Sample Processor

The present invention relates to a device for processing samples, in particular clinical samples in preparation for analysis, for instance by means of a nucleic acid amplification method, in particular the polymerase chain reaction (PCR), as well as novel elements and procedures which may be utilised in such devices.

The analysis of fluid samples, for example clinical or environmental samples, may be conducted for several reasons. One current area of interest is the development of a method for positively identifying biological material in a fluid sample, for example a clinical or environmental sample. Such a method would allow for early diagnosis of disease states, which in turn would enable rapid treatment and infection control, or the identification of environmental contaminants and the like. There are many techniques by which very sensitive analysis of samples can be carried out including for example nucleic acid amplification techniques such as the polymerase chain reaction (PCR).

International patent application WO 2005/019836 discloses an apparatus for processing a fluid sample which comprises a rotatable platform and a moveable arm which can be raised and lowered. Te platform is provided with chambers for housing the sample and reagents. Components such as a cutter, heater, optical detector, sonicator, magnet and sheath are housed in the platform and may be releasably attached to the arm for movement relative to the chambers. The components are used to move the sample _ and/or reagent between chambers (such as magnets and sheaths), to pierce the seal of chambers (such as cutters) and to carry out physical processes on the content of the chambers (such as heaters and sonicators).

Examples of sheaths for magnets useful in transferring magnetic beads or particles and thus any reagents attached thereto are described for example in WO2005/019836.

If desired also, processing components such as heaters, sonicators etc. which may be required to treat reagents or reagent mixtures to ensure that they are in a desired physical state and any time during the procedure, may also be removeably housed on the apparatus.

Where components such as sonicators or heaters are fitted to the apparatus in this way, they are generally intended for repeated use and for immersion with a sample, in particular a liquid sample within a chamber.

This in itself, may cause some problems as the use of a non-disposable device in such a way that it comes into direct contact with a sample liquid brings the risk of contamination. Over time, these components may become soiled or tarnished, thus increasing the risk of such contamination.

A first aspect of the invention provides an integral magnet and heater device.

This has the advantage that where the apparatus includes both a magnet to facilitate removal of beads or particles from one chamber to another, a heater may be incorporated into the magnet so that the same element may fulfil both functions.

In one embodiment, the integral magnet and heater device comprises a heating element and a magnet.

The heating element may be a resistive device, for example a cartridge heater which typically comprises resistive wires embedded in a thermally insulating material.

The integral magnet and heater device may further comprise a temperature sensor. The device may further comprise a temperature control by which the device can be set.

In a preferred embodiment, the device is an elongate body and wherein the magnet is located on one end of the elongate body. The magnet may be located at one end of the elongate body. Alternatively, the magnet may be located around the periphery of the heating element.

For example, heating elements may be incorporated into a core of a bar magnet and this may be used both for the transport of beads or particles, or the heating of vessel or chamber contents.

The magnet is chosen which has a field strength which remains effective up to at least 100°C, which is sufficient for aqueous reactions. Preferably the magnet is a permanent magnet.

In any of the embodiments described above, the integral magnet and heater device may be used both for the transport of beads or particles, or the heating of vessel or chamber contents.

In that instance, any disposable sheath utilised to cover the magnet when it is deployed in the apparatus is suitably of a heat conducting polymer as described above. Such combined magnet/heaters form a further aspect of the invention and may be used, for example, to expedite solvent evaporation from retained magnetic particles; to heat liquids to aid dissolution of reagents; to facilitate the desorption of compounds bound to the surface of magnetic particles, (in particular, nucleic acids);

for degassing of liquids; or to effect or assist the lysis of cellular material, e.g. to release nucleic acids.

A second aspect of the invention provides apparatus for sample preparation or analysis, the apparatus comprising:

one or more reagents or sample chambers

an integral magnet and heater device which is movable relative to the one or more reagent or sample chambers.

The apparatus may comprise a cartridge comprising a body section adapted to hold a sealed sample vessel; and apparatus adapted to receive said cartridge.

A third aspect of the present invention provides apparatus for sample preparation or analysis, the apparatus comprising:

one or more reagent or sample chambers

a reusable processing component

and a sheath adapted to cover the reusable processing component during use.

The applicants have found that the risk of contamination by repeated use of a reusable processing component can be minimized by placing a sheath, which is disposable, over the processing component before use. In particular, where a processing component such as a heater is used repeatedly during a particular chemical, biochemical procedure or assay, a new disposable sheath is suitably applied on each occasion.

The apparatus may comprise a cartridge comprising a body section adapted to hold a sealed sample vessel; and apparatus adapted to receive said cartridge.

Sheaths of this type are suitably removeably housed on the cartridge housing the one or more reagent or sample chambers in a similar manner to the mechanical elements described above, so that they are readily available and can be accessed and positioned using the arm in a similar fashion. Thus, for example, the sheath may be provided with a lip or flange, able to interact with a fork on the moveable arm of the apparatus and lifted into position around the processing component as necessary.

After use, they may be returned to the cartridge for disposal or disposed of directly.

The sheath is suitably made of a plastics or elastomeric material, and where they are intended for use in conjunction with reusable heaters, they are preferably made of a thermally conducting plastic, for example plastic filled with boron nitride or a commercially available "cool polymer" material, so as to minimize any loses in heater efficiency.

A fourth aspect of the present invention provides a sheath adapted to cover a reusable processing component of an apparatus during use. Such sheaths form a further aspect of the invention.

Where heaters are provided in the apparatus, they suitably incorporate temperature sensors, so that the temperature of a reagent or sample in which they are immersed can be determined. When a sheath as described above is used, some calibration of the apparatus will be necessary to ensure that these readings are accurate.

A suitable calibration method for calibrating the heater when used in combination with a sheath comprises the steps of immersing the sheath containing the heater in a liquid bath (e.g.

water bath; varying the temperature of the heater; record the temperature readings of heat sensor of the heater and the temperature of the liquid bath; and using the correlation between the temperature readings of the heat sensor of the heater and the temperature of the liquid bath to provide calibration data.

The data can be used to create a calibration file that is either used in software as a look-up table to convert the sensor signals to accurate temperatures or to work out a mathematical transform for the signals from the heat sensor.

In a particular embodiment, where the apparatus includes both a magnet to facilitate removal of beads or particles from one chamber to another, a heater may be incorporated into the magnet so that the same element may fulfil both functions. For example, heating elements may be incorporated into a core of a bar magnet and this may be used both for the transport of beads or particles, or the heating of vessel or chamber contents.

In that instance, any disposable sheath utilised to cover the magnet when it is deployed in the apparatus is suitably of a heat conducting polymer as described above. Such combined magnet/heaters form a further aspect of the invention.

The cartridge also suitably contains further elements which are useful in the subsequent procedures to which the sample are required to be subjected.

Such further elements may include one or more reagent chambers for holding reagents or materials required to continue the analysis of the sample. These reagents or materials, which include wash solutions, diluents or buffers as well as reagents used in the subsequent procedure, are suitably predispensed into the reagent chambers.

Where this involves sample preparation, for example to extract nucleic acid from samples suspected of containing cells, such reagents may include lysis reagents for example chaotrophic salts, bacteriophages, enzymes (which may lyophilized), detergents, antibiotics the like. Where the subsequent procedure involves sample analysis, other reagents such as dyes, antibodies, enzymes (including for example polymerase enzymes for PCR), buffers, salts such as magnesium salts, may be included in further reaction chambers on the cartridge. However, the range of possible reagents is very large and they will be selected on a "case-by-case" basis, depending on the nature of the chemical or biochemical reaction or analysis or assay to which the sample is subjected.

The reagents may be present in solid or liquid form. When they are predispensed in solid form, these may be as a solid powder, bead, capsule or pressed tablet form, or they may be adhered to magnetic particles or beads, such as silica beads as is well known in the art.

Reagent chambers containing predispensed reagents are suitably sealed for example using foil seals which may be piercable within the apparatus using cutters. These may be integral with the apparatus, but in a particularly preferred embodiment, a cutter is removeably housed in the cartridge, for example within an appropriately shaped recess or aperture in the body section, so that it is available for use in relation to the particular chemical or biochemical reaction, analysis or assay being carried out.

Other mechanical elements in addition to the cutter, in particular those which may be of a disposable nature, which are useful in or otherwise facilitate further chemical or biochemical

reaction, physical processing, analysis or assay of the sample, may also be removeably housed on the cartridge. Such elements may include devices required to move samples, reagents or materials from one chamber to another, such as pipettors, magnets or sheaths therefore, as well as small devices such as filters, stoppers, mixers, caps etc. which may require to be introduced into chambers in the course of the chemical, biochemical or analytical procedures or assays.

If desired also, processing components such as heaters, sonicators etc. which may be required to treat reagents or reagent mixtures to ensure that they are in a desired physical state and any time during the procedure, may also be removeably housed on the cartridge.

Mechanical elements such as cutters, pipettors, magnets or sheaths therefore, as well as other sheaths as detailed more fully below, and processing components as described above, will collectively be referred to hereinafter as "moveable components".

In such cases, the apparatus is provided with means for accessing these moveable components and for moving them as necessary so that they can fulfil the required function in the chemical, biochemical, analytical or assay procedure. In particular, the apparatus may comprise a moveable arm which is able to interact with any moveable component on the cartridge.

The moveable arm, which is for example, a robotic arm, is suitably provided with a grab device, so that it can pick up any moveable components housed on the cartridge and lift it up out of its associate recess or aperture. Suitable grab devices are known in the art. The may include forked elements which are arranged to removeably interact with appropriately positioned flanges on the moveable components, but may also comprise

controllable grabbing arms, able to close around an exposed upper portion of one of the moveable components. Again, the moveable components may include particular adaptations such as flanges or recesses which are arranged to interact with grabbing arms to facilitate movement.

The apparatus is designed such that a moveable component held on the arm may be positioned above an appropriate reaction or reagent chamber within the cartridge. The arm may be moveable laterally as well as vertically in order to achieve this. However, in a particular embodiment, the arm itself is moveable only in a single dimension which is vertically, and a transport means for the cartridge is provided, suitably as part of the apparatus, so as to allow it to be moved in a lateral direction that the arm may be positioned directly above each element on the cartridge including reaction chambers, reagent chambers as well as moveable components, so as to allow the desired sequence of events to occur. Where the arm may be moveable laterally as well as vertically, the requirements for the horizontal transport means for the cartridge may be reduced.

When electrically operated processing components such as a heater or sonicators are supplied in this way, it may be useful if the connection between the processing component and the arm of the apparatus were also to provide an electrical connection sufficient to provide power to the processing component during use. However, such elements may be more conveniently housed within the apparatus itself, and arranged to be delivered for example to the appropriate chamber on the cartridge at the required time. The arm itself or an adjunct to the arm on which the processing component such as the heater or sonicator is fitted, may be used in order to ensure that the component can be positioned as necessary in relation to a chamber on the cartridge.

The apparatus may also comprise devices such as thermal cyclers, optical readers such as fluorimeters, as well as data processing devices arranged to collect, analyse and/or record signals from any chamber within the cartridge or apparatus. The selection and arrangement of suitable devices within the apparatus will depend upon the nature of the chemical and biochemical reaction or assay being conducted, and will be within the ambit of the skilled person.

The inclusion of multiple moveable components and chambers on a cartridge opens up the possibility that the sample preparation and/or analysis may be carried out in a largely self-contained unit comprising the cartridge. Such units, including where all chambers are moveable components, may be readily disposable after use to avoid further contamination risks. Furthermore, by conducting an assay in a single cartridge, it is possible to reduce the risk of errors in sample labelling since the cartridge itself may be labelled at the time of introduction of the sample, for example using a standard bar code labelling system, and the label will remain with the sample throughout the analytical procedure.

All processes are suitably carried out automatically by programming the apparatus to move the relevant components, reagents etc. into contact with each other in an appropriate sequence. For example, as described in WO2005/019836 the sample can be subject to a nucleic acid extraction procedure, followed by a PCR reaction. However, many other procedures in which safe sample delivery is required may be undertaken using the invention by appropriately designing the apparatus and programming it accordingly. The application of such robotic techniques is well known in the art.

When the process includes a thermal cycling step such as a PCR, the apparatus will suitably include a thermal cycling device. The vessel in which the thermal cycling is carried out may be positioned on the cartridge if required. However, alternatively, where the arrangement of the cartridge and the apparatus is such that the preparation of the sample only is carried out on the cartridge, a particularly suitable arrangement is that the prepared sample ends up in a removeable reaction chamber, which is then transferred to a specific thermal cycling area (as illustrated for example in WO2005/019836). However, this may not always be necessary and the incorporation of a chamber which may be thermally cycled on the cartridge would be advantageous in that it would allow further simplification of the apparatus.

Use of electrically conducting polymer as a heater for thermal cycling in particular in PCR reactions, as described and claimed in WO 9824548 (the content of which is incorporated herein by reference), provides a particularly compact and versatile system for use in conjunction with the system of the present application, since the ECP may be readily incorporated into a reaction chamber which is housed, if necessary removeably housed) on the cartridge.

Generally, the ECP is used to coat a reaction vessel which comprises essentially two parts, a relatively wide-mouth upper section for receiving the sample, and a lower sealed capillary tube which then acts as the reaction vessel. At least the lower sealed capillary tube comprises ECP which effectively acts as a highly controllable resistance heater, when electrical contacts are placed across it.

The invention will now be particularly described by way of example with reference to the accompanying diagrammatic drawings in which:

Figure 1 shows a plan view of a cartridge useful in the system of the invention;

Figure 2 is a schematic perspective view of a cartridge useful in the system of the invention which is about to receive a sample vessel;

Figure 3 is a perspective view of the cartridge of Figure 2 with a sample vessel in place within the holder;

Figure 4 is a perspective view of the cartridge of Figure 3 in a "closed" position;

Figure 5 is an end view of the cartridge of Figure 4;

Figure 6 is an end view of the cartridge of Figure 3;

Figure 7 is a schematic diagram showing how a cartridge of the invention may be introduced into a apparatus in which a chemical, biochemical or other type of assay or processing may be conducted;

Figure 8 illustrates a cartridge of the invention in position in a receiving section of an apparatus;

Figure 9 is a schematic diagram illustrating a system for filling a capillary tube, which forms a further aspect of the invention;

Figure 10 illustrates a sheath for use in the invention;

Figure 11 illustrates a side view of a combined heater and magnet;

Figure 12 is a cross section of the lower part of the combined heater and magnet of Figure 11; and

Figure 13 illustrates a side view of a heating element for use in the combined heater and magnet of Figures 11 and 12.

The cartridge shown in Figure 1 includes a body section (1) which is of a rigid plastic material and is of generally oblong section. A clip feature is provided to facilitate location of the cartridge when it is placed in the instrument. A central longitudinal channel (2) is provided in the upper surface (3) of the body section (1). The channel (2) is open at one end but is does not extend the full length of the body section (1) so that it terminates in an end ridge (4) of the body section. The channel (2) has a generally curved base (5) and is shaped so that it could accommodate a tube (6) with a sealing cap (7). The channel 2 is inclined downwards towards the ridge (4) so that a liquid sample contained within the tube (6) will flow towards the cap (7).

In the illustrated embodiment, the tube accommodates a swab (8) which is fixed to the cap (7) by way of a support (9).

The cartridge also contains a reaction chamber (10). A piercing needle (not shown) extends between the chamber (10) towards the cap (7) with a piercing tip at the end adjacent the cap (7). The cap (7) suitably includes a piercable membrane (11) (Figure 2) in the upper surface thereof.

When the tube (6) is in position in the channel (2), the cap (7) is sufficiently far removed from the piercing needle to ensure

that it is not breached. However, the cartridge (1) is designed to be positioned within an apparatus (not shown), which is provided with an actuator able to apply pressure to the base of the tube (6) in the direction of the arrow. This forces the membrane (11) of the cap (7) against the piercing needle, which passes through the membrane (11) and thus breaches the seal.

Any liquid within the tube (6) is able to flow out through a channel in the needle into the reaction chamber 10, where it may be subject to further processing. However, no operator contact with the contents of the tube (6) has taken place at this point and so the risk of contamination is minimised.

The cartridge (1) also includes in side sections a number of components or elements which may be utilised in an automated analytical process. For instance, it contains a number of foil sealed reservoirs (12) which may contain liquid reagents such as buffers, washes etc. which may be required for the desired processing of a sample. Others (13) may contain reagents such as solid reagents such as PCR beads useful in the subsequent processing of the sample.

In addition in this instance, the cartridge includes a series of movable components including two pipettors 14, a stopper 15 and a sheath 16 which may fit for example over a magnet used to move magnetic reagent beads from one chamber to another on the cartridge as required. These moveable components are accommodated within appropriately shaped apertures in the upper surface (3) of the body section (1). They are arranged so that an upper region projects above the upper surface (3) so that they are accessible for a grabbing arm of an apparatus. They may be provided with suitable annular flanges to facilitate this, or to assist in the lifting operation, for example as described in WO2005/019836.

In this case also, there is a provided in the cartridge (1), a reaction vessel (17) which is coated with an electrically conducting polymer, and so which, when connected to a suitable electrical supply, can subject the contents to a thermal cycling procedure such as that required for PCR.

The arrangement of this vessel will be discussed in more detail hereinafter in relation to other illustrated embodiments.

The cartridge illustrated in Figure 2 contains many common elements although these are slightly differently arranged to suit the particular apparatus and chemical, biochemical or analytic procedure or assay being carried out. However, in this case, a holder (18) for the tube (6) is provided. The holder (18) is also tubular in shape and is capable of holding the tube (6) such that the cap (7) abuts against the end (Figure 3).

The holder (18) may be retained against the cartridge body (1) in an upright sample vessel receiving position by means of a clasp (20) (Figures 5 and 6) disposed at the free end of the channel (2).

Once a tube (6) has been loaded into the holder (18), it is removed from the clasp (20), and inserted into the channel (2). A flange (19) provided on the side of the holder (18) is arranged to engage in a snap fit locking arrangement with a corresponding groove in the ridge (4) of the body section (1), but only if the tube (6) is snugly fitted into the holder (18) (Figure 4).

At this point, the tube (6) and the cap (7) are substantially completely encased within the cartridge and holder and so are not accessible for fracture etc. A space (22) for a label for a bar-code reader to identify the cartridge and a window (23) to allow

a bar-code on the sample tube to be read may be provided on the flange (19) and holder (18) respectively.

Sample labels may be applied at this point to the cartridge for example bar code labels which may be applied to an end region (21) of the body section (1), so as to facilitate tracking of the sample through the analytical procedure.

The base of the holder (18) includes a small aperture (24) (Figure 6). The aperture (24) is shaped to allow an actuator of the apparatus into which the cartridge is introduced to pass through and so urge the tube (6) towards the piercing needle provided at the region of the ridge (4)

Once the actuator has passed through the aperture (24), the cartridge is effectively "locked" and cannot then be opened. The actuator is then withdrawn whilst the sample tube remains in position at least until the end of the analytical procedure.

The cartridge (1) is shaped so that it may be received into a receiving section of a suitable apparatus. This is illustrated schematically in Figure 7. In that case, the cartridge receiving section of the apparatus (36) comprises a support (37) provided with a recess (38), into which the cartridge (1) snugly fits. The support (37) is retractable into the body of the apparatus (36), for processing. The support (36) is itself moveable (see arrows) so as to align any particular part of the cartridge (1) with an interacting element (39), which may be moveable in a vertical direction.

A similar arrangement is illustrated in Figure 8. In this case, the cartridge (1) is provided with a lip (40) which engages the upper surface of the support (37) when the cartridge is in position within the recess (38). The holder (18) is arranged so

that when the support (37) is retracted into the body of the apparatus, the actuator for opening the tube (6) and can enter through the aperture (11) to release sample into the sample vessel (10) prior to the processing procedure. If required, locking or other engagement means may be provided to fix the cartridge (1) in position on the support (37).

Thus in use, a sample is collected for example for chemical, biochemical analysis, investigation or assay. If the sample is a liquid sample, it is suitably placed directly in a tube (6) which is sealed with a cap (7). Preferably the volume of the sample is known or is measured, in particular if the nature of the investigation being carried out is qualitative in nature. The sample tube may be inscribed with maximum and minimum fill lines to facilitate the dispensing of the liquid sample and to provide a means of checking that the sample volume is within the required limits. If the sample has been collected on a swab, then the swab (8) itself is placed in the tube together with a suitable and preferably known volume of eluent and the tube (6) is then sealed with a cap (7). The tube is then suitably shaken to ensure that any sample is transferred from the swab (8) to the eluent, although this may not be necessary if the volume of the liquid is sufficient to ensure that the swab remains immersed in the liquid.

Then either directly, or when it reaches a laboratory, the tube (6) is placed in a holder (18) of a cartridge. The holder is then inserted into the channel (2) of the body section (1) of a cartridge and the cartridge itself is labelled, before being placed into an appropriate cartridge receiving section of an apparatus (designed to effect the necessary procedures so as to effect the chemical, biochemical or analytical procedures or assays on the sample.

At this point, an actuator on the apparatus is caused to pass through the aperture (24) in the base of the holder (18) so as to urge the tube (7) towards the hollow piercing needle at the ridge end of the cartridge. Sufficient pressure is applied to the tube (6) by the actuator (24) to ensure that the rubber seal (11) in the cap (7) is breached by the needle.

Because the tube (6) is inclined downwards towards the ridge (4), the liquid contained therein will run through the hollow piercing needle directly into the reaction chamber (10) on the cartridge.

The apparatus is then able to effect processing, for example using robotic procedures known in the art. A vertically moveable arm is suitably used to effect the processing, whilst the cartridge is moveable, for example by Cartesian motion, so that the appropriate chamber or component on the cartridge is aligned with the arm at any one time.

The possibility for assay design using this procedure is limitless, as all that it is necessary to do in any particular case is to ensure that reagent containers on the cartridge and that suitable other components such as the moveable components described hereinbefore, are provided either on the cartridge or integrated appropriately into the apparatus.

A particular example of such a procedure is illustrated in WO2005/019836.

To summarise that procedure however, a sample within the chamber 10 which is known or suspected of containing cells of interest is subject to cell lysis. This may be achieved for example by preloading the chamber 10 with a chemical lysis agent such as guanidine hydrochloride, by adding such a reagent taken from a reagent container for example using a pipettor 14, by

introduction of a sonicator which is suitably integral with the apparatus or a combination of these. Where reagents are obtained from a sealed container 12 on the cartridge, they may be accessed following piercing of the foil lids with a cutter, which itself may be a moveable component on the cartridge or an integral part of the apparatus.

Magnetic beads which are suitably coated with a binding agent such an antibody specific for a particular target analyte or nucleic acid generically, such as "Magnesil®" silica beads are then introduced, for example using a magnet which is inserted into a sheath 16 and brought into contact with beads when it attraction is required (for example to pick the beads out of a container) and removed from the sheath when the beads are required to be deposited, for instance once the sheath has been positioned inside the reaction chamber 10.

After allowing the analyte such as any nucleic acid to become adhered to the beads, they may be removed from the reaction chamber (10) and placed into a different reaction chamber, which may have been foil sealed until the seal was broken by a suitable cutter before addition of the analyte. The beads may be moved through one or more wash chambers, optionally present on the cartridge, at this time if required.

Analyte may then be eluted from the beads for example by adding the beads to an eluent, which is preferably hot, contained in a chamber (12). Heating of the eluent may take place by introducing a heater provided on the apparatus, which is preferably encased within a protective disposable sheath 16 as described above. However, in the event that it is not, it may be subject to washing steps using wash liquids which may be contained in reagent chambers which are optionally on the cartridge.

A sheath (16) is shown in more detail in Fig 10 and comprises a hollow cylindrical body (40), sealed at its lower end (42). The upper end (44) has an opening, surrounded by a flange (46) which is able to interact with a fork on the moveable arm of the apparatus, so that the sheath can be lifted into position around the processing component (for example the heater) as necessary. The sheath is sized, so that when positioned in an aperture in the cartridge, the flange (46) projects above the upper surface of the cartridge. The sheath is made from a thermally conducting plastics or elastomeric material, for example "CoolPoly" materials available from Cool Polymers, Inc, thereby enabling heat from a heater positioned within it to pass through the sheath into the content of the chamber. The sheath preferably has a thickness in the range of 0.25mm to 0.75mm its thinness assisting in heat transfer.

A combined heater and magnet (52) used in the cartridge is illustrated in Figs 11 and 12. Fig 11 shows a side view of the heater and magnet assembly and Fig 12 shows the lower portion of the assembly in cross-section. The combined heater and magnet (52) has an elongate body, (50) with a thermally conductive (preferably mild steel) casing (54) which houses a heating element. An assembly body (66) is located at one end of the elongate body (50) and is provided with a clamp (68) which clamps the elongate body (50) onto an actuator arm (70). An insulating shim (72) separates the clamp (68) from the elongate body (50).

A heating element is inserted into the casing (54) of the combined heater and magnet assembly, for example as shown in Fig 13 which is a side view of a suitable heater element (64). A suitable heating element is one used in soldering irons, for example a 50 Volt heating element supplied by Antex, part no. SD50E. Such heating elements typically have a resistive wire

embedded in an insulating material, for example magnesium oxide or a ceramic.

An integral temperature sensor (not shown) is also supplied, enabling the temperature to be controlled. Electrical connections (58) extend from the heating element (64) through the assembly body (66), which provide power to the heating element (64) and temperature sensor. The combined heater and magnet assembly may be moved by the actuator arm (70) as illustrated by the arrow. Alternatively, the assembly body may (66) be provided with a flange (not shown) which is able to interact with a fork on the moveable arm of the apparatus, to enable the combined heater and magnet to be moved.

Fig 12 shows a cross section of the elongate body (52) of the combined heater and magnet. A permanent magnet (62) and heating element (64) are located within the casing (54). The permanent magnet (62) is located at the opposite end to the assembly body (66). Permanent magnets are commercially available which maintain their field strength up to over 180°C. A suitable magnet, such as an N27SH grade sintered Neodymium-Iron-Boron disc magnet is available from MMG Mag Dev Limited. As PCR reactions are aqueous reactions, the magnet only needs to maintain its field strength up to 100°C.

Reagents suitable for carrying out a PCR reaction may also be prepared in a reaction chamber, for example by addition of a suitable buffer, in particular one containing purified nucleic acid extracted from the sample, to lyophilised beads of PCR reagents. Again, such procedures may be effected automatically within the apparatus by moving elements such as the cutter, pipettors etc so as to ensure that the appropriate reagent transfers occur.

Once a PCR reaction mixture has been prepared on the cartridge, it is suitably transferred into the reaction chamber 17, which is thermally cyclable as a result of an ECP coating. Filling is achieved by means of a modified pipettor and the procedure is illustrated in Figure 7.

As illustrated, the pipettor comprises a plastics body (25) provided with a series of annular flanges (26) which facilitate the collection of the pipettor by an arm of the apparatus. A cap member (27) has a resilient upper diaphragm (28) with a projection (29) intended to interact with an actuator provided on the apparatus, so as to allow controlled operation of the pipettor.

The lower section (30) of the pipettor is substantially elongate and of a sufficiently small diameter to enter a capillary tube (31). The capillary tube (31) is sealed at the lower end (32) and so forms a closed reaction vessel. The lower surface (32) is suitably transparent so that the progress of any reaction carried out in the vessel can be viewed. This means that, for example where the PCR is carried out in the presence of a fluorescent signalling system, it can be monitored throughout (real-time PCR). The upper portion (33) of the reaction vessel is of a wider cross section, but the walls in the region of the juncture of the upper portion (33) and capillary tube (31) are tapered so as to provide a guide for the lower section of the pipettor (30) as it enters the capillary tube (31).

An electrically conducting polymer layer (34) surrounds the capillary tube, and is connectable to an electrical supply by way of upper and lower electrical contacts (35, 36).

In use, the pipettor 14 is raised out of its housing with the cartridge by the interaction of the arm with the flanges 26, and

lowered into a reaction chamber containing the prepared PCR reaction mixture. The pipettor actuator, driven by a stepper motor is deployed to depress the diaphragm (28) so as to draw the reaction mixture up into the pipettor body (25).

The pipettor is then raised out of the chamber by the moveable arm of the apparatus, the cartridge is moved so that the pipettor is located above the reaction vessel (17), and then lowered, until the lower section (30) of the pipettor (14) is substantially at the base (32) of the capillary tube.

The actuator for the diaphragm (28) is once again activated to expel the contents into the reaction vessel (17). At the same time, the arm is deployed to raise the pipettor (14) out of the reaction vessel (17). The movement of the arm and the actuator are co-ordinated so that the pipettor (14) leaves the capillary tube (31) at a suitable rate to provide bubble free filling.

The accuracy and controllability of the actuator and the arm as a result of the use of suitable controlling stepper motors, means that such an operation is possible.

Once the reaction vessel (17) has been filled in this way, a suitable cap or stopper may be applied to the upper section (33) to close the vessel. The electrical contacts 35, 36 may be connected so as to allow a thermal cycling process, for example a PCR reaction, to be conducted, within the reaction vessel (17) without further movement.

Suitably, the PCR includes one of the conventional signalling sytems such as the Taqman™ or ResonSense™ methodologies and this is monitored through a transparent base (32) of the tube.

Once complete, the cartridge may be removed from the apparatus and discarded.

The systems and elements described herein therefore provide an effective and efficient way of conducting a variety of procedures, in particular chemical, biochemical or analytical assays, whilst minimising risks of contamination and false positive results which this may introduce.

Claims

1. Apparatus for sample preparation or analysis, the apparatus comprising:

an integral magnet and heater device, comprising a heating element and magnet;

characterised in that the integral magnet comprises a permanent magnet and wherein the apparatus further comprises one or more reagent or sample chambers, the integral magnet and heater device being movable relative to the one or more reagent or sample chambers to enable transport of magnetic beads or particles or heating of the chamber contents; and a sheath adapted to cover the integral magnet and heater device during use.

2. A device according to claim 1 wherein the heating element is a resistive device.

3. A device according to any preceding claim further comprising a temperature sensor.

4. A device according to any preceding claim further comprising a temperature control by which the temperature of the device can be set.

5. A device according to any preceding claim wherein the device is an elongate body and wherein the magnet is located on one end of the elongate body.

6. A device according to any of claims 1 to 4 wherein the device wherein the magnet is located around the periphery of the heating element.

7. A device according to any preceding claim further wherein the permanent magnet has a field strength which remains effective up to at least 100°C.

8. A system according to any one of the preceding claims wherein the sheath is provided as a moveable component on the apparatus.

9. A system according to any one of the preceding claims wherein the sheath is of a thermally conducting plastics or elastomeric material.

10. An integral heater and magnet device for use in the apparatus according to any one of claims 1 to 9.