US007109477B2

(12) **United States Patent**
Kuzan et al.

(10) **Patent No.: US 7,109,477 B2**
(45) **Date of Patent: Sep. 19, 2006**

(54) **AUTOMATIC SAMPLE LOADER FOR USE WITH A MASS SPECTROMETER**

(75) Inventors: **Pawel Kuzan**, Oakville (CA); **Andrew Emili**, Toronto (CA)

(73) Assignee: **Engineering Services Inc.**, Toronto (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 18 days.

(21) Appl. No.: **10/813,571**

(22) Filed: **Mar. 31, 2004**

(65) **Prior Publication Data**

US 2005/0218318 A1 Oct. 6, 2005

(51) **Int. Cl.**
H01J 49/04 (2006.01)
B01D 59/44 (2006.01)

(52) **U.S. Cl.** **250/288**; 250/281; 250/282; 250/428; 250/435; 250/440.11; 73/864.91

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,879,458 A * 11/1989 Brunfeldt et al. 250/288
5,037,611 A * 8/1991 Ledford, Jr. 422/63
6,558,630 B1 * 5/2003 Degn et al. 422/100
6,864,487 B1 * 3/2005 McMurtry et al. 250/442.11
6,866,461 B1 * 3/2005 DeWinter et al. 414/222.07

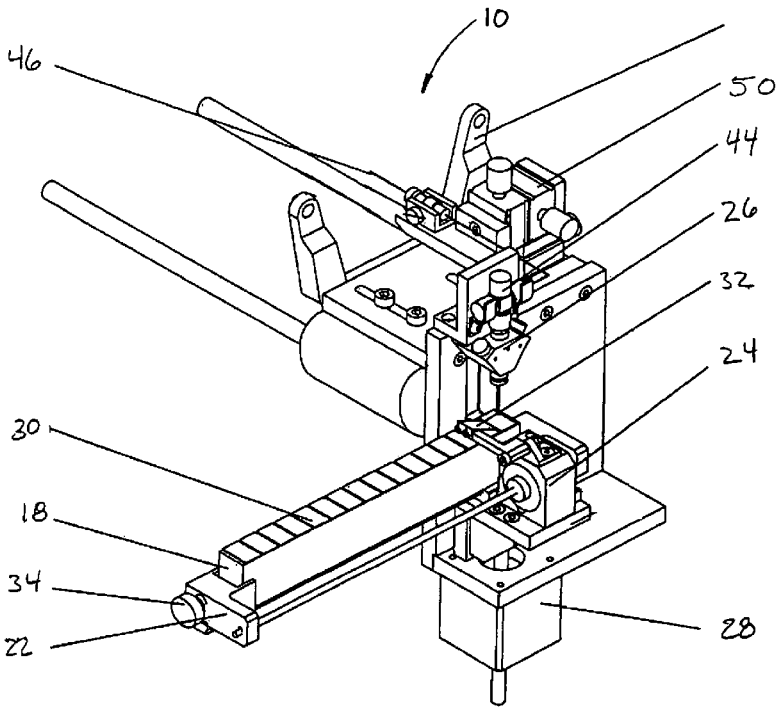
* cited by examiner

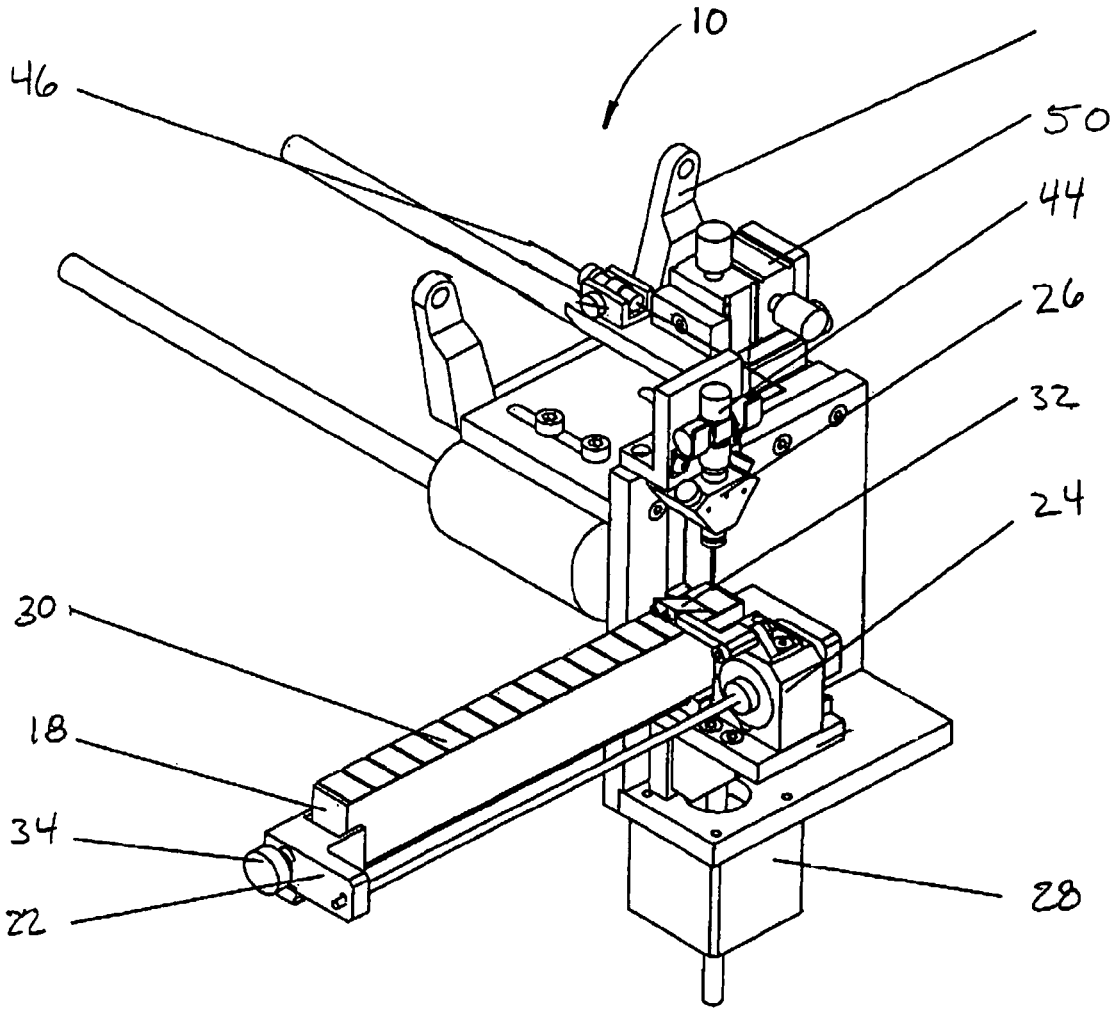
Primary Examiner—Nikita Wells
(74) *Attorney, Agent, or Firm*—Nancy E. Hill; Hill & Schumacher

(57) **ABSTRACT**

An automatic sample loader is for use in association with a mass spectrometer and at least one vial containing a sample. The loader includes a vial block, an insertion head, an insertion tube, a mechanism for pushing the sample out of the vial and a mechanism for moving the insertion head relative to the vial. The vial block has at least one vial cavity and each vial cavity is adapted to receive a vial. The insertion head is adapted to be sealingly engageable in the vial cavity. The insertion tube is operably connected to the mass spectrometer through the insertion head, such that the tube extends into the vial when the insertion head is sealingly engaged in the vial cavity. The pushing mechanism is adapted to push the sample out of the vial and into the tube. The moving mechanism is adapted to move the insertion head relative to the vial block from an engaged position to a disengaged position.

16 Claims, 3 Drawing Sheets





F1G. 1

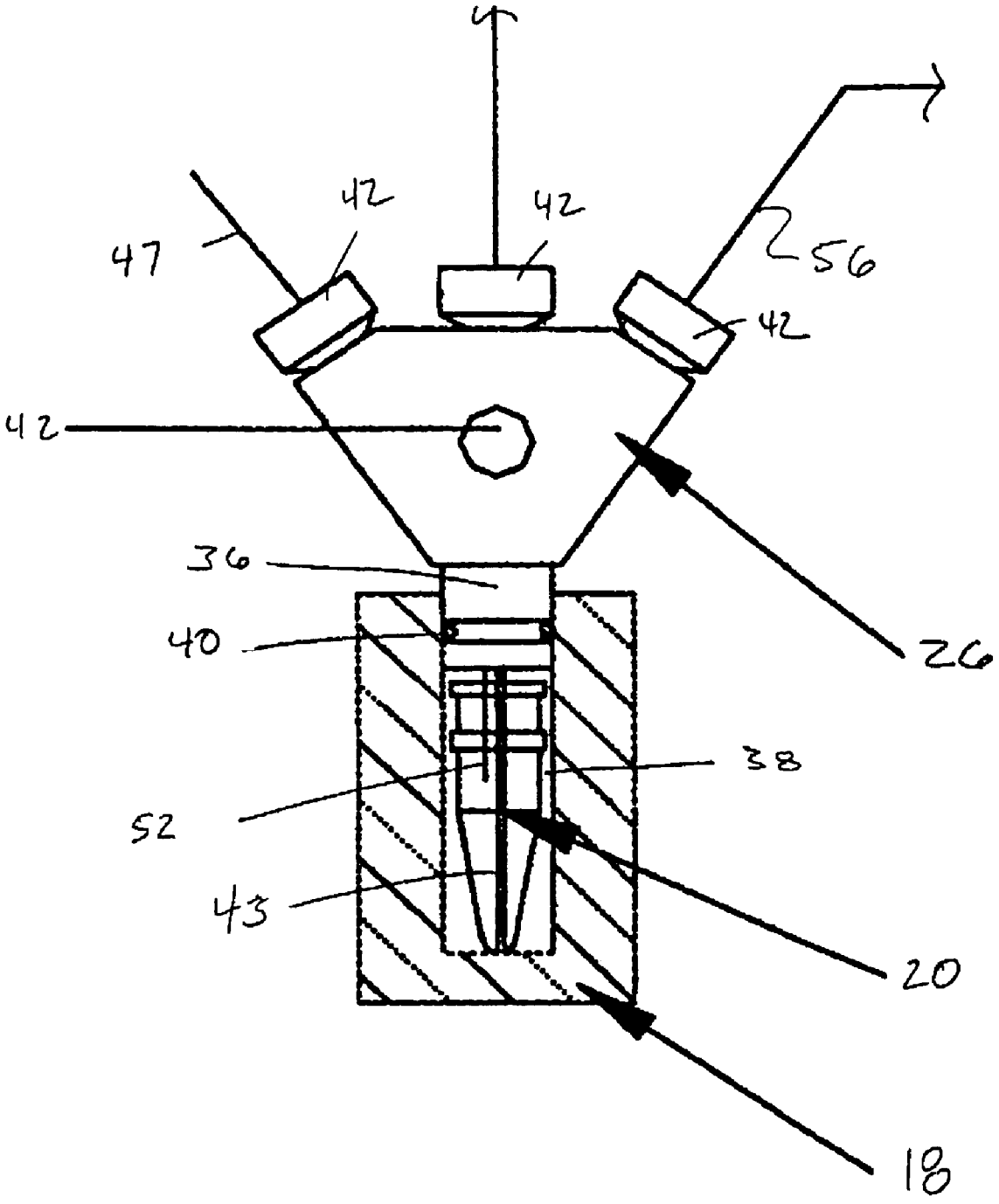


FIG. 2

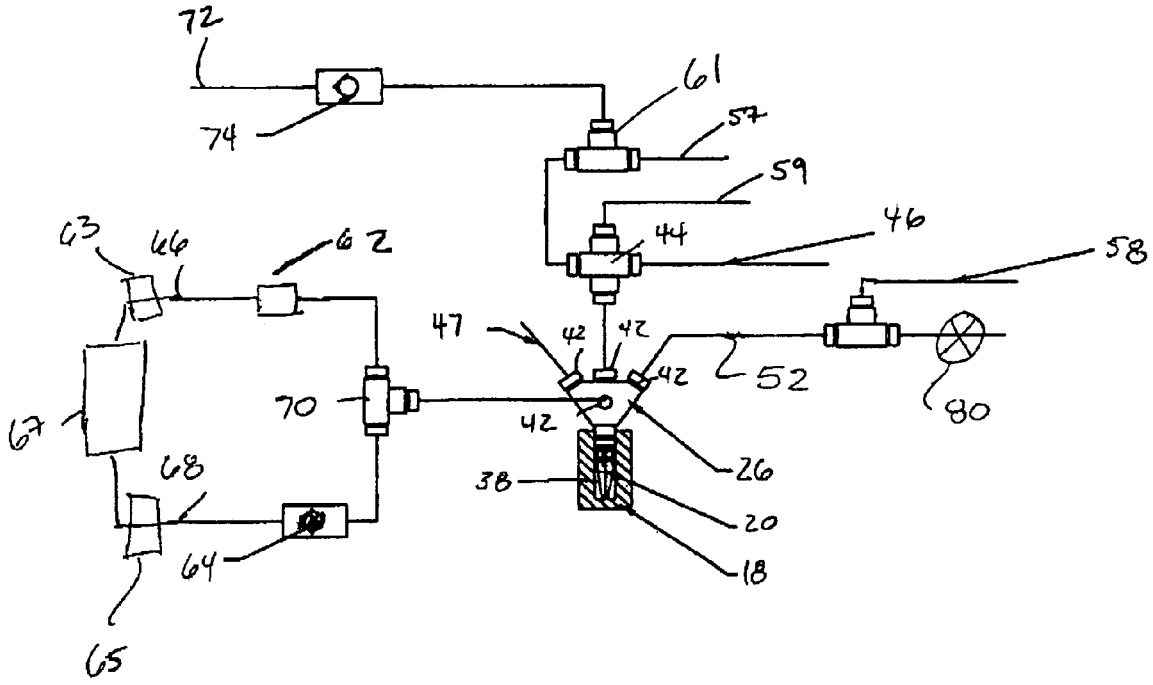

72
74
61
57
59
46
44
58
63
66
62
47
42
42
42
52
80
67
70
42
26
38
20
18
68
64
65

FIG. 3

AUTOMATIC SAMPLE LOADER FOR USE WITH A MASS SPECTROMETER

FIELD OF THE INVENTION

This invention relates to support equipment for mass spectrometers and in particular an automatic sample loader for use in association with a mass spectrometer.

BACKGROUND OF THE INVENTION

Mass spectrometers are well known and are used in the analysis of a wide array of substances. The use and effectiveness of the mass spectrometers can be enhanced by providing a variety of optional support equipment. One such useful optional support equipment is an automatic sample loader or autosampler. Typically these are intended for the analysis of biochemical samples. One example of such a product is the Surveyor Autosampler™ from Thermo Finnigan. Although the design and capabilities of commercial autosamplers vary, they are, in general, effective in automatically loading liquid samples from a variety of containers, including source plates, vials, test tubes, etc. However, the methods these autosamplers use to handle sample material are not suitable for very low volume (typically below 20 μl) biological samples. Typically, a commercial autosampler first aspires the sample from its container and injects it into the sample loop of a specialized injection valve, when the valve is in load position. The valve is then switched to inject position and a metering pump pumps buffer to flush the sample from the sample loop through interconnecting tubing and into the mass spectrometer column.

Although this process works well for larger, chemical samples, it is not considered satisfactory for small biological samples for a number of reasons. For example a large part of the sample, sometimes as much as fifty percent (50%) is lost in the process due primarily to large dead volume (typically about 40 μl) on the intake side of the sample loop. As well this process is not desirable for small biological samples because the sample comes in contact with relatively large surfaces of conduits on its way from the container to the column and inevitably, some of the molecules attach to the walls, which leads to further loss of sample material and cross-contamination as the leftover material mixes with the newly transferred sample in the following cycle. Further the sample is diluted by the buffer, which requires larger volumes of the mixture to be pumped through the column.

As a result of these shortcomings small biological samples need to be loaded to the mass spectrometer column manually. This requires lab personnel to continuously attend to the operation of the instrument.

Accordingly it would be desirable to provide an autosampler that may be used with small biological samples.

SUMMARY OF THE INVENTION

The present invention is directed to an automatic sample loader for use in association with a mass spectrometer and at least one vial containing a sample. The loader includes a vial block, an insertion head, an insertion tube, a mechanism for pushing the sample out of the vial and a mechanism for moving the insertion head relative to the vial. The vial block has at least one vial cavity and each vial cavity is adapted to receive a vial. The insertion head is adapted to be sealingly engageable in the vial cavity. The insertion tube is operably connected to the mass spectrometer through the insertion head, such that the tube extends into the vial when the insertion head is sealingly engaged in the vial cavity. The pushing mechanism is adapted to push the sample out of the vial and into the tube. The moving mechanism is adapted to move the insertion head relative to the vial block from an engaged position to a disengaged position.

In another aspect of the invention there is provided a method of loading a sample for a mass spectrometer. The method includes the steps of:

advancing a vial cavity having a vial with a sample therein into a predetermined position relative to an insertion head;

lowering the insertion head into the vial cavity;

coupling the insertion head into the vial cavity;

applying pressure to the vial cavity whereby the sample is drawn into the insertion head;

de-coupling the insertion head from the vial cavity.

Further features of the invention will be described or will become apparent in the course of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

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

FIG. **1** is a perspective view of the automatic sample loader constructed in accordance with the present invention;

FIG. **2** is an enlarged sectional view of a vial cavity and an insertion head of the automatic sample loader of the present invention; and

FIG. **3** is a schematic view of liquid and compressed gas systems of the automatic sample loader of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The automatic sample loader of the present invention includes three main components namely the mechanical assembly, the control enclosure and the pressure regulator assembly.

The control enclosure is preferably a separate box (not shown on any of the drawings) that contains all electronic components and pneumatic valves **62**, **64** (described in more detail below).

Referring to FIG. **1** the mechanical assembly of the autosampler is shown generally at **10**. In order to reduce the length of the interconnecting tube, the mechanism is mounted directly in front of the mass spectrometer (not shown).

A vial holding block **18** contains a plurality of cavities **38** (shown in FIGS. **2** and **3**) adapted to receive a plurality of vials **20** (shown in FIG. **2**). The block **18** is mounted on a 2 degree-of-freedom linear positioning stage **22**. Block **18** is held in position with a block clamp **34**. Each vial **20** contains a sample. Horizontal block actuator **24** is used to move the block **18** horizontally in order to align subsequent vial cavities with the insertion head **26**. Vertical block actuator **28** is used to raise the block **18** so that the insertion head **26** may be coupled with the selected vial cavity. To prevent evaporation of the sample material, each cavity in the vial holding block **18** is covered with a lid **30**. An Arm **32** is used to remove the lids **30** from their respective cavities prior to the insertion of the insertion head **26**. Sequence of horizontal actuator **24** moves is used to slide the lids **30** along the top surface of the block **18**. It will be appreciated by those skilled in the art that there may be a number of different

ways to remove lids **30** and the invention is not limited to the use of an arm to remove the lids **30**.

Referring to FIGS. **2** and **3** insertion head **26** has a cylindrical protrusion **36** at the bottom thereof that matches the openings of vial cavities **38** in the block **18**. An O-ring seal **40** is used to assure a leak-proof connection between the block **18** and the insertion head **26**. Insertion head **26** has four pressure ports **42** for passing three tubes and one electrical conduit into the vial cavity **38**. A passage (not shown) aligned with the center of the cylindrical protrusion **36** is used for the interconnecting tube **43**. Interconnecting tube **43** extends downwardly from the cylindrical protrusion **36** such that the distal end of the tube reaches the bottom of the vial **20**. The three tubes may, but need not, be identical in regard to material and diameter. All three tubes open to the cavity **38**. The interconnecting tube **43** extends to the bottom of the vial (for sample pick-up); the waste tube **52** extends partway into the vial (for buffer or waste removal); the compressed gas tube (from tee **70** shown in FIG. **3**) does not extend past the bottom of the cylindrical protrusion **36**. Adapter **44** is used to connect the interconnecting tube **43** to the mass spectrometer column **46** and to the metering pump line **72** (shown in FIG. **3**).

Mass spectrometer column **46** is connected to adapter **44**. Mass spectrometer column **46** is supported by a 3 degree-of-freedom adjustment stage **50** (shown in FIG. **1**). The adjustment stage **50** is used to accurately align the tip of the column **46** with the inlet orifice of the mass spectrometer (not shown).

The automatic sample loader of the present invention uses sensors to detect the presence of a sample in the vial. Preferably electronic sensors are used. An electronic circuit measures impedance between a first electrode **47** inserted into the vial **20** and a second electrode **57** connected to adapter **61** (as shown in FIG. **3**). The first electrode **47** in the vial **20** extends parallel to the interconnecting tube **43** and is positioned in pressure port **42**. A third electrode **59** is attached to adapter **44** and is for use by the mass spectrometer. Open contact between first 47 and second **57** electrodes indicates that there is no liquid between the electrodes and therefore the entire sample has been pushed out of the vial. A waste removal line electrode **58** is provided in buffer or waste removal line **52** and a similar method is used to detect the presence of liquid in the waste removal line **52** (shown in FIG. **3**).

A schematic diagram of the liquid and compressed gas system or pressure regulator assembly is shown in part of FIG. **3**. The vial cavity **38** with the insertion head coupled to it can be pressurized from either load pressure valve **62**, or measurement pressure valve **64**. Load pressure valve **62** is on load pressure line **66** and similarly measurement pressure valve **64** is on measurement pressure line **68**. Load pressure valve **62** is connected to a load pressure regulator **63** and measurement pressure valve **64** is connected to measurement pressure regulator **65**. Each of these is connected to gas cylinder **67**. Load pressure line **66** and measurement pressure line **68** are connected to pressure line adaptor **70** which in turn is connected to one of the ports **42**. Fluids can be removed from the vial cavity through waste removal line **52**.

During the sample loading stage of the cycle the sample flows from the vial through the interconnecting tube **43** into the mass spectrometer column **46** via one of the ports **42**. Load pressure is applied to the sample cavity to push the sample out of the vial **20**. Waste removal valve **80** and waste removal line **52** are closed throughout the sample loading part of the cycle.

During the sample analysis stage of the cycle buffer is supplied by an external metering pump via metering pump line **72**. An inline check valve **74** is provided on metering pump line **72** A small portion of buffer flows into the mass spectrometer column **46**, while the majority flows into the vial through the interconnecting tube. Measurement pressure is applied to the vial cavity **38** in order to maintain the required flow of buffer through the column **46**. Waste removal valve **80** opens from time to time to remove excess buffer from the vial.

Waste removal valve **80** is also used to release pressure from the vial cavity **38** after each part of the cycle.

In operation the following sequence of steps are executed for each sample processed by the system. Firstly there is a sample load stage and thereafter there is a sample analysis stage. In the sample load stage, firstly a vial **20** is advanced into position by horizontal actuator **24** moving vial holding block **18** in the positioning stage **22**. The insertion head **26** is then coupled with the vial cavity **38** by raising the holding block **18** with vertical actuator **28**. Thereafter a sample load pressure is applied to the vial cavity **38**. The sensor is then used to monitor the end-of-sample, that is the sensor is used to determine when generally the entire sample has been pushed out of the vial **20**. When the end-of-sample is detected, the pressure is released and the sample analysis stage begins. In the sample analysis stage sample analysis pressure is applied to the vial cavity **38**. This pressure is generally lower than the sample load pressure. The sample analysis pressure is applied throughout the sample analysis stage. A preprogrammed combination of buffers is supplied during the sample analysis stage to the vial cavity **38** via the metering pump line. When the end-of-analysis signal is received from the mass spectrometer the next cycle is started. From time to time excess buffer is removed from the vial using the waste removal line **52** and waste valve **80**. Although there is a sensor provided for the purpose of detecting presence of liquid in the waste line, in practice, since the pump output is constant, the waste removal valve is controlled by a simple on/off sequence.

The invention described herein provides a method and equipment for very-low-loss automatic injection of samples into the mass spectrometer column. The automatic sample loader performs a series of cycles, each consisting of two stages: namely sample loading and sample analysis.

During each cycle a vial **20** containing the sample is enclosed in a sealed vial cavity **38**. A short section of tubing **43** connected on one end to the mass spectrometer column **46** and to the metering pump line **72** is inserted into the vial **20**, such that the end of tube **43** reaches the bottom of the vial **20**. The vial cavity **38** is also connected to the pressurized gas lines **66**, **68** and to the waste removal line **52**.

During the sample loading stage the metering pump does not supply any liquid. Pressure applied to the vial chamber will therefore push the sample through the interconnecting tube **43** and into the mass spectrometer column **46**. A sensor is provided to detect the condition when the entire sample has been pushed out of the vial **20**. When this condition is detected, automatic loader triggers the mass spectrometer and the metering pump, and switches to sample analysis stage.

During the sample analysis stage gas pressure (typically lower than the pressure used for sample loading) is applied to the vial chamber and the metering pump supplies a steady flow of preprogrammed combination of buffers. Small portion of the liquid flows through the mass spectrometer column and carries the sample material into the instrument. The majority of pump output flows through the intercon-

necting tube into the vial. This liquid flushes and cleans the interconnecting tube **43**, thus eliminating sample cross-contamination. The excess of the buffer supplied by the metering pump is removed from the vial through the waste removal line **52**.

As used herein, the terms "comprises" and "comprising" are to be construed as being inclusive and opened rather than exclusive. Specifically, when used in this specification including the claims, the terms "comprises" and "comprising" and variations thereof mean that the specified features, steps or components are included. The terms are not to be interpreted to exclude the presence of other features, steps or components.

It will be appreciated that the above description related to the invention by way of example only. Many variations on the invention will be obvious to those skilled in the art and such obvious variations are within the scope of the invention as described herein whether or not expressly described.

The invention claimed is:

1. An automatic sample loader for use in association with a mass spectrometer and at least one vial containing a liquid sample, the loader comprising:

a vial block having at least one vial cavity, each vial cavity adapted to receive a vial;

an insertion head adapted to be sealingly engageable in the vial cavity;

an insertion tube operably connected to the mass spectrometer through the insertion head, such that the tube extends into the vial when the insertion head is sealingly engaged in the vial cavity;

a means for pushing the liquid sample out of the vial and into the tube;

and a means for moving the insertion head relative to the vial block from an engaged position to a disengaged position.

2. An automatic sample loader as claimed in claim **1** wherein there are a plurality of vial cavities in the vial block and further including a means for advancing the vial block relative to the insertion head.

3. An automatic sample loader as claimed in claim **2** further including a two degree of freedom linear positioning stage and wherein the vial block is positioned in the positioning stage and movement of the positioning stage moves the vial block relative to the insertion head.

4. An automatic sample loader as claimed in claim **3** wherein each vial cavity includes a liftable lid and each lid is adapted to be lifted prior to moving into the engaged position.

5. An automatic sample loader as claimed in claim **3** wherein the insertion head includes a plurality of pressure ports and the insertion tube is connected through one of the plurality of pressure ports and the insertion tube extends into the vial when in the engaged position.

6. An automatic sample loader as claimed in claim **5** further including a waste tube which extends through another of the plurality of pressure ports in the insertion head.

7. An automatic sample loader as claimed in claim **6** further including a compressed gas tube which extends through another of the plurality of pressure ports in the insertion head whereby gas is pushed into the vial through the compressed gas tube and the contents of the vial are pushed into the insertion tube thus providing means for pushing the liquid sample out of the vial.

8. An automatic sample loader as claimed in claim **7** further including a sensor.

9. An automatic sample loader as claimed in claim **8** wherein the sensor includes a first electrode extendable into the vial and a second electrode and wherein an impedance measure therebetween provides an indication of the amount of the liquid sample in the vial.

10. An automatic sample loader as claimed in claim **9** further including a waste removal electrode connected to the waste tube.

11. An automatic sample loader as claimed in claim **10** further including a three degree of freedom adjustment stage adapted to support a mass spectrometer column which is operably connected to the mass spectrometer.

12. A method of loading a sample for a mass spectrometer comprising the steps of:

advancing a vial cavity having a vial with a liquid sample therein into a predetermined position relative to an insertion head;

lowering the insertion head into the vial cavity;

coupling the insertion head into the vial cavity;

applying pressure to the vial cavity whereby the liquid sample is drawn into the insertion head;

de-coupling the insertion head from the vial cavity.

13. A method of loading as claimed in claim **12** further including the step of determining if the vial is empty.

14. A method of loading as claimed in claim **13** further including the step of applying a buffer to the vial.

15. A method of loading as claimed in claim **14** further including the step of removing waste.

16. A method of loading as claimed in claim **12** wherein a plurality of vial cavities are provided in a vial block.

* * * * *