SOLID SUPPORT

The present invention relates to a solid support comprising a polymer, a method of preparing a support and the use of the support in solid phase processes. The support is useful in a wide range of physical and chemical processes where interaction with a substrate is required for example solid phase organic synthesis, solid phase extraction, solid phase reagents, immobilisation of species, cell culture, catalysis, chromatography and in medical diagnostics.

Solid support materials useful in solid phase synthetic processes are known. A wide range of physical and chemical processes employ solid support materials including by way of example synthesis of organic molecules, in particular peptides and oligonucleotides, immobilization of species, support in catalysis, ion exchange, extraction of species from a material and chromatography.

Synthesis of an organic molecule in multiple-stages typically involves numerous isolation steps to separate intermediates, produced at each stage, before progressing to the subsequent stage in which the intermediates are utilised as feedstocks. These processes may be time-consuming, expensive and may be inefficient as regards yield. The intermediates often require purification to remove excess reagents and reaction by-products and procedures such as precipitation, filtration, bi-phase solvent extraction, solid phase extraction, crystallization and chromatography may be employed.

Solid phase synthesis offers some advantages over solution phase synthesis. For example, isolation procedures used in solution phase synthesis may to some extent be avoided by reversibly attaching the target molecule to a solid support. Excess reagents and some of the side-products may be removed by filtration and washing of the solid support. The target molecule may be recovered in high or even essentially quantitative yield in some processes. Recovering high yields in solution phase synthesis is often difficult. In addition, the time required to perform operations on a solid support is typically much less than that required to carry out a comparable stage in a solution phase synthesis.

Immobilization of species in a range of processes is also known. For example, polymer supports are commonly used for the immobilization of catalysts for use in traditional organic chemistry including chemo and bio catalysis. Immobilized enzymes may be employed in a wide range of

CONFIRMATION COPY

processes including organic chemical reactions or for chiral resolution, for example the use of immobilized Penicillin amidase for the resolution of secondary alcohols (E. Baldaro et al. Tet. Asym. 4, 1031, (1993) and immobilized Penicillin G amidase is also used for the hydrolysis of Benzylpenicillin in the manufacture of Amoxicillin (Carleysmith, S. W. and Lilly, M.D.. Biotechnol. Bioeng., 21, 1057-73, 1979).

Solid supports, for example polymer beads may also used to immobilize biological macromolecules for medical and diagnostic applications. Examples of this application include immobilization of proteins, monoclonal antibodies and polyclonal antibodies. Cell culture is commonly carried out on solid supports with specific surface characteristics and morphology. Immobilized enzymes may be employed as sensors to generate a signal, for example the detection of glucose by the glucose oxidase/peroxidase coupled enzyme system, in which the presence of glucose generates hydrogen peroxide which in turn is the substrate for peroxidase for the oxidation of a wide variety of substrates to provide a coloured, fluorescent or luminescent signal.

A variety of fluors whose fluorescence is sensitive to specific cations or anions may be immobilized on polymers beads to indicate concentrations of specific ions including hydrogen ions for pH measurement.

Polymeric particles are often used in chromatography where the solid supports are termed stationary phases. In certain modes of chromatography the cost of stationary phases may be high and restrict usage. The physical nature of the stationary phase may not be adequate in some applications to gain full effectiveness. For instance, soft polymers are often used for affinity, ion-exchange and gel permeation chromatography but may not be effectively used at high flow rates because of the deformable nature of the particles. Rigid macroporous polymers used in other modes of chromatography may often be mechanically friable and subsequently suffer from a short lifetime.

The application of solid supports or stationary phases in chromatographic separations is very extensive including for example complex high-technology separations used in the pharmaceutical and biotechnology industry for the purification of high value products using preparative chromatography and large-scale separations employed in the mining industry. A large portion of the world's Palladium, a critical component in catalytic converters and other

industrial processes, may be refined using immobilized crown ethers (Traczyk, F.P.; Bruening, R.L.; Izatt, N.E. "The Application of Molecular Recognition Technology (MRT) for Removal and Recovery of Metal Ions from Aqueous Solutions"; In Fortschritte in der Hydrometallurgie; 1998, Vorträge beim 34. Metallurgischen Seminar des Fachausschusses fuer Metallurgische Aus-und Weiterbildung der GDMB; 18-20 November 1998; Goslar).

The use of polymeric particles in solid phase extraction and in the preparation of solid phase reagents is also known in the chemical, pharmaceutical and biotechnology industry.

Known solid phase supports generally comprise polymer particles of a particular size and physical nature to suit the application. For ease of use these polymer particles are often spherical and have a defined particle size distribution. The spherical nature of the particles improves the flow and filtration characteristics of the polymer. Although the uses of solid supports have operational advantages there are disadvantages to the solid phase approach. For example, commercially available supports commonly used for solid phase synthesis of peptides and oligonucleotides may be expensive. Polymeric particles may typically be made by a dispersion or emulsion polymerization process in which a solution of monomers is dispersed in an immiscible solvent (continuous phase) prior to initiation of the polymerization. The polymer particles formed are typically then filtered, washed and classified. These processes are disadvantageous in some respects including monomer loss to the continuous phase, generation of a range of particle sizes and generation of fine particles during the polymerization. Loss of monomers to the continuous phase may be inefficient in terms of both raw material and environmental costs. Classification of the polymer particles to isolate the particle size required for a particular application may be a laborious and complex process, typically involving sieving and (or) air classification which may lead to losses in yield. 'Fines' particles are usually produced. These fines may be problematic in isolation of the polymer beads and may require additional processing, for example settling and decantation for their removal..

In addition to undesirable costs of manufacture and wastage during preparation certain disadvantages may arise with the physical properties of the known polymeric particles. Microporous polymers and macroporous polymers are generally used and their manufacture may be expensive and complex.

Microporous polymers have a relatively low level of cross-linker which allows the polymer particles to solvate and consequently swell in suitable solvents. However, microporous polymeric particles are generally soft and generally not suitable for use at a high flow rate in a packed column bed. In addition, the soft particles may be compressed undesirably and cause fouling, for example during filtration often leading to compressive intrusion into the sinter or mesh being used.

Macroporous polymers have a high level of cross-linker in the polymer matrix and contain large pores. These polymer particles are generally rigid and have good flow characteristics in packed columns. Rigid macroporous and macroreticular particles are more suited to high flow rates in packed column beds. However, due to the rigid nature the particles may be fragile and fail structurally under physical stress.

Problems associated with the costs of production, wastage, physical integrity of the support and poor product performance may be ameliorated by providing a preformed solid bead with a hole which effectively is used as a container for the polymer support.

In a first aspect the invention provides a solid support comprising polymer-impregnated beads wherein the bead has a hole(s) in or preferably through the bead and a polymer disposed within the hole(s).

The term "polymer" as employed herein includes inorganic polymers, of which silica would be one example and organic polymers of which polystyrene would be one example.

Advantageously, the beads are rigid and mechanically robust and may be utilized at high flow rates in packed column beds. The beads also filter readily in batch-wise operations allowing for rapid processing.

The bead suitably comprises an inert material. Suitably the inert material is selected from glass, ceramic, polymer, metal, for example steel, wood and other natural material. In the preferred embodiment the bead is preformed from glass. Glass seed beads commonly used in the jewellery industry are particularly useful for this application. They are manufactured on a large scale and are not costly and provide a support of useful dimensions and structural integrity.

Suitably, the beads are spherical, near to spherical or ellipsoidal. The spherical nature of the bead is advantageous in many applications and facilitates for example, packing in columns and improved flow characteristics over a bed during filtration. However, irregular, oval and other shapes of bead may be used.

In another embodiment short pieces of tubing may be used.

The invention may employ beads of any size but the larger the polymer plug in the hole in the bead, the less efficient the diffusion of a material into the polymer. Preferably the hole in the bead has a diameter of less than 2mm, particularly less than 1mm and more preferably 0.01 to 0.75mm, 0.01 to 0.5mm and especially 0.05 to 0.5mm in the dimension perpendicular to the axis of the hole through the bead. The smaller the bead, the better the diffusion within the polymer where a material is being bound or absorbed and also the closer the packing between beads.

Suitably the bead is not more than 2mm, preferably not more than 1.5mm, desirably not more than 1.2 mm in diameter. Preferably the bead is at least 0.01mm and desirably at least 0.05mm in diameter. In a preferred embodiment, the bead is from 0.1 to 1.2mm, more preferably 0.1 to 1.0 and desirably 0.3 to 0.8mm in diameter. In general, it is preferred for the bead to be as small a diameter as possible from a functional perspective but this is to be balanced with the economics of producing a smaller bead. Optimally, the bead has a diameter of 0.4 to 0.7mm.

The present invention is distinguished from porous supports in that the bead preferably comprises a single hole and furthermore the hole is of dimensions greater than those typically associated with a porous material. Suitably, the solid support comprises a single plug or mass of polymer within the hole. The bead may be porous but it is necessary to also have a hole in addition to any pores which may be present. The hole is suitably dumb-bell shaped or tumescent (broader in the middle) which assist in the physical retention of the polymer in the hole or may be cylindrical.

In a preferred embodiment, the hole of the bead is lined with the polymer such that a substrate may pass though the bead with the polymer lining. This provides a more accessible surface area for contact and may improve flow of the substrate through the bead.

Suitable beads may be obtained commercially, for example from Miyuki beads and from Toho beads or may be made by cutting capillary tubing into short pieces then heating these to a temperature just below the point at which the glass melts. At this temperature the small pieces of capillary tubing shrink back to form beads.

Typically 11/0 and 15/0 size glass seed beads are readily available. A 15/0 size bead for example, measures approximately 1.15mm in the direction of the hole and is approximately 1.55mm wide.

Suitably the polymer is formed in the hole of the bead. The polymer may be bound covalently to the bead directly or indirectly. Where the bead is made of a material having active sites, for example wood provides hydroxyl groups in the cellulose material, the polymer may be bound directly. Where the bead is made of a more inert material, for example glass, it may be desirable to treat the bead to provide active sites to which the polymer may bind. Where the bead comprises glass it is suitably treated with an etching agent, preferably a fluoride etching solution, for example hydrogen fluoride solution and ammonium bifluoride solution to provide a surface suitable for reaction with a derivative.

Desirably, the bead is derivatised to provide active sites for reaction with a polymer. Known materials and processes for derivatizing a glass surface may be employed. In an especially preferred embodiment, the derivative comprises a silane and comprises an active site to bind to the polymer. Preferably the active site is a vinyl group.

The silane group is suitably of formula $-(O)_nSi[(CH_2)_p[Z]_qCR=CR_2]_{(4-n)}$ in which n is from 1 to 3, p is from 0 to 6 wherein R is independently H or alkyl, q is 0 or 1 and Z is a divalent linking group.

Preferably Z is of formula $-(CH2]_r$ NRC(O)- wherein r is from 1 to 6.

In a particularly preferred embodiment, the support comprises a glass bead having a silane group bound to it wherein the silane group is selected from $-O_3SiCH=CH_2$ and $-O_3Si(CH_2)_3NHCOCH=CH_2$. Preferably the $-O_3SiCH=CH_2$ group is derived from triethoxyvinyl silane. Preferably the $-O_3Si(CH_2)_3NHCOCH=CH_2$ group is derived from aminopropyl trimethoxy silane which is reacted with the glass and the amine group is then reacted with acryloyl chloride.

The polymer may be any suitable material according to the desired application. In a preferred embodiment, the polymer is an organic polymer and is selected from a polymer resin, polyacryl amide, polystyrene, cellulose, polydimethylacrylamide, polymethylmethacrylate, polyurea, polyacryloylmorpholine and polybetahydroxy ester, Polyhipe, polyalkylene glycol, for example polyethylene glycol and polypropylene glycol and polysaccharide, for example agarose.

The polymer may be an inorganic polymer and is suitably selected from alumina, silica and other metal oxides.

The polymer may be reacted further to provide particular functionality for a given application. Suitably, the polymer is reacted with a compound having at least two functional groups, one for reacting with the polymer and the other to provide free functionality for use in the desired application. In a preferred embodiment, the polymer, for example polydimethylacrylamide and polyacryloylmorpholine copolymers with N-acryloyl sarcosine methyl ester, is reacted with a diamine compound, for example ethylene diamine. Amine functionalised supports for example are suitable for use in peptide synthesis, oligonucleotide synthesis and solid phase organic chemistry.

An amine functionalised support may be further functionalised, for example by conversion to a carboxylic acid using succinic acid as desired. By way of example, an amine functionalised support may be treated with N-hydroxysuccinimide and 1-Ethyl-3-[3-dimethylaminopropyl]carbodimide hydrochloride in preparation for immobilising a protein, for example protein A.

In a further embodiment, the support comprises the bead and a polymer and an additional material, within the hole of the bead. An example of an additional material includes an inert material for example a chemically inert material having a high absorbency. An especially preferred inert material is Polyhipe. Polyhipe is porous and highly absorbent. This material is particularly preferred for applications in which a material is to be absorbed by the support.

A solid support according to the invention may also comprise a functional material supported by the polymer. Examples of suitable functional materials include a catalyst, an initiator species for

organic synthesis, for example for peptide synthesis, a pharmaceutical active, an agrochemical active, a macromolecule, an enzyme, a nucleic acid sequence and a protein.

The invention is particularly useful in supporting precious metal catalysts, for example palladium catalysts. A particular advantageous example is palladium acetate. In a preferred embodiment, palladium acetate is supported on polyurea.

The solid support of the invention may be produced by an efficient and relatively simple process. The invention provides in a second aspect a method for producing a solid support material comprising the steps of providing a bead having a hole therethrough contacting the bead with a monomer or solution of a monomer, effecting polymerisation of the monomer so as to form a polymer and optionally subjecting the bead comprising the polymer to further treatment to remove polymer from the surface of the bead.

Suitably the polymerisation is initiated by processes known to those skilled in the art. For example, beads containing a monomer or a solution of the monomer is added to a solvent which is immiscible with the monomer solvent and heated to effect polymerisation. Where the monomer solution is aqueous, the solvent is for example kerosene.

The polymer may be dried or cured by conventional means, for example heating and ultra violet irradiation.

Preferably, once the polymer is formed the beads comprising the polymer are subjected to physical abrasion, for example in a roller mill, so as to remove polymer from the external surface of the beads leaving polymer located in the hole(s) of the beads.

Suitably, as the beads are exposed to the constituent monomers or a solution of the constituent monomers of the intended polymer support, capillary action retains this solution in the hole(s) and the polymer is formed by known initiation processes known to those skilled in the art of polymerization.

Optionally, the method of producing a solid support material comprises the step of treating the surface of the bead to provide active sites prior to contacting the bead with the monomer or the solution of the monomer.

Glass beads used in the jewellery and textile trade are commonly known as seed beads. The use of seed beads has a particular advantage in that the polymer plug is suitably dumbbell shaped or tumescent and as such the polymer will be physically restrained due to its shape. The polymer plug is itself suitably immobilized within the hole of the bead due to the shape.

If preferred the polymer plug may be covalently linked to the rigid bead either during the polymerization or subsequent to the polymerization. Alternatively, one or more of the constituent monomers can be covalently linked to the bead surface prior to initiation of the polymerization.

When the polymer is restrained in the hole due to physical constraints and is covalently bonded to the surface of the bead, the polymer-bead combination is particularly robust.
The solid support of the invention may be used in any chemical or physical process in which a solid support is used.

In another embodiment, the invention provides a solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and the wall of the hole comprises a layer of polymer so as to provide a ring of polymer in the hole of the bead.

A support having a lining or ring of polymer rather than a plug may be produced by the same process as those having a plug of polymer but by using a more dilute polymer solution. By tailoring the concentration of the polymer solution, the thickness of the lining may be controlled. In a preferred embodiment, the lining is at least 1 micron and desirably at least 5 microns thick and may be as thick as the size of the hole in the bead allows to ensure there is still a ring of polymer rather than a solid plug. Suitably, the lining is up to 100 microns, preferably up to 50 microns and more preferably up to 20 microns thick. Especially preferred ranges are 1 to 100 microns, 5 to 100 microns, and 5 to 50 microns thick.

A support having a lining of polymer, for example from 1 to 20 microns thick, is especially advantageous in cell culture and medical diagnostics applications

The solid support is particularly useful for solid phase synthesis of an organic species, particularly macromolecules. In a preferred embodiment the solid support may be employed in the synthesis of peptides, oligonucleotides or oligosaccharides. Polydimethylacrylamide as the polymer support is particularly advantageous in synthesis of peptides.

The solid support of the invention is also useful for solid phase extraction to remove species from a liquor which is contacted with the support, whether in batch form or as a flow over the support, for example ion extraction and ion exchange.

The solid support of the invention is especially useful in immobilising species including solid phase reagents, metal and other catalysts, bio-catalysts, enzymes, proteins, antibodies including polyclonal and monoclonal antibodies, whole cells and polymers. The invention is particularly advantageous in supporting enzymes, for example horse radish peroxidase and glucose oxidase, particularly in combination with polydimethylacrylamide and other similar hydrophilic polymers.

The present invention is especially useful in affinity chromatography, for example in the immobilisation of affinity ligands for example Protein A. Affinity chromatography is used predominantly for the separation of biological products for example biopharmaceuticals. The affinity ligand is suitably immobilised on a stationary phase. This ligand has a particular affinity for a component of a biological mixture to be contacted with the support. The affinity may be based on any form of interaction for example a specific biological interaction such as seen with an enzyme and substrate, a receptor and ligand and an antigen and antibody.

In a preferred embodiment the affinity ligand comprises Protein A and is used to interact with immunoglobulins. Protein A binds to the Fc region of several immunoglobulin antibodies and many biopharmaceuticals are based on immunoglobulins.

In a further embodiment the invention provides a solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and a polymer disposed within the hole and the polymer comprises immobilised Protein A.

In the art, stationary phases having large molecules, for example protein A are available in two forms where the support is either a macroporous resin or a softer support with lower levels of cross-linking. The macroporous resins suffer from low surface area and subsequently low loading. The softer supports are manufactured with enough cross-linker to provide enough rigidity for use in low to medium pressure chromatography. However, these are still relatively highly cross-linked and cannot be readily penetrated by biological macromolecules. As a result

the bands observed in a chromatographic separation are relatively broad and not all of the immobilised ligand is accessible.

Advantageously, the present invention allows for the immobilisation of suitable polymers with extremely low levels of cross-linking consequently providing improved diffusion and access to all active sites in the polymer.

In a further preferred embodiment, the invention provides a solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and the wall of the hole comprises a layer of polymer so as to provide a ring of polymer in the hole of the bead and the polymer comprises immobilised Protein A.

In a further embodiment, the solid support may be employed as a support in the field of cell culture particularly stem cell culture. Polyhydroxyesters either as blocks or coated plates are often used in the culture of stem cells. With these systems the cells are often difficult to recover and are often dislodged from the polymer surface by physical stress. In this system the physical stress on the cell-polymer interaction is reduced due to the caged environment, that is, the polymer is within the bead rather than on its outer surface, and additionally the polymer is provided in a more useable physical form in comparison to block polymers or coated plates.

The solid support may be employed in applications involving electro-conducting and light emitting polymers. The solid support containing light emitting polymers may be arranged on display panels.

The support of the invention may be used to immobilize species including antibodies, oligonucleotides, enzymes or fluors and may be positioned in an array, with each support assaying a different component of a solution. Beads having ligands covalently attached to polymers bound to the surface may be employed as 'wells'. Specific binding of a target ligand such as an antigen or complementary DNA or RNA sequence may then be detected using established methods.

The solid support of the present invention is useful in the preparation of a stationary phase for chromatographic separation, for example affinity chromatography, ion exchange

chromatography, reversed phase chromatography, normal phase chromatography, chiral chromatography and gel permeation chromatography..

In a further application, the solid support may be used as an absorbent. In this application, it is especially advantageous if the support contains an inert, absorbent material bound to the beads and to which the polymer is bound. Polyhipe is a particularly preferred inert material. The solid support may be used to absorb household spillages, for example tea, coffee and wine, or may be used in larger-scale applications for example, to absorb oil from spillages. The absorbent support may be used to absorb the spillage and then physically removed or, in the case of oil spillage in a body of water, effectively trap the oil and then sink to the bottom of the body of water.

The solid support of the invention may be used as a carrier to carry a compound which is to be released over a period of time, for example a pharmaceutical or agrochemical compound or composition. This use provides a means of tailoring a dosage regime of the compound according to the loading of the compound in the support. In the case of a pharmaceutical, this may be advantageous in assisting the correct dosage of an active, for example with continuous slow release rather than requiring a patient to take periodic large doses, for example in chemotherapy.

In a preferred embodiment the invention provides a solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and a polymer disposed within the hole and further comprising a pharmaceutical compound or composition.

The solid support of the present invention may be applied to any chemical biological or physical solid state process where polymer supports are presently employed.

The invention is particular useful in medical diagnostic tests such as immunoassays. Accordingly the invention further provides a medical diagnostic method for detecting the presence of a compound in a sample providing a solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and a polymer disposed within the hole and a functional material, such as an enzyme, for example horseradish peroxidase, supported by the polymer in the support for selectively reacting with or binding to the compound in the sample and contacting the sample with the solid support.

The beads may also be loaded or packed into a column and the hole and interstitial spaces filled with polymer to form a monolith. The invention further provides a solid support monolith comprising a plurality of solid support material beads according to the invention packed in a mass, for example a column arrangement, and optionally comprising a polymer in the interstitial spaces.

As desired, the interstitial spaces between the beads in a monolith could be filled with a different polymer to that held within the hole of the bead. In another embodiment the interstitial spaces between the beads in a monolith may be filled with a different component such as a cell culture nutrient for example. In this example the cells may be cultured on the polymer matrix inside the hole.

The polymer in the hole of the bead may be coloured for example using a dye to provide aesthetic or functional characteristics.

The invention also includes embodiments in which beads having a polymer plug or lining further comprise a smaller bead having a polymer plug or lining with in the hole of the larger bead. The polymer in the smaller bead may be the same or different to that in the larger bead.

Figures 1 to 4 each shows illustrative embodiments of the solid support of the invention in a plan view, a side view and a cross section. Figures 5 and 6 show etched glass beads for use in the invention. Figures 7 to 9 show photographs of the solid supports of the invention.

In Figure 1, the hole (2) in the bead (1) has a polymer (3) disposed therein. From the cross-section view, the ends (4) of the polymer are of greater diameter than the centre of the polymer (5) and provides a dumbell shaped cross-section and the polymer (3) is physically held within the hole (2) providing enhanced strength to the support.

Figure 2 shows a support in which the polymer plug (3) is generally cylindrical.

In Figure 3, the polymer plug (4) is generally cylindrical and the bead (1) is tubular shaped.

Figure 4 shows a solid support of the invention having a tumescent shaped hole (2) in the bead (1) and the polymer (3) is thicker within the hole than at the ends so providing a means of physically retaining the polymer plug in the hole (2).

The etched glass beads in Figures 5 and 6 are shown prior to receiving a polymer plug or lining. In Figure 5, an etched 15/0 bead is shown next to a smaller 0.25mm glass bead and, in Figure 6, next to a smaller 0.65mm glass bead.

Figure 7 shows a 15/0 etched glass bead with a polymer plug in the hole of the bead.

Figure 8 shows a group of 15/0 glass beads with a polymer plug in the holes of the beads, the polymer having been coloured with Ninhydrin to show the polymer more clearly.

Figure 9 shows a 15/0 etched glass bead with a ring of polymer stained with Ninhydrin lining the hole of the bead.

The invention is illustrated by the following non-limiting examples.

Example 1 – Preparation of Beads having Active Surface

1. Bead etching

Size 15/0 glass beads (144g) were placed in a 250cm^3 Polypropylene bottle and covered with Dip'n Etch, a solution of ammonium bifluoride (100cm^3). The bottle was placed in an ultrasonic bath for 6h then left for 16h.

The beads were washed with water (10 x 50cm^3), aqueous sodium hydroxide (15%w/v, 10 x 50cm^3), water (10 x 50cm^3), aqueous hydrochloric acid (1mol/dm^3, 10 x 50cm^3) then water (10 x 50cm^3). The beads were then dried at 100°C for 1h (yield 138g, B I).

A batch of size 11/0 beads (100g) were etched using the same procedure yielding 97g of etched beads (BII).

2. Reaction of etched beads with vinyltriethoxysilane

30g of etched size 15/0 beads were placed in a polypropylene bottle and covered with a solution of vinyltriethoxysilane in methanol (40cm^3, 1:1v/v) and water (1cm^3) added. The mixture was

placed in an ultrasonic bath for 1 hour and then washed with acetone and dried under a stream of nitrogen to yield vinyl functional beads (BV I).

3. Reaction of etched beads with aminopropyltrimethoxysilane

30g of etched size 15/0 beads (30g, B I) were placed in a polypropylene bottle and covered with a solution of aminopropyltrimethoxysilane in methanol (40cm^3, 1:1v/v) and water (1cm^3) added. The mixture was placed in an ultrasonic bath for 1 hour and then washed with acetone and dried under a stream of nitrogen to yield aminopropyl functional beads (BAm I).

4. Reaction of aminopropyl functionalised beads with acryloyl chloride

Aminopropyl functionalised beads prepared above (30g, BAm I) were covered in dichloromethane (30cm^3) and acryloylchloride (5cm^3) was added followed by 4-methylmorpholine (5cm^3). The mixture was swirled, allowed to stand for 1 hour then washed with dichloromethane (3x30cm^3) before drying in a stream of nitrogen to yield acrylamide functional beads (BAc I).

Example 2- Preparation of Solid Supports

1. Polymerisation of polydimethylacrylamide

N,N-Dimethylacrylamide (100mmol, 9.9g), N-acryloylsarcosine methyl ester (13mmol, 2.0g) and bis-acryloylethylenediamine (5mmol, 0.82g) and water (3cm^3) were placed in a round bottom flask. Aqueous ammonium persulfate (0.75g in 2cm^3) was added. The acrylamide beads prepared in section 4 of Example 1, above (30g. BAc I) were immediately added to the monomer solution and a slight vacuum applied to remove air bubbles from the holes of the beads.

Excess monomer solution was drained off using a stainless steel sieve. The sieve containing the beads was then placed in a bath of kerosene at 80°C ensuring that all of the beads were immersed in the kerosene.

After 2h the sieve containing the beads was placed in a bath of cold water and allowed to stand for 1h. The beads now containing the polymer encapsulated within the holes was transferred to a conical flask along with a magnetic stirrer bar. Water (50cm^3) was added and the mixture stirred on a magnetic stirrer for 5 minutes. The supernatant containing small irregular particles of polymer eroded from the surface of the beads was removed by decantation. This washing

process was repeated until the supernatant contained no discernible particles of polymer. The bead-polymer composite solid support (BP I) was stored under water.

2. Reaction of bead-polymer composite with ethylenediamine

The water on bead-polymer composite prepared above (~33g, BP I) was drained off and the beads covered with ethylenediamine. The mixture was allowed to stand overnight (~16h) then washed with water (10x50cm^3).

The amine functional beads (BPAm I) were stored under water. The solid support is suitable for use in peptide synthesis.

3. Polymerisation of Polyhipe in 11/0 beads

Styrene (3cm^3), divinylbenzene (7cm^3) and sorbitane monooleate (Span 80) (2cm^3) were placed in a beaker and stirred at 200rpm and water (300cm^3) containing ammonium persulfate (0.75g) was added slowly until a smooth emulsion formed.

Size 11/0 etched beads (30g, BII) were mixed with ~50cm^3 of this emulsion in a round bottom quick fit flask. A slight vacuum was applied to expel air from the holes of the beads and the mixture was heated at 60°C for 2h.

The solid block that formed was broken up with a spatula and water (~50cm^3) added. Water (50cm^3) was added and the mixture stirred on a magnetic stirrer for 5 minutes. The supernatant containing small irregular particles of polymer eroded from the surface of the beads was removed by decantation. This washing process was repeated until the supernatant contained no discernible particles of polymer. The bead-polymer composite was dried at 100°C overnight and stored dry (BP II).

4. Polymerisation of Polyhipe in 15/0 beads

Size 15/0 etched beads (34g) were mixed with ~50cm^3 of the emulsion prepared in Example 2 -3 above and subjected to the same procedure. The bead-polymer composite formed was dried at 100°C overnight and stored dry (yield 34.5g, BP III).

5. Polymerisation of polyacryloylmorpholine within BP III

4-Acryloylmorpholine (90mmol, 12.65g), N-acryloylsarcosine methyl ester (15mmol, 2.36g) and bis-acryloylethylenediamine (2mmol, 0.35g) and water (1cm^3) were placed in a round bottom flask. Aqueous ammonium persulfate (0.5g in 1cm^3) was added. The Polyhipe beads prepared in Example 2-4, above (34.55g. BP III) were immediately added to the monomer solution and a slight vacuum applied to eliminate any remaining air bubbles from the holes of the beads.

Excess monomer solution was drained off using a stainless steel sieve. The sieve containing the beads was then placed in a bath of kerosene at 80°C ensuring that all of the beads were immersed in the kerosene. As an alternative to heating under immersion in kerosene, the beads could be subjected to ultra violet irradiation at room temperature.

After 2h the sieve containing the beads was placed in a bath of cold water and allowed to stand for 1h. The beads now containing the polymer encapsulated within the holes was transferred to a conical flask along with a magnetic stirrer bar. Water (50cm^3) was added and the mixture stirred on a magnetic stirrer for 5 minutes. The supernatant containing small irregular particles of polymer eroded from the surface of the beads was removed by decantation. This washing process was repeated until the supernatant contained no discernible particles of polymer. The bead-polymer composite (BP IV) was stored under water.

50 beads were removed and dried at 100°C overnight (181mg). The final weight corresponded to addition of 1g of polymer per 10g of glass beads.

6. Reaction of bead-polymer composite with ethylenediamine

The water on bead-polymer composite prepared above (BP IV) was drained off and the beads were covered with ethylenediamine. The mixture was allowed to stand overnight (~16h) then washed with water (10x50cm^3). The amine functional beads (BPAm II) were stored under water and were suitable for use in peptide synthesis.

Example 3 - Synthesis of Leu-Enkephalinamide

1. Coupling of internal reference amino acid

Amine functional beads (11.8cm^3, BPAm II as produced in Example 2-6) were placed in a glass chromatography column (17mm diameter) and washed under gravity with aliquots (10x10cm^3) of N,N-dimethylformamide (DMF).

Fmoc-Ala-OH (1.25g, 4mmol) (Fmoc = 9-fluorenylmethyloxycarbonyl) and 2-(1H-benzotriazol-1-yl)-N, N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) (1.21g, 3.8mmol) were dissolved in DMF (3cm^3). 4-Methylmorpholine (NMM) (0.528cm^3, 4.8mmol) was added and the mixture pre-activated for 2-3 minutes before adding to the column and allowing to drain onto the beads under gravity.

The coupling reaction was complete by Ninhydrin assay within 3h. The beads were washed under gravity with aliquots (10x10cm^3) of DMF.

Piperidine/DMF (10cm^3, 20%v/v) was added to the column and allowed to drain onto the beads under gravity. The reaction was allowed to stand for 10 minutes. A second treatment with Piperidine/DMF (10cm^3, 20%v/v) for 20 minutes was carried out and the beads washed with DMF (10x10cm^3).

2. Coupling of linkage agent

Fmoc-Am-Rink-OH (2.05g, 3.8mmol) was coupled in 5 hours as assayed and then treated with piperidine/DMF using the procedure set out in Example 3-1 with the exception that Fmoc-Am-Rink-OH was used instead of Fmoc-Ala-OH.

3. Coupling of Fmoc-Leu-OH

Fmoc-Leu-OH (1.32g, 4mmol) was then coupled in 4 hours as assayed and treated with piperidine/DMF using the procedure set out in Example 3-1 with the exception that Fmoc-Leu-OH was used instead of Fmoc-Ala-OH.

4. Coupling of Fmoc-Phe-OH

Fmoc-Phe-OH (1.55g, 4mmol) was then coupled in 16 hours as assayed and treated with piperidine/DMF using the procedure set out in Example 3-1 with the exception that Fmoc-Phe-OH was used instead of Fmoc-Ala-OH.

5. Coupling of Fmoc-Gly-OH

Fmoc-Gly-OH (1.19g, 4mmol) was then coupled in 16 hours as assayed and treated with piperidine/DMF using the procedure set out in Example 3-1 with the exception that Fmoc-Gly-OH was used instead of Fmoc-Ala-OH.
hed with DMF (10x10cm^3).

6. Coupling of Fmoc-Gly-OH

Fmoc-Gly-OH (1.19g, 4mmol) was then coupled in 16 hours as assayed and treated with piperidine/DMF using the procedure set out in Example 3-1 with the exception that Fmoc-Gly-OH was used instead of Fmoc-Ala-OH.

7. Coupling of Fmoc-Tyr(tBu)-OH

Fmoc-Tyr(tBu)-OH (1.84g, 4mmol) was then coupled in 16 hours as assayed and treated with piperidine/DMF using the procedure set out in Example 3-1 with the exception that Fmoc-Tyr(tBu)-OH was used instead of Fmoc-Ala-OH.

8. Peptide cleavage

The beads were washed with dichloromethane (5x10cm^3) and trifluoroacetic acid (TFA) containing water (10cm^3, 5%v/v) was added and drained onto the beads under gravity. The polymer within the beads turned red indicating that the cleavage was progressing. After 10 minutes a further aliquot of TFA (10cm^3) was added and the mixture left to cleave for 1 hour.

The beads were washed with TFA (5x10cm^3). The combined TFA cleavage solutions and washes were reduced to an oil on a rotary evaporator. The oil was triturated with diethyl ether to form a white solid. The ether removed by decantation and the peptide air dried for 2h (yield 308mg).

The peptide was shown to contain one major component by reversed phase HPLC and had the expected molecular weight as determined by MALDI-TOF mass spectrometry.

Example 4 - Immobilisation of Enzymes

1. Coupling of glucose oxidase and horseradish peroxidase to solid support

Glucose oxidase (aspergillus niger, 27.6mg) was dissolved in sodium acetate (5.5cm^3, 0.1mol/dm^3 pH 5.5). Horseradish peroxidase (25.7mg) was dissolved in sodium acetate (5.14cm^3, 0.1mol/dm^3 pH 5.5.

Aliquots of these solutions (3cm^3) were separately dialysed against water (500cm^3) for one hour and then against sodium acetate (500cm^3, 0.1mol/dm^3 pH 5.5). Each preparation was dialysed against further sodium acetate (200cm^3, 0.1mol/dm^3 pH 5.5) for 3 hours.

Periodate oxidation of the carbohydrate on each enzyme was performed by adding aliquots of cold sodium-m-periodate ($0.27cm^3$, $88mmol/dm^3$) to $2.7cm^3$ volumes of each dialysed enzyme solution in $5cm^3$ polypropylene tubes. The tubes were wrapped in aluminium foil to protect the contents from light and mixed on a bottle roller for 20 minutes. The reaction was quenched by addition of a ten fold dilution of glycerol in water ($20mm^3$) and mixing quickly.

Reaction by-products were removed by extensive dialysis of each oxidised enzyme solution against $300cm^3$ volumes of $0.1mol/dm^3$ MES, $0.15mol/dm^3$ NaCl, pH 5.0 for 1 hour in a fridge. Further dialysis of each bead preparation was performed against $300cm^3$ volumes of this buffer for 1 hour and then overnight against $300cm^3$ in a fridge. A final dialysis of each preparation against $400cm^3$ of the buffer was performed. These oxidised enzyme preparations were stored refrigerated until required.

Bead batch BPAm I as produced in Example 2-2 was added in water to duplicate $10cm^3$ polypropylene tubes to give approximately $1cm^3$ packed volumes. The supernatants were decanted and left in water ($10cm^3$) overnight in a fridge. A further water wash ($10cm^3$) and washes with $0.1mol/dm^3$ sodium phosphate, $0.15mol/dm^3$ NaCl, pH 7.4 ($3x10cm^3$) were performed with 10 minutes of mixing each time on a bottle roller. A final extended 30 minute wash of each bead preparation was performed and the supernatant volumes reduced to approximately $1.5cm^3$.

To convert the primary amines on the beads to protected hydrazine's, the beads were treated with succinimidyl 4-hydrazinonicotinate acetone hydrazone (SANH). In practice, SANH (25mg) was dissolved in dimethylsulfoxide (DMSO) ($1.2cm^3$) and aliquots ($0.3cm^3$) added to each of the bead preparations and vortexed. 0.1M sodium phosphate, 0.15M NaCl, pH 7.4 buffer ($1.5cm^3$) was added to each tube and mixed on a bottle roller for 4 hours at room temperature. Supernatants were aspirated and washes ($3x10cm^3$) were performed with the buffer, followed by washes with water ($3x10cm^3$). The beads were then washed with $0.1mol/dm^3$ MES, $0.15mol/dm^3$ NaCl, pH 5.0 ($4x10cm^3$) to leave the bead preparations as pellets.

Coupling of each of the oxidised enzymes via their aldehydes to the SANH-modified beads was carried out by adding to each bead pellet $1cm^3$ of either oxidised glucose oxidase or oxidised horseradish peroxidase, as appropriate, and mixing for 3 hours at room temperature in the dark.

Supernatants were aspirated and each bead preparation washed with of the pH 5.0 buffer ($5x10cm^3$) followed by water ($5x10cm^3$), each time shaking briefly the bead suspensions and then carefully aspirating the supernatants. Bead preparations stored in $10cm^3$ volumes of water in a fridge (BPAm II-Horseradish Peroxidase and BPAm II-Glucose Peroxidase).

Example 5 - Testing of immobilised enzymes

Immobilised Horseradish peroxidase

Immobilised horseradish peroxidase beads produced in Example 4 were washed in phosphate buffered saline (PBS) three times for 2 minutes each wash. The PBS was poured away and a staining medium consisting of aqueous sodium phosphate $0.1mol/dm^3$) containing hydrogen peroxide ($0.35mmol/dm^3$) and diaminobenzidine ($0.5mg/cm^3$) adjusted to pH6.4 with citric acid was added. After 5 minutes the beads stained dark brown throughout indicating both the presence of the enzyme and confirming that the enzyme was active.

Staining was carried out at 37°C. Beads were washed to remove staining medium and photographed x 50 on a Nikon inverted microscope.

Immobilised glucose oxidase

Immobilised glucose oxidase beads were washed in phosphate buffered saline (PBS) three times for 2 minutes each wash. The PBS was poured away and a staining medium consisting of D-glucose ($42mmol/dm^3$), phenazine methosulphate ($0.1mg/cm^3$) and nitroblue tetrazolium ($0.5mg/cm^3$) all in PBS pH6.9 was added. After 5 minutes the beads stained dark blue throughout indicating both the presence of the enzyme and confirming that the enzyme was active.

Staining was carried out at 37°C. Beads were washed to remove staining medium and photographed x 50 on a Nikon inverted microscope.

Example 6 - Immobilisation of Protein A

Coupling of rProtein A to Beads.

A packed bed volume ($5cm^3$) of bead batch BPAm II as produced in Example 2-6 was dispensed into a $50cm^3$ polypropylene tube. Surplus water was decanted and the bead preparation washed with water ($5x40cm^3$), re-suspending the beads each time and allowing them to settle

under gravity. Washes with sodium borate (0.1mol/dm^3, pH8.3, 4x40cm^3) were similarly performed and the beads left refrigerated overnight in a further 50cm^3 of this buffer.

To convert the amines on the beads to carboxylic acid groups they were treated with succinic anhydride. Succinic anhydride (1.2g) was dissolved in DMSO (60cm^3). The borate buffer was decanted from the beads and aliquots (30cm^3) of this succinic anhydride solution were added to the bead preparation, shaken briefly and mixed on a bottle roller for 6 hours at room temperature. The bead preparation was washed with water (8x40cm^3), re-suspending the beads each time briefly and aspirating the supernatant. Aliquots of morpholinoethanesulfonic acid (MES) buffer (25mmol/dm^3, pH 5.0, 40cm^3) were added and the beads which were then left overnight in a fridge. Further washes of the beads with this buffer (2x40cm^3) were performed and the beads left as a pellet.

N-hydroxysuccinimide (1.6g) was dissolved in cold MES buffer (25mmol/dm^3, pH 5.0, 32cm^3) and an aliquot (15cm^3) of this solution added to the bead pellet and mixed briefly. 1-Ethyl-3-[3-dimethylaminopropyl]carbodimide hydrochloride (EDC, 1.6g) was dissolved in MES buffer (25mmol/dm^3, pH 5.0, 32cm^3) and an aliquot (15cm^3) of this solution added to the bead preparation. The bead preparation was mixed for 30 minutes on a bottle roller to activate. The supernatant was decanted and each preparation quickly washed with MES buffer (25mmol/dm^3, pH 5.0, 5x40cm^3) to leave the beads as a pellet.
Immediately, aliquots (10cm^3) of a solution of rProtein A (15cm^3, 4mg/cm^3 in 25mmol/dm^3 MES, pH 5.0) was added to the bead preparation and coupling allowed to proceed for two hours at room temperature with mixing on a bottle roller. Supernatant was decanted and an aliquot (30cm^3) of Trizma-HCl, pH 7.4 added and mixed for two hours to block any remaining N-hydroxysuccinimide esters. The supernatant was decanted and water washes (8x40cm^3) performed on the bead preparation and the beads left in water (10cm^3) (BPAm II-Protein A).

Example 7 – Use as an absorbent

A solid support as produced in Example 2-3 above was used to absorb a spillage of red oil in a quantity a number of times the mass of the support. On applying the solid support to the spillage, the red oil was absorbed entirely by the solid support illustrating the use of the support as an absorbent.

Example 8 - Encapsulation of Palladium Acetate

The aminofunctionalised beads, BAm I, (1g) beads prepared according to Example 1, part 3 were added to a solution of palladium acetate (0.1g) and poly(phenyl isocyanate-co-formaldehyde) (0.64g) in chloroform (0.86g) and left for 5 minutes. A vacuum was applied momentarily and the beads transferred to a sieve and the excess palladium acetate/ poly(phenyl isocyanate-co-formalldehyde) solution was drained off. The sieve containing the beads were immersed in a water bath and left overnight to allow complete polymerisation. The beads were washed with DMF and left stirring in DMF for a further 24 hours to ensure all polymeric debris was removed from the outside of the beads. The beads were washed with water and allowed to air dry.

Example 9

Etching of glass surface on new beads

Small glass beads with a hollowed out centre (new beads Figure 4, 3.86g) were placed in a 50cm^3 Polypropylene bottle and covered with Dip'n Etch [ammonium bifluoride] solution (10cm^3). The bottle was placed in an ultrasonic bath for 2h then left for 16h.

The beads were washed with water (10 x 5cm^3), aqueous sodium hydroxide (15%w/v, 10 x 5cm^3), water (10 x 5cm^3), aqueous hydrochloric acid (1mol/dm^3, 10 x 5cm^3) then water (10 x 5cm^3). The beads were then dried at 100°C for 1h (yield 2.8g).

Reaction of etched beads with aminopropyltrimethoxysilane

A solution of aminopropyltrimethoxysilane (0.1cm^3) in ethanol:water (5cm^3, 95:5v/v) was prepared and allowed to stand for 10minutes. Etched beads prepared above (2g) were placed in a polypropylene bottle and covered with this pre-activated solution. The mixture was placed in an ultrasonic bath for 1 hour and then washed with acetone and dried under a stream of nitrogen to yield aminopropyl functional beads. The beads were then cured at 110°C for 2h.

Reaction of aminopropyl functionalised beads with acryloyl chloride

Aminopropyl functionalised beads prepared above (2g) were covered in dichloromethane (2cm^3) containing 4-methylmorpholine (0.5cm^3) and a solution of acryloylchloride (0.5cm^3) in dichloromethane (2cm^3) was added slowly over 5minutes. The mixture was swirled, allowed to stand for 1 hour then washed with dichloromethane (3x5cm^3) before drying in a stream of nitrogen to yield acrylamide functional beads.

Polymerisation of polydimethylacrylamide

N,N-Dimethylacrylamide (10mmol, 1g), N-acryloylsarcosine methyl ester (1.3mmol, 0.2g) and bis-acryloylethylenediamine (0.25mmol, 0.04g) and water (0.3cm^3) were placed in a round bottom flask. Aqueous ammonium persulfate (0.08g in 0.2cm^3) was added. The acrylamide beads prepared above (2g) were immediately added to the monomer solution and a slight vacuum applied to remove air bubbles from the holes of the beads.

Excess monomer solution was drained off using a stainless steel sieve. The sieve containing the beads was then left under a UV lamp overnight.

The sieve containing the beads was placed in a bath of cold water and allowed to stand for 1h. The beads now containing the polymer encapsulated within the holes was transferred to a conical flask along with a magnetic stirrer bar. Water (5cm^3) was added and the mixture stirred on a magnetic stirrer for 5 minutes. The supernatant containing small irregular particles of polymer eroded from the surface of the beads was removed by decantation. This washing process was repeated until the supernatant contained no discernible particles of polymer. The bead-polymer composite solid support was stored under water.

Example 10

Reaction of etched beads with aminopropyltrimethoxysilane

A solution of aminopropyltrimethoxysilane (1cm^3) in ethanol:water (50cm^3, 95:5v/v) was prepared and allowed to stand for 10minutes. Etched size 15/0 beads (30g, B I) were placed in a polypropylene bottle and covered with this pre-activated solution. The mixture was placed in an ultrasonic bath for 1 hour and then washed with acetone and dried under a stream of nitrogen to yield aminopropyl functional beads. The beads were then cured at 110°C for 2h.

Reaction of aminopropyl functionalised beads with acryloyl chloride

Aminopropyl functionalised beads prepared above (30g) were covered in dichloromethane (15cm^3) containing 4-methylmorpholine (5cm^3) and a solution of acryloylchloride (5cm^3) in dichloromethane (15cm^3) was added slowly over 5minutes. The mixture was swirled, allowed to stand for 1 hour then washed with dichloromethane (3x30cm^3) before drying in a stream of nitrogen to yield acrylamide functional beads.

Polymerisation of polydimethylacrylamide

N,N-Dimethylacrylamide (100mmol, 9.9g), N-acryloylsarcosine methyl ester (13mmol, 2.0g) and bis-acryloylethylenediamine (5mmol, 0.82g) and water ($3cm^3$) were placed in a round bottom flask. Aqueous ammonium persulfate (0.75g in $2cm^3$) was added. The acrylamide beads prepared above (30g) were immediately added to the monomer solution and a slight vacuum applied to remove air bubbles from the holes of the beads.

Excess monomer solution was drained off using a stainless steel sieve. The sieve containing the beads was then left under a UV lamp overnight.

The sieve containing the beads was placed in a bath of cold water and allowed to stand for 1h. The beads now containing the polymer encapsulated within the holes was transferred to a conical flask along with a magnetic stirrer bar. Water ($50cm^3$) was added and the mixture stirred on a magnetic stirrer for 5 minutes. The supernatant containing small irregular particles of polymer eroded from the surface of the beads was removed by decantation. This washing process was repeated until the supernatant contained no discernible particles of polymer. The bead-polymer composite solid support was stored under water.

Example 11

A solid support having a lining was produced. The procedure of Example 2 was followed with the exception that the level of water and ammonium persulphate was doubled to $6cm^3$ water and 1.5g in $4cm^3$ ammonium persulphate solution respectively. Beads having a polymer lining approximately 50 microns thick were produced.

CLAIMS

1. A solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and a polymer disposed within the hole.
2. A solid support according to claim 1 wherein the bead comprises an inert material.
3. A solid support according to claim 2 wherein the inert material is selected from glass, ceramic, polymer, wood (or other natural material) and metal.
4. A solid support according to any one of the preceding claims wherein the bead is generally spherical or ellipsoidal.
5. A solid support according to any one of claims 1 to 3 wherein the bead is tubular.
6. A solid support according to any one of claims 1 to 3 wherein the bead is an irregular shape.
7. A solid support according to any one of the preceding claims wherein the hole in the bead has a longitudinal cross-section of a generally dumb-bell shape
8. A solid support according to any one of claims 1 to 6 wherein the hole in the bead has a longitudinal cross-section of a generally tubular shape
9. A solid support according to any one of claims 1 to 6 wherein the hole in the bead has a longitudinal cross-section of a generally tumescent (broader at the centre) shape
10. A solid support according to any one of the preceding claims wherein the polymer within bead has a particle size of less than 2mm
11. A solid support according to any one of the preceding claims wherein the polymer within bead has a particle size of 0.01 to 0.5mm
12. A solid support according to any one of the preceding claims wherein the polymer is formed in the hole of the bead.
13. A solid support according to any one of the preceding claims wherein the polymer is bound covalently to the bead directly or indirectly.
14. A solid support according to any one of the preceding claims wherein the bead comprises glass and has been treated with an etching agent to provide active sites suitable for reaction with a derivative for linking to the polymer.
15. A solid support according to any one of the preceding claims wherein the bead is derivatised with a silane to provide active sites for reaction with a polymer.
16. A solid support according to claim 15 wherein the active site is a vinyl group.
17. A solid support according to claim 15 or claim 16 wherein the silane group is of formula :

$-(O)_nSi[(CH_2)_p[Z]_qCR=CR_2]_{(4-n)}$ in which n is from 1 to 3, p is from 0 to 6 wherein R is independently H or alkyl, q is 0 or 1 and Z is a divalent linking group.

18. A solid support according to claim 17 wherein Z is of formula $-(CH2]_r$ NRC(O)- wherein r is from 1 to 6.

19. A solid support according to any one of claims 15 to 18 wherein the silane group is selected from

$-O_3SiCH=CH_2$ and $-O_3Si(CH_2)_3NHCOCH=CH_2$.

20. A solid support according any one of the preceding claims wherein the active site comprises a functional group other than a silane which functional group is capable of covalent bond formation between the bead and the polymer

21. A solid support according to any one of the preceding claims wherein the polymer is selected from polyacrylamide, a polystyrene, a cellulose, a polydimethyl acrylamide, a polydimethylmethacrylate, a polyurea, polyacryloylmorpholine, a polybetahydroxy ester, Polyhipe, a polyalkylene glycol, and a polysaccharide.

23. A solid support according to any one of the preceding claims wherein the support comprises an inert material within the hole of the bead and the polymer is bound to or, where the inert material is porous, is retained within the pores of the inert material.

24. A solid support according to claim 21 wherein the inert material comprises Polyhipe or a porous inorganic polymer such as a porous silica.

25. A solid support according to any one of the preceding claims further comprising a functional material supported by the polymer.

26. A solid support according to claim 25 wherein the functional material is selected from a catalyst, an initiator species for peptide synthesis, an initiator species for oligonucleotide synthesis, an initiator species for solid phase organic synthesis, a pharmaceutical active, an agrochemical active, a protein or other biological macromolecule.

27. A solid support according to any one of the preceding claims wherein the polymer is in the form of a solid plug in the hole in the beads.

28. A solid support according to any one of claims 1 to 26 comprising polymer-impregnated beads wherein the bead has a hole through the bead and the wall of the hole comprises a layer of polymer so as to provide a ring of polymer in the hole of the bead.

29. A solid support according to claim 28 wherein the layer of polymer has a thickness of 1 to 100 microns.

30. A medical diagnostic product for detecting the presence of a compound in a biological sample for analysis comprising a solid support according to any one of claims 1 to 26

and comprising a functional material bound or retained by the support which functional material has a specific binding site for interaction with the compound in the biological sample.

31. A medical diagnostic product according to claim 30 wherein the functional material comprises an enzyme supported by the polymer.

32. A monolith comprising a solid support according to any one of claims 1 to 29 contained in a column.

33. A medical diagnostic method for detecting the presence of a compound in a biological sample providing a solid support comprising polymer-impregnated beads wherein the bead has a hole through the bead and a polymer disposed within the hole and a functional material supported by the polymer in the support for selectively reacting with or binding to the compound in the biological sample and contacting the biological sample with the solid support.

34. A method for producing a solid support material comprising the steps of providing a bead having a hole therethrough contacting the bead with a monomer or solution of a monomer, effecting polymerisation of the monomer so as to form a polymer and optionally subjecting the bead comprising the polymer to further treatment to remove undesired polymer from the surface of the bead.

35. A method according to claim 34 in which the monomer or a solution of the monomer, is added to the beads and polymerisation is carried out in the presence of a solvent which is immiscible with the monomer or monomer solvent.

36. A method according to claim 34 or claim 35 in which the beads comprising the polymer are subjected to physical abrasion so as to remove polymer from the external surface of the beads leaving polymer located in the hole of the beads.

37. Use of a solid support according to any one of claims 1 to 32 in a chemical, biological or physical process

38. Use according to claim 37 of a solid support for solid phase synthesis of a species selected from peptides, oligonucleotides, oligosaccharides.

39. Use according to claim 37 of a solid support for solid phase extraction.

40. Use according to claim 37 of a solid support for solid phase organic chemistry.

41. Use according to claim 37 of a solid support for immobilisation of a species selected from solid phase reagents, metal and other catalysts, bio-catalysts, enzymes, proteins, antibodies including polyclonal and monoclonal antibodies, whole cells and polymers.

42. Use according to claim 37 of a solid support for cell culture.

43. Use according to claim 37 of a solid support in preparation of a stationary phase for chromatographic separation.

44. Use according to claim 37 of a solid support as an absorbent.