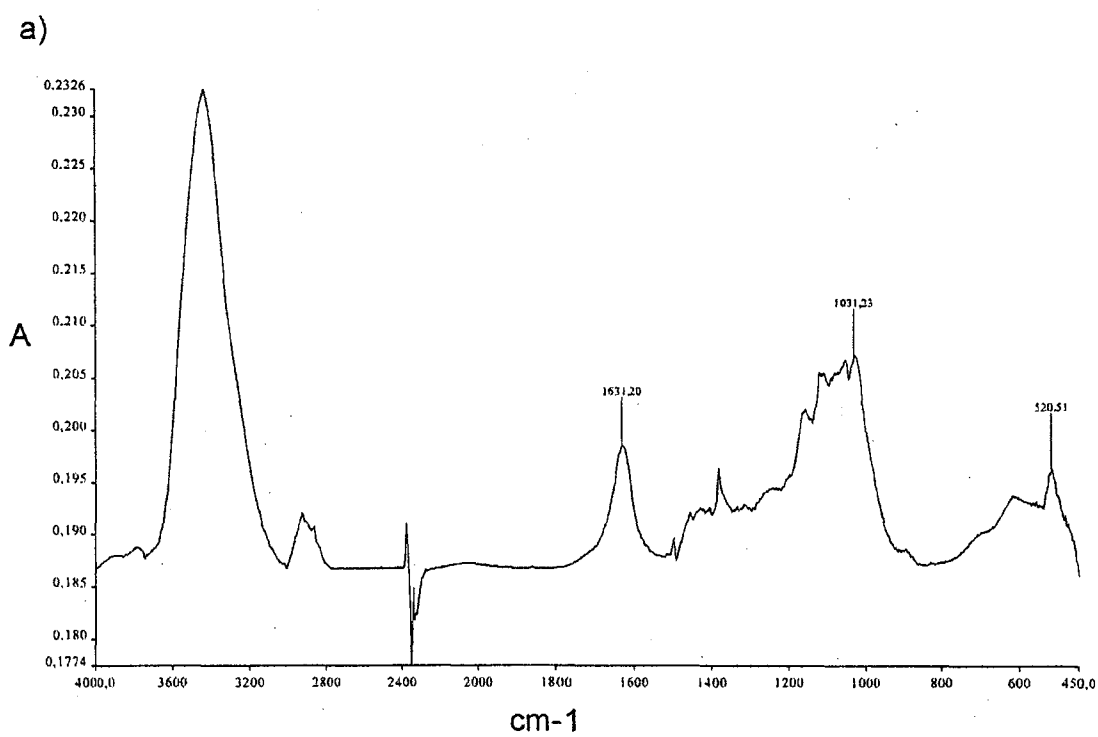


FIG. 11

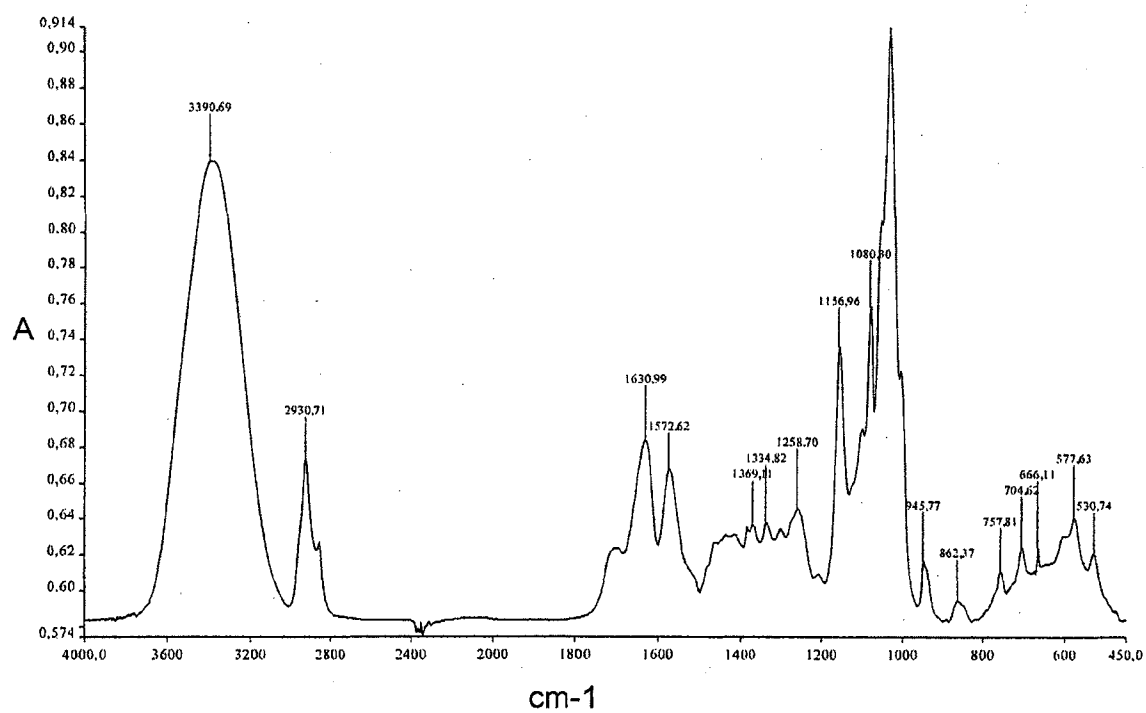


FIG. 12

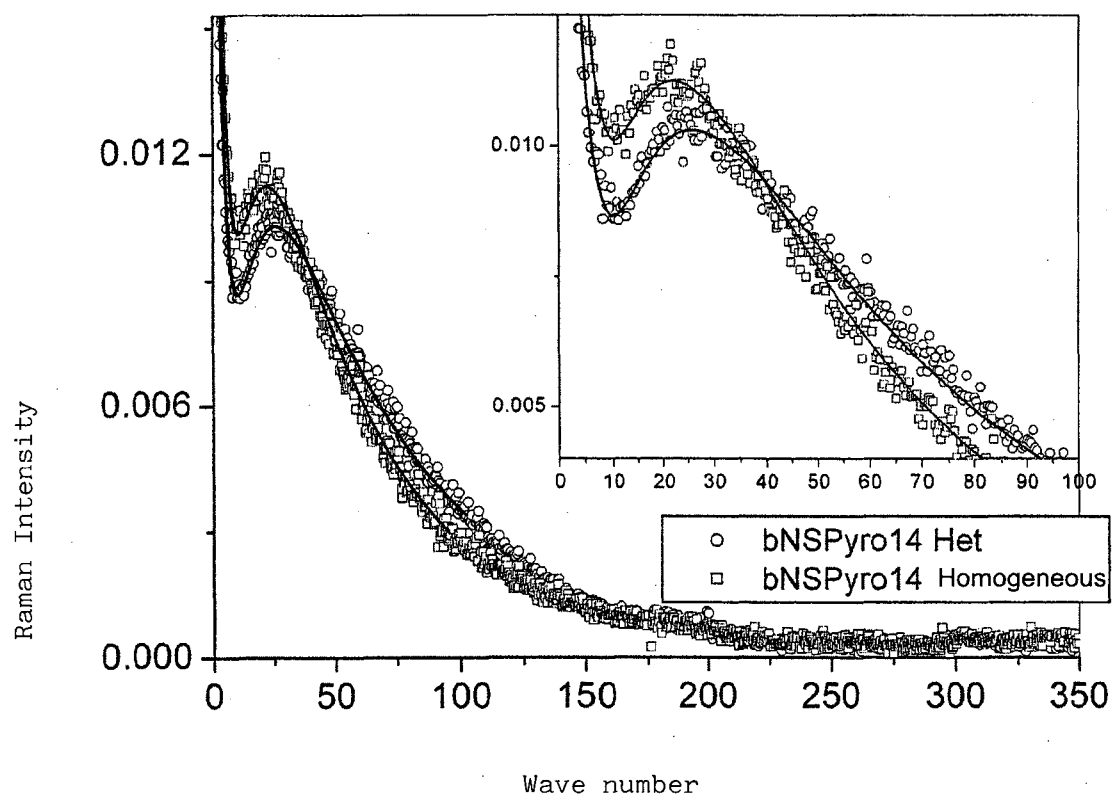


FIG. 13

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2012/052144

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C08B37/00  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, COMPENDEX, INSPEC, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                          | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | US 6 197 757 B1 (PERRIER ERIC [FR] ET AL)<br>6 March 2001 (2001-03-06)                                                      | 1-9,12                |
| Y         | claims; examples<br>-----                                                                                                   | 10,11,13              |
| X         | WO 03/085002 A1 (SEA MARCONI TECHNOLOGIES<br>DI W [IT]; TROTTA FRANCESCO [IT]; TUMIATTI<br>WA) 16 October 2003 (2003-10-16) | 12,13                 |
| Y         | cited in the application<br>examples 1-4<br>-----                                                                           | 10,11,13              |
| X         | WO 98/22197 A1 (UNIV CALIFORNIA [US]; MA<br>MIN [US]; LI DEQUAN [US])<br>28 May 1998 (1998-05-28)                           | 12,13                 |
| Y         | examples 1,2<br>-----                                                                                                       | 10,11,13              |

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 August 2012

Date of mailing of the international search report

10/09/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Vaccaro, Eleonora

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/052144

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date         |
|-------------------------------------------|---------------------|----------------------------|-----------------------------|
| US 6197757                                | B1                  | 06-03-2001                 | DE 19932216 A1 27-01-2000   |
|                                           |                     |                            | ES 2155793 A1 16-05-2001    |
|                                           |                     |                            | FR 2780901 A1 14-01-2000    |
|                                           |                     |                            | IT T0990599 A1 10-01-2000   |
|                                           |                     |                            | JP 3437797 B2 18-08-2003    |
|                                           |                     |                            | JP 2000038402 A 08-02-2000  |
|                                           |                     |                            | KR 20000011579 A 25-02-2000 |
|                                           |                     |                            | NL 1012517 C2 11-01-2000    |
|                                           |                     |                            | US 6197757 B1 06-03-2001    |
| -----                                     |                     |                            | -----                       |
| WO 03085002                               | A1                  | 16-10-2003                 | AU 2002304737 A1 20-10-2003 |
|                                           |                     |                            | CA 2481832 A1 16-10-2003    |
|                                           |                     |                            | EP 1492822 A1 05-01-2005    |
|                                           |                     |                            | JP 2005524724 A 18-08-2005  |
|                                           |                     |                            | US 2005154198 A1 14-07-2005 |
|                                           |                     |                            | WO 03085002 A1 16-10-2003   |
| -----                                     |                     |                            | -----                       |
| WO 9822197                                | A1                  | 28-05-1998                 | AU 7299198 A 10-06-1998     |
|                                           |                     |                            | CN 1238709 A 15-12-1999     |
|                                           |                     |                            | EP 0939667 A1 08-09-1999    |
|                                           |                     |                            | JP 2001504879 A 10-04-2001  |
|                                           |                     |                            | KR 20000057206 A 15-09-2000 |
|                                           |                     |                            | WO 9822197 A1 28-05-1998    |
| -----                                     |                     |                            | -----                       |