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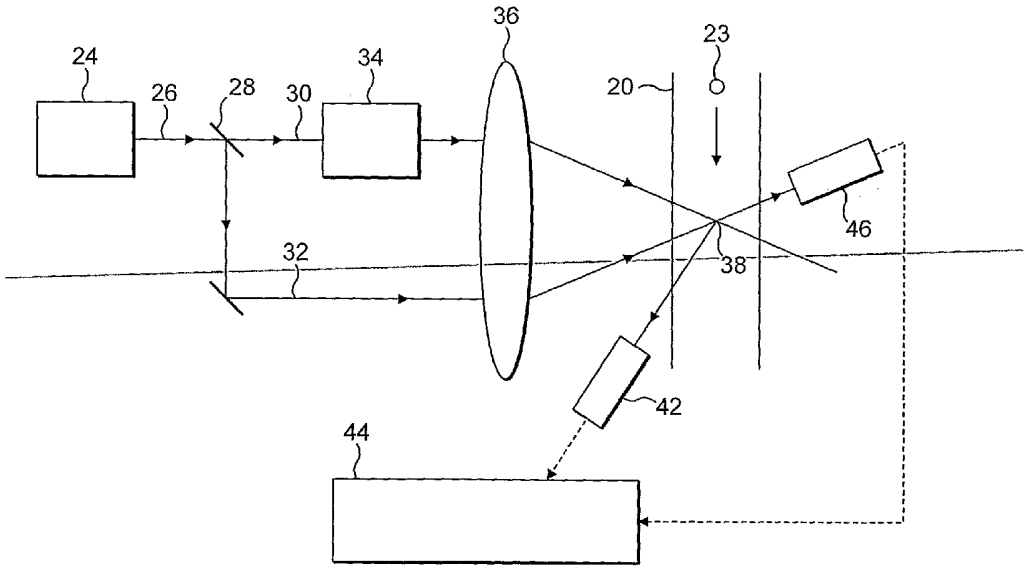
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(54) **Title:** METHOD OF MONITORING A FREEZE DRYING PROCESS



(57) **Abstract:** In a method of monitoring a freeze drying process conducted in a chamber (12) housing a sample (14) to be freeze dried, a set of optical interference fringes (40) is formed from the crossing of two coherent light beams (30,32) within a duct (20) conveying water molecules (23) from the chamber (12) to a condenser (22). A detector (42,46) detects light diffused by the water molecules (23) as they pass through the interference fringes (40) to determine the presence of water molecules (23) within the duct (20). From the detected light, information regarding the water molecules (23), for example, velocity and amount, can be obtained.

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METHOD OF MONITORING A FREEZE DRYING PROCESS

The present invention relates to a method of, and apparatus for, monitoring a freeze drying process, and to freeze drying apparatus including such monitoring apparatus.

Freeze drying is a process that removes from a product water in the form of ice. Freeze drying is particularly useful in the pharmaceutical industry, as the integrity of the products is preserved during the freeze drying process and product stability can be guaranteed over relatively long periods of time.

Freeze drying apparatus typically comprises a freeze drying chamber for receiving a plurality of containers or vials containing the product to be freeze dried. The chamber usually includes a number of shelves, each of which can be raised and lowered within the chamber relative to a loading position at which the vials can be loaded on to the shelf. Access to the chamber for automated loading and removal of vials is generally through a rectangular opening, or slot, formed in a wall or in the main door of the chamber. A moveable slot door selectively opens and closes the slot.

In the freeze drying process, the temperature of the chamber is initially reduced to freeze the product within the vials. The chamber is then evacuated while being heated to cause the frozen ice to sublimate into water vapour. The water vapour is drawn from the chamber by a vacuum pump, and is condensed within a condensation chamber in communication with the freeze drying chamber. Ice condensed within the condensation chamber can be removed in a later stage. The driving force for the water vapour transport is the pressure difference between vacuum chamber and condenser chamber. This pressure difference is caused by the fact that the condenser is kept at a lower temperature than the frozen product. The vacuum pump serves as a facilitating element, in terms of minimising the 'mean free path length'.

In order to minimise the duration of the freeze drying process, and thus maximise sample through-put and reduce costs, it is desirable to monitor the freeze drying process in order to determine when one or more stages of the freeze drying has been completed. However, it is important that any monitoring of the freeze drying process should have minimum influence on the product being freeze dried, particularly when the product is a pharmaceutical product, and on the automated loading and unloading mechanisms used to load and unload the shelves of the freeze drying chamber.

In a first aspect, the present invention provides a method of monitoring a freeze drying process conducted on a sample housed in a chamber, the method comprising the steps of forming a set of optical interference fringes within a path along which water molecules drawn from the sample during the freeze drying process are conveyed from the chamber, and detecting light diffused by water molecules as they pass through the interference fringes.

The interference fringes are preferably formed from the crossing of two coherent light beams, leading to spatially defined lines of maximum and minimum intensity. From the detected light, not only can the presence of water molecules be detected, but also one or more characteristics the water molecules drawn from the sample can be obtained. For example, the velocity of the water molecules passing through the interference fringes can be determined from the frequency of the diffused light, and the amount of water passing through the interference fringes can be determined from the amplitude of the diffused light. This can provide continuous, accurate information regarding the status of the freeze drying process at a well-defined location, namely the location of the interference fringes. As this information is obtained remotely from the chamber in which the freeze drying is being performed, there is no influence on the sample, the freeze drying process or any other operations conducted within the chamber.

The information obtained from the diffused light can be used to control the freeze drying process within the chamber. For example, the end point of the sublimation of the water molecules from the sample can be detected from the absence of any diffused light and thus from the lack of any water molecules passing through the interference fringes. Once this end point has been detected, appropriate control actions can be taken, for example a subsequent step of the freeze drying process can be commenced.

The interference fringes may be conveniently formed within a duct for conveying the water molecules from the chamber, at least part of the duct being substantially transparent to the light from which the interference fringes are formed. Where the fringes are formed from light having a near-infrared wavelength ("NIR light"), for example, a wavelength in the range from 700 to 2500 nm, or from light having a terahertz frequency ("terahertz radiation"), for example, a frequency within the range from 100 GHz (10^{11} Hz) to 30 THz ($3x10^{13}$ Hz), the duct, or at least windows in the duct for permitting light to enter and leave the duct, may be formed from glass or plastics material. The light source from which the interference fringes are formed is preferably tuneable so that the light is emitted therefrom with an appropriate wavelength.

The interference fringes may be scanned across the duct in order to provide a profile of the characteristics of the water molecules across the width of the duct, rather than just in, say, the middle of the duct. Using common optical instrumentation like lenses and mirrors, the positioning of the fringe pattern can be adjusted at will. Thus it can be possible to acquire position-resolved information. This information can be useful to determine local inhomogeneities or anomalies that cannot be otherwise acquired. The interference fringes may alternatively, or additionally, moved along the duct at a constant velocity, for example by using a Bragg cell or a rotating slit pattern to form a set of interference fringes moving along the duct. This can create a 'bias' signal, which can enable a distinction to be made between positive and negative flow directions. The movement of the fringes in this manner may be desirable

when the fringes are formed at a location close to a bend or other structural discontinuity at which the flow of water molecules may not be unidirectional.

When NIR light or terahertz radiation is used to generate the interference pattern, the light transmitted through the molecules as they pass through the duct may be analysed spectroscopically to determine one or more physical and/or chemical characteristics of the water molecules. These characteristics include, but are not limited to, "fingerprinting" or characterisation of the water molecules, and temperature. By detecting the light transmitted through the water molecules as they pass through the duct, time domain waveforms can be obtained. These time domain waveforms may be transformed using a Fourier transformation algorithm into frequency domain waveforms. Certain materials can be analysed through frequency-dependent absorption, dispersion, and reflection of NIR light and terahertz radiation. With regard to the present invention, water molecules have a characteristic absorption of NIR light and terahertz radiation, and so by monitoring light transmitted through the water molecules as they pass through the duct, characteristics, such as the size and/or temperature, of the water molecules output from the chamber can be determined. Furthermore, from the width of pulses obtained from frequency domain waveforms, an indication of the pressure within the chamber can be obtained.

Another application of the information from the frequency-domain data is the analysis of the structure of the velocity pattern. As is known from fundamental literature on turbulence, the frequency spectrum of a continuously recorded velocity signal can provide much structural information on the velocity field. This in turn can provide further insight in the freeze drying process and the interference with mechanical structures like shapes of ducts, shapes of valves, etc.

The method can also be used to measure the velocity pattern in the condenser. This is important to improve the reliability of the freeze dryer in

relation to optimum space occupation. Usually the condensers are designed to a rather high overcapacity to assure undisturbed freeze drying processes, but at the same time this type of design has a very high space requirement.

In a second aspect, the present invention provides apparatus for monitoring a freeze drying process conducted on a sample housed in a chamber, the apparatus comprising means for forming a set of optical interference fringes within a path along which water molecules drawn from the sample during the freeze drying process are conveyed from the chamber, and means for detecting light diffused by water molecules as they pass through the interference fringes.

In a third aspect, the invention provides freeze drying apparatus comprising a chamber for housing a sample to be freeze dried, a duct for conveying from the chamber water molecules drawn from the sample during the freeze drying, means for forming a set of optical interference fringes within the duct, and means for detecting the light diffused by the water molecules as they pass through the fringes.

Features described above relating to a method aspect of the invention are equally applicable to apparatus aspects, and vice versa.

Preferred features of the present invention will now be described with reference to the accompanying drawings, in which:

Figure 1 illustrates schematically a freeze drying apparatus;

Figure 2 illustrates one example of an apparatus for forming interference fringes within a duct of the freeze drying apparatus of Figure 1 and for detecting light diffused from water within the duct;

Figure 3 illustrates the interference fringes in more detail; and

Figure 4 illustrates another example of an apparatus for forming interference fringes within a duct of the freeze drying apparatus of Figure 1 and for detecting light diffused from water within the duct.

With reference first to Figure 1, a freeze drying apparatus 10 comprises a freeze drying chamber 12 for receiving a plurality of containers or vials 14 containing the product to be freeze dried. The chamber 10 includes a number of shelves 16, each of which can be raised and lowered within the chamber 12 to a loading position at which the vials 14 can be loaded on to the shelf 16. Access to the chamber 12 for automated loading and removal of vials is generally through a rectangular opening, or slot, formed in a wall or in the main door of the chamber. A moveable slot door selectively opens and closes the slot. A vacuum pump 18 for evacuating the chamber 12 during a freeze drying process is connected to the chamber 12 by a duct 20. A condenser 22 is provided within the duct 20, or within a separate condenser chamber, for condensing water vapour drawn from the samples contained within the vials 14 during the freeze drying process.

Figure 2 illustrates an example of an apparatus for detecting the presence of water molecules 23 within the duct 20 during the freeze drying process. The apparatus comprises a light source 24. The light source 24 may be a laser configured to emit a beam of light 26 having a near-infrared wavelength ("NIR light") within the range from 700 to 2500 nm, or a laser configured to emit a beam of light 26 having a terahertz frequency ("terahertz radiation") within the range from 100 GHz (10^{11} Hz) to 30 THz ($3x10^{13}$ Hz). The light source 24 is preferable tuneable so that light of a desired wavelength or frequency can be emitted therefrom. The beam of light 26 is incident on a beam splitter 28, which splits the light into two laser beams 30, 32 of the same intensity. The first beam passes through a compensator 34 to assure coherence between

the two beams 30, 32, and the two beams 30, 32 are incident upon a lens 36 that focuses the laser beams on a single point 38 located within the duct 20.

The duct 20 is preferably formed from material, such as glass or plastics material, which is substantially transparent to the laser beams 30, 32. Alternatively, the duct 20 may be formed with a number glass or plastics windows through which light enters and leaves the duct 20.

As illustrated in Figure 3, a set of inference fringes 40 comprising spatially defined lines of maximum and minimum intensity is generated at the focal point of the lens 36. The fringe interval d_f is given by the expression

$$d_f = \lambda / 2\sin\frac{\theta}{2}$$

where λ is the wavelength of the laser beams 30, 32 and θ is the intersecting angle of the laser beams 30, 32. As a water molecule moves through the duct 20 perpendicularly to the fringes 40, light is scattered or diffused by the molecule. A first detector 42 detects the diffused light. The detector 42 may comprises an array of individual detectors 34 each for detecting NIR light or terahertz radiation incident thereon. For example, for terahertz radiation the imaging array may be provided by any suitable array of detectors, for example the detectors manufactured by Picometrix Inc., in which a microfabricated antenna structure is deposited over a fast photoconductive material, such as GaAs. The antenna structure serves to concentrate the incident radiation upon the surface of the GaAs layer, which creates a photocurrent within the detector.

In the example illustrated in Figure 2, the first detector 42 is located on the same side of the duct 20 as the light source 24. However, the first detector 42 may be located in any suitable location for detecting the light diffused by the water molecules. For instance, the first detector 42 may be located on

the opposite side of the duct 20 to the light source 24, or may be located between the light source 24 and the lens 36, as desired. The first detector 42 outputs to a controller 44 electrical signals indicative of the diffused light incident thereon. The signals received by the controller 44 are in the form of a succession of sinusoidal bursts, each of which is generated by the passage of a water molecule through the fringes 40. Where there are many water molecules passing through the fringes 40 at a constant speed, the signal received by the controller 44 is a continuous signal. In either event, the received signal has a frequency f_d that is linearly proportional to the velocity v_m of the water molecule through the duct 20, and given by the expression

$$f_d = \frac{v_m}{d_f}$$

Therefore, not only can the presence of water molecules within the duct 20 be detected from the light diffused from the fringes 40, but the velocity of those water molecules can also be determined. In addition, the amplitude of the signal conveyed to the controller 44 is indicative of the amount of water passing through the fringes 40. By moving the lens 36 towards and away from the duct 20, the set of interference fringes 40 may be scanned across the width of the duct 20. This can enable a velocity and/or amplitude profile to be obtained for water molecules conveyed through the entire width of the duct 20. As the water molecules are drawn from the chamber during a freeze drying process, the molecules pass through the fringes at a sub-atmospheric pressure.

Further information regarding the status of the freeze drying process conducted within the chamber 12 can be determined by detecting light transmitted through the water molecules passing through the duct 20. As illustrated in Figure 2, a second detector 46, similar to the first detector 42, is provided on the opposite side of the duct 20 for detecting light transmitted through the water molecules located within the path of one of the laser beams

30, 32., and of outputting signals indicative of the detected light to the controller 44. Water molecules have a distinctive absorption of NIR light and terahertz radiation, and from the signals received by the controller 44, from the second detector 46, information regarding the temperature of the water molecules and the pressure in the chamber 12 can be obtained.

From the signals received from the detectors 42, 46, the controller 44 can control the freeze drying process conducted within the chamber 12. For example, the controller is able to determine when there are substantially no water molecules within the duct 20, and thus determine the end of the sublimation of water from the samples contained within the vials 14 located in the chamber 12. The controller 44 can then commence another stage in the freeze drying process.

Figure 4 illustrates another example of an apparatus for detecting the presence of water molecules 23 within the duct 20 during the freeze drying process. The example of Figure 4 differs from the example of Figure 2 insofar as the beam splitter 28 and compensator 34 have been replaced by a Bragg cell 50 for splitting the beam of light 26. As is known, a Bragg cell a glass crystal with a vibrating piezoelectric crystal attached to the glass crystal. The vibrations generate acoustical waves, which create local maxima and minima within the glass crystal and cause the glass crystal to ac like an optical grid. The output of the Bragg cell is two beams of equal intensity with frequencies f_0 and f_{shift}. These are focused into optical fibres bringing them to lens 36.

The frequency shift obtained by the Bragg cell 50 makes the set of interference fringes move at a constant velocity v_f along the duct 20. Consequently, the received signal has a frequency f'_d that is given by the expression

$$f_d' = \frac{v_m - v_f}{d_f}$$

Water molecules which are not moving will generate a signal of the shift frequency f_{shift}., whilst water molecules moving in opposing directions within the duct will generate respective signals of different frequencies.

CLAIMS

1. A method of monitoring a freeze drying process conducted on a sample housed in a chamber, the method comprising the steps of forming a set of optical interference fringes within a path along which water molecules drawn from the sample during the freeze drying process are conveyed from the chamber, and detecting light diffused by water molecules as they pass through the interference fringes.

2. A method according to Claim 1, wherein the interference fringes are formed from the crossing within the duct of two coherence light beams.

3. A method according to Claim 1 or Claim 2, wherein the interference fringes are formed within a duct for conveying the water molecules from the chamber, at least part of the duct being substantially transparent to the light from which the interference fringes are formed.

4. A method according to Claim 3, wherein the interference fringes are periodically moved across the duct.

5. A method according to Claim 3, wherein the interference fringes are moved along the duct.

6. A method according to any of Claims 3 to 5, wherein the light transmitted through the water molecules as they pass through the duct is detected, and at least one time domain waveform is obtained from the transmitted light, the time domain waveform being used to determine one or more characteristics of the water molecules passing through the duct.

7. A method according to Claim 6, wherein said at least one time domain waveform is used to generate at least one frequency domain waveform from which said one or more characteristics of the water molecules passing through the duct are determined.

8. A method according to Claim 7, wherein the pressure within the chamber is determined from the frequency domain waveforms.

9. A method according to any preceding claim, wherein the interference fringes are formed from light emitted from at least one tuneable light source.

10. A method according to any preceding claim, wherein the interference fringes are formed from light having a near-infrared wavelength.

11. A method according to any of Claims 1 to 9, wherein the interference fringes are formed from light having a terahertz frequency.

12. A method according to any preceding claim, wherein the velocity of the water molecules passing through the interference fringes is determined from the frequency of the diffused light.

13. A method according to any preceding claim, wherein the amount of water passing through the interference fringes is determined from the amplitude of the diffused light.

14. A method according to any preceding claim, wherein the water molecules pass through the interference fringes at a sub-atmospheric pressure.

15. Apparatus for monitoring a freeze drying process conducted on a sample housed in a chamber, the apparatus comprising means for

forming a set of optical interference fringes within a path along which water molecules drawn from the sample during the freeze drying process are conveyed from the chamber, and means for detecting light diffused by water molecules as they pass through the interference fringes at a sub-atmospheric pressure.

16. Freeze drying apparatus comprising a chamber for housing a sample to be freeze dried, a duct for conveying from the chamber water molecules drawn from the sample during the freeze drying, means for forming a set of interference fringes within the duct, and means for detecting the light diffused by the water molecules as they pass through the fringes.

17. Apparatus according to Claim 16, wherein at least part of the duct is substantially transparent to the light from which the interference fringes are formed.

18. Apparatus according to Claim 16 or Claim 17, comprising means for moving the interference fringes across the duct.

19. Apparatus according to Claim 16 or Claim 17, wherein the interference fringe forming means is configured to form a set of interference fringes moving along the duct.

20. Apparatus according to any of Claims 15 to 19, wherein the means for forming the interference fringes comprises means for forming two converging coherent light beams that cross to form the interference fringes.

21. Apparatus according to any of Claims 15 to 20, comprising means for detecting light transmitted through the water molecules as they pass through the duct, means for generating at least one time domain

waveform from the transmitted light, and means for determining therefrom one or more characteristics of the water molecules passing through the duct.

22. Apparatus according to Claim 21, comprising means for obtaining at least one frequency domain waveform from said at least one time domain waveform, and for determining therefrom said one or more characteristics.

23. Apparatus according to Claim 22, comprising means for determining the pressure within the chamber from the frequency domain waveforms.

24. Apparatus according to any of Claims 15 to 23, wherein the fringe forming means comprises a tuneable light source and means for producing two intersecting light beams from light emitted from the light source.

25. Apparatus according to Claim 24, wherein the light source is configured to emit light having a near-infrared wavelength.

26. Apparatus according to Claim 24, wherein the light source is configured to emit light having a terahertz frequency.

27. Apparatus according to any of Claims 15 to 26, comprising means for determining the velocity of the water molecules passing through the interference fringes from the frequency of the diffused light.

28. Apparatus according to any of Claims 15 to 27, comprising means for determining the amount of water passing through the interference fringes from the amplitude of the diffused light.

29. Apparatus according to any of Claims 15 to 28, comprising means for controlling a freeze drying process conducted within the chamber in dependence on input received from the detecting means.

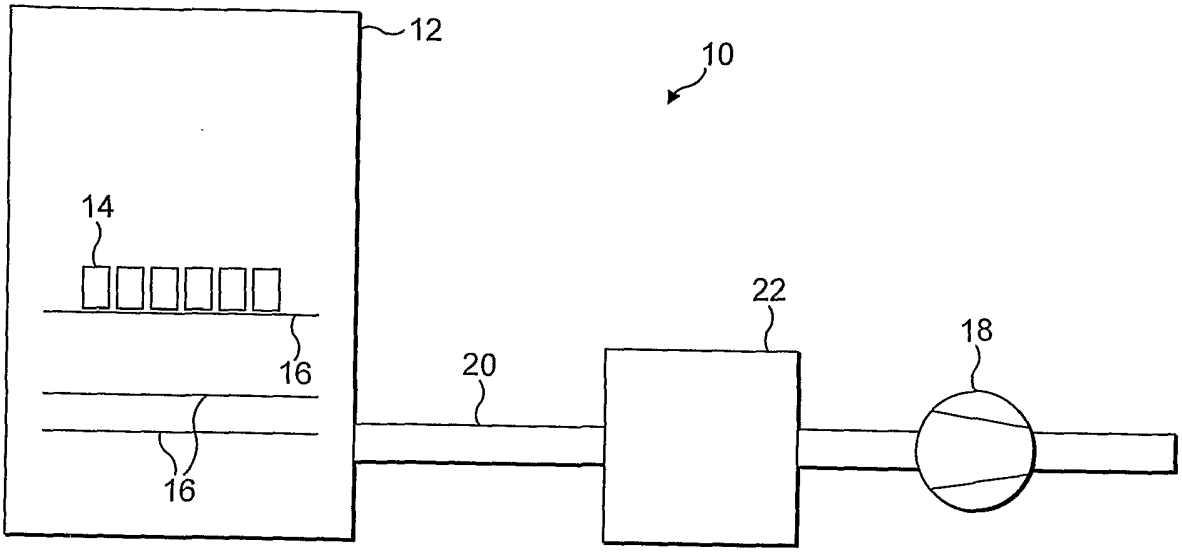


FIG. 1

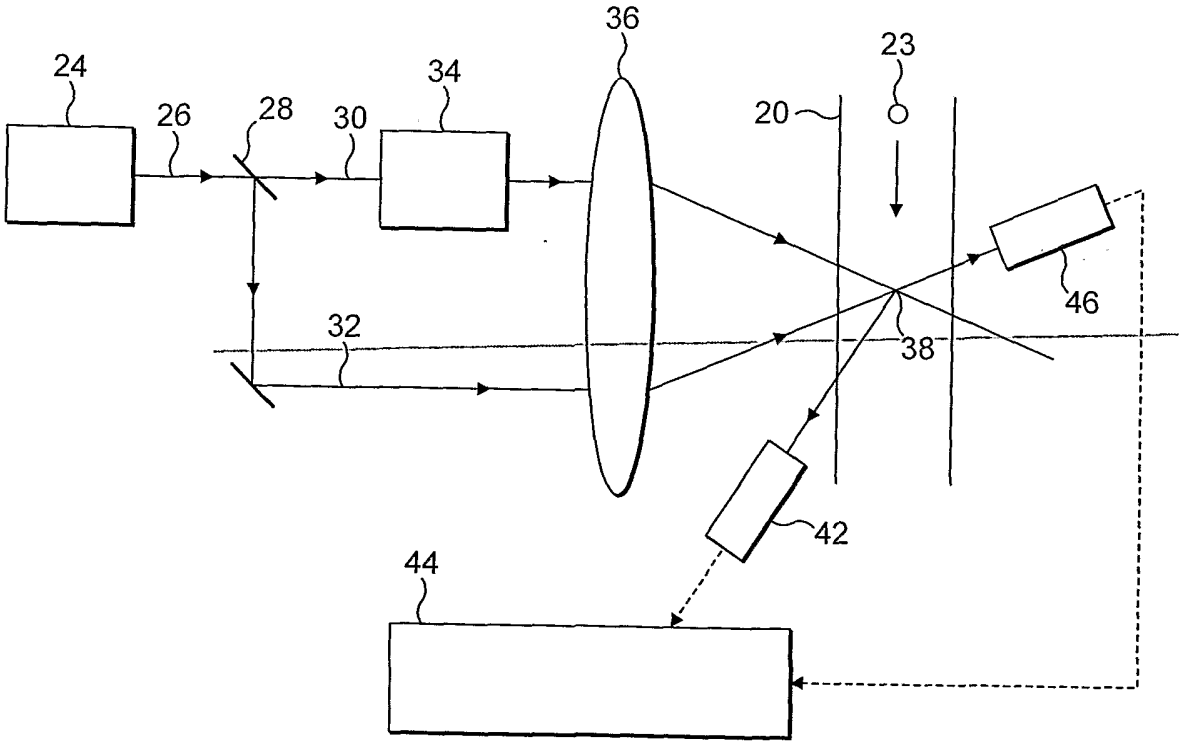


FIG. 2

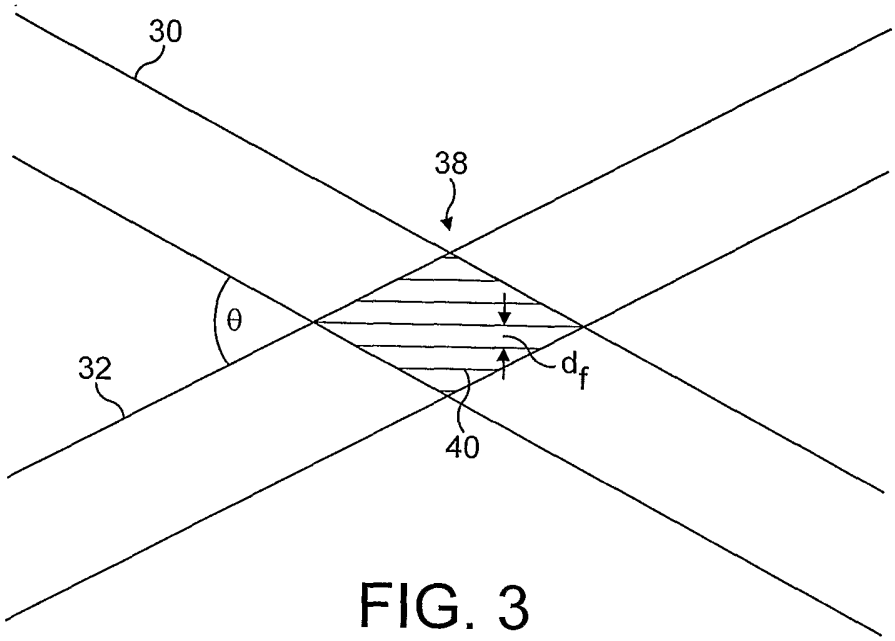


FIG. 3

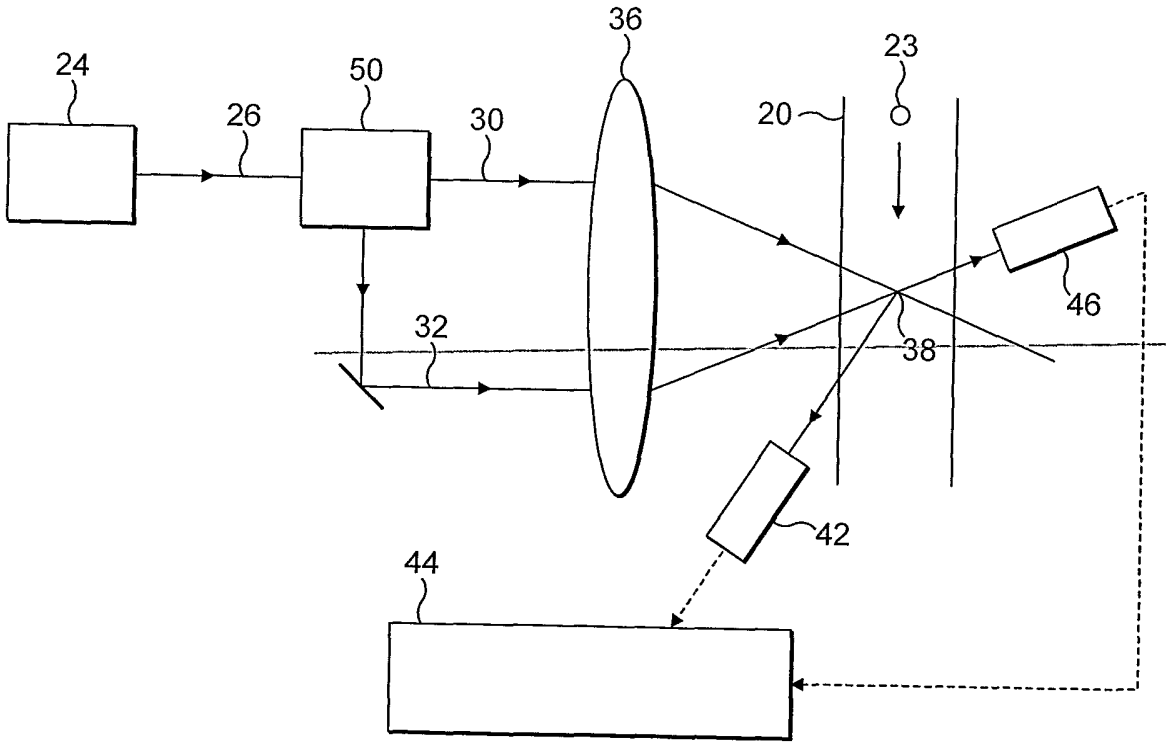


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/000552

A. CLASSIFICATION OF SUBJECT MATTER
INV. F26B5/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
F26B G01F G01N

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2006	02/05/2006

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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