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CA 2727299 C 2017/02/14

(11)(21) **2 727 299**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(86) **Date de dépôt PCT/PCT Filing Date:** 2009/06/08
(87) **Date publication PCT/PCT Publication Date:** 2009/12/17
(45) **Date de délivrance/Issue Date:** 2017/02/14
(85) **Entrée phase nationale/National Entry:** 2010/12/08
(86) **N° demande PCT/PCT Application No.:** EP 2009/057056
(87) **N° publication PCT/PCT Publication No.:** 2009/150134
(30) **Priorité/Priority:** 2008/06/09 (EP08104315.0)

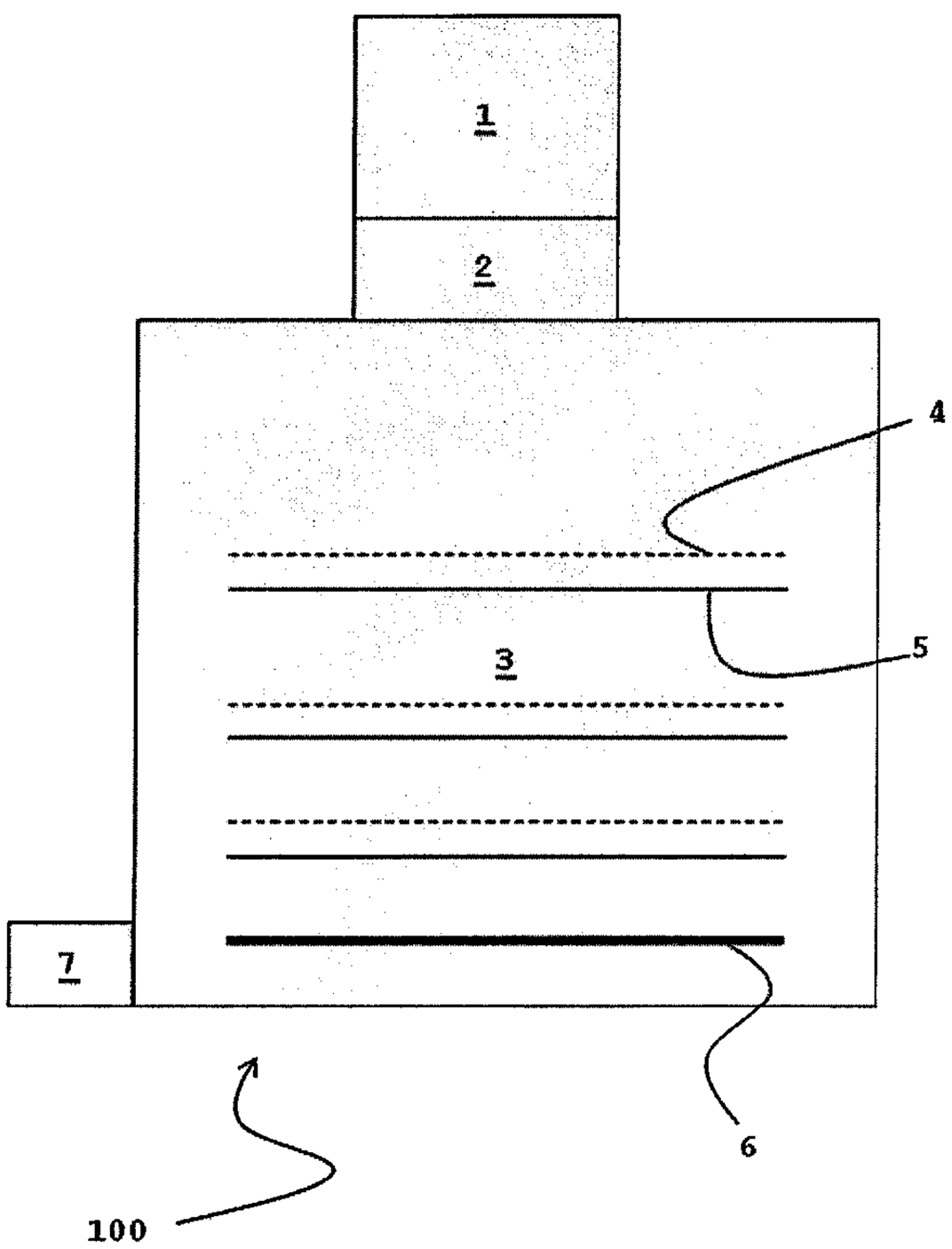
(51) **Cl.Int./Int.Cl.** ***G01N 13/00*** (2006.01)

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(54) **Titre : DISPOSITIF ET PROCEDE DE DETERMINATION DES PROPRIETES DE FORMULATIONS D'AEOROLS**
(54) **Title: DEVICE AND METHOD FOR DETERMINING THE PROPERTIES OF AEROSOL FORMULATIONS**



(57) **Abrégé/Abstract:**
A device (100) for determining the solution rate and release kinetics of aerosol formulations comprises an inhaler (2) connected to a cascade impacter (3), wherein a membrane (6) is disposed on a filter plate of the cascade impacter (2), and an air-liquid model system with a device for collecting measured data

Abstract

A device (100) for determining the solution rate and release kinetics of aerosol formulations comprises an inhaler (2) connected to a cascade impacter (3), wherein a membrane (6) is disposed on a filter plate of the cascade impacter (2), and an air-liquid model system with a device for collecting measured data

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WO2009/150134 PCT/EP2009/057056

DEVICE AND METHOD FOR DETERMINING THE PROPERTIES OF AEROSOL FORMULATIONS

The invention relates to a device for determining the solution rate and release kinetics of an aerosol formulation and a corresponding method therefor.

The following description relates to the testing of pharmaceutical formulations for inhalation in vitro. In particular it relates to the evaluation of the solution or release characteristics of medicaments which are deposited in the lungs after being inhaled. It also relates to the evaluation of formulations which persist as solids in the lung tissue for a significantly longer time than the dissolved form of the substances present. Hitherto, so called "dissolution tests" have been used for inhalants, which are operated either as a sealed system (beaker method, rotary basket method, blade stirrer apparatus) or as an open system (throughflow method). The release medium used is generally an aqueous solution which is intended to simulate the physiological environment of the target organ. The active substance is taken from the release device at defined times and determined analytically.

After inhalation the particles are deposited in different areas of the lungs depending on their aerodynamic properties. The main influencing variables are the particle size, the particle morphology and the particle porosity. For use by inhalation, particles measuring 1-5µm, for example, are produced for depositing in the alveolar region.

Non-water-soluble solid formulations aggregate within minutes in the release medium, depending on their concentration, to form larger structures (~100µm to a few mm), which in certain circumstances contain additional air inclusions. These form additional diffusion barriers and thereby influence the solution or release characteristics of the formulation. A dramatic apparent slowing down of release is the consequence. The present systems do not make it possible to make any

pronouncement as to the actual release characteristics of poorly soluble particles for inhalation.

Moreover, most particle manufacturing methods result in particle mixtures with a relatively broad size distribution. Only the so called fine content of the mixture is deposited in the lungs during inhalation, while a considerable proportion (about 30-70%) of the mixture impacts in the pharynx and is therapeutically ineffective for topical application to the lungs. As the release characteristics are also influenced by the particle size, the therapeutically inactive fraction leads to an apparent delay in the in vitro release of the active substance. The systems currently used do not allow the fine content to be separated from the total population of the particles, which means that it is difficult to give any information as to the fine content.

To summarise, there are currently no standardised test systems which make it possible to investigate the release characteristics of inhalants in which the fine content is taken into consideration and in which the particles in dispersed form are brought into contact with the release medium.

Furthermore, determining the active substance content generally requires laborious analysis, often using high performance liquid chromatography (HPLC).

Moreover, the particles are submerged in the release medium. In the lungs, however, the particles rest on an interface between the lung fluid and the gaseous phase (air-liquid interface). Recently published results show that the release characteristics of solid formulations in the air-interface model behave differently than in the liquid-liquid-interface system.

The following studies recently published as contributions to conferences (posters) show proposed solutions to the disadvantages described above:

- T. Riley et al., Respiratory Drug Delivery, 2008: A filter membrane was fixed to a stage plate of an NGI (New Generation Impactor). A dry powder formulation was then expelled through an MDI (metered dose inhaler) into the NGI. The stage plate and the air flow conditions were selected so that the result was deposition of 4.46µm particles on the membrane. The

membrane was then placed in a dissolution cell and simulated lung fluid was passed through it by the throughflow method. The active substance released was then determined using a sampler and analytical equipment provided downstream. This set-up makes it possible to investigate the fine content, provided that the placing of the membrane on the stage plate does not interfere with the operation of the NGI.

A disadvantage of this is that the apparatus can only be operated in throughflow mode.

- Y.J Son et al., Respiratory Drug Delivery, 2008; this set-up also comprises the use of the NGI. In this case the filter membrane was placed in a container after the depositon test and used to measure the release of the active substance in a sealed dissolution test as described above.

The aim of the invention is to provide an apparatus for determining the solution rate and release kinetics of aerosol formulations, by means of which a concentration of active substance can be measured continuously during the release process. In addition, a corresponding method should be provided.

The application discloses a test system for determining the solution rate and release kinetics of aerosol formulations, comprising an inhaler, which is connected to a cascade impactor, while a hydrophilic membrane is disposed on a filter plate of the cascade impactor and after being charged with particles in the cascade impactor the membrane is placed in a Franz diffusion cell, wherein a first compartment for receiving a liquid release medium is disposed underneath the membrane, so that the membrane is in contact with a release medium, and wherein an air chamber is formed as a second compartment above the membrane, and wherein medium from the first compartment is carried to a device for measurement data acquisition, the membrane consisting of a material selected from among acrylic copolymer, polyethylene sulphone, polysulphone, cellulose, cellulose derivatives, cellulose esters and regenerated cellulose, and the membrane has a maximum thickness of 100µm.

The application also discloses a process for determining the solution rate and release kinetics of aerosol formulations, comprising the steps of (i) releasing an aerosol that is to be measured from an inhaler by means of a cascade impactor, wherein a membrane is disposed on a filter plate in the cascade impactor and (ii) measuring particles immobilised on the membrane by means of a Franz diffusion cell, wherein in the Franz diffusion cell a first compartment for receiving a liquid release medium is disposed underneath the membrane and an air chamber is formed as a second compartment above the membrane, and with a device for measurement data acquisition, using a hydrophilic membrane made of a material selected from along acrylic copolymer, polyethylene sulphone, polysulphone, cellulose, cellulose derivatives, cellulose esters and regenerated cellulose, and the membrane having a maximum thickness of 100µm.

In the apparatus, first of all a preferably standard commercial inhaler is provided with which, in normal operation, a person can administer an active substance. It may be, for example, a portable inhaler of the kind known under the trade mark HandiHaler®. Using the inhaler a dry powder formulation is dispersed so as to obtain a dry powder aerosol of the kind used for administration in humans.

Another embodiment also encompasses the use of an inhaler for applications in animals, e.g. an inhaler of the Dry Powder Insufflater DP4® type made by the company Penncentury.

Also provided is a cascade impactor, for example of the kind made by Anderson Samplers, Atlanta, USA. In a cascade impactor, nozzle plates arranged one behind

the other with reducing nozzle diameters and impact surfaces arranged between the nozzle plates are used to filter a gas current laden with dust. The reduction in cross section increases the velocity of the gas. Whereas fine particles follow the gas current at slow speeds, larger particles are deposited on the filter disc. Thus, individual fractions with different particle sizes are obtained. Finally, a membrane serves to trap the remaining particles that have not yet been deposited, the membrane being arranged in front of the filter plate, when viewed in the direction of flow. Thus, particles of a specific size from a total population of particles are received on a membrane, preferably the fine content of the total population, and are immobilised on the membrane. Theoretically, all the particles could be immobilised in dispersed form on the membrane.

The depositing of the inhalable fraction is preferably carried out by placing this filter on the filter plate of the Anderson Cascade Impactor. Delivery is then carried out in accordance with Pharm. Eur. 2.9.18 (European Pharmacopoeia, 6th edition 2008, Apparatus D - Anderson Cascade Impactor), while only the deposition plates that are not used for the deposition of particles from 0 to 5µm in size are placed in the cascade impactor, so that all the particles smaller than 5µm are deposited on the filter.

Finally, using an air-liquid model system the membrane is brought into contact with a release medium and an active substance concentration is monitored continuously during the release process using a device for detecting measurement data. The particles immobilised on the membrane are not exposed to any other forces such as shear forces, mechanical forces and the like during the contact with the release medium and depending on the situation they rest on an air interface in vivo.

The advantage of the invention is that a particle fraction that would actually be delivered from an inhaler and deposited in the lungs of a person can be tested for its solution or release characteristics. The air-liquid model system simulates the deposition environment of the lungs and there is continuous detection of measurement data using the apparatus, so that the analytical effort involved in the testing process is significantly less than in the prior art. For example, pharmaceutical aerosol formulations can be tested at the research and development

phase and during manufacture and toxicological tests on lung pressure can be carried out with particles from the environment.

Obviously, in principle, any desired particles or medicinally active substances or mixtures of substances may be investigated. Moreover, the delivery of the particles from an inhaler onto a membrane using a cascade impactor can be spatially separate from the actual investigation of the membrane using the air-liquid model or in a single joint apparatus with, for example, an automated transfer of the membrane from the cascade impactor into an air-liquid model.

The use of the cascade impactor does not interfere in a particle separation process within the various nozzles or stages, as a result of which the particles actually deposited on the membrane are not affected. The immobilisation of the particles on the membrane is maintained even during the release process into the release medium in the model system, as the particles are not subjected to any additional forces. Within the air-liquid model system the conditions are simulated to be the same as in a patient's lung, as the particles rest on a liquid-air interface. Thus the particles are not subjected to any changes other than those that take place during dissolution in the release medium. Finally, continuous measurement data acquisition is possible.

The membrane on which the particles are deposited in the cascade impactor and which is suitable for use in the air-liquid model system is characterised in that it is made of a material that can be wetted with water. In particular, a membrane is suitable according to the invention if it has hydrophilic properties and is not water-soluble. By hydrophilic filter materials are meant those materials that have a high affinity for water, which can be wetted with virtually any liquid and can be used for aqueous solutions. Hydrophilic filter materials are preferably selected from among acrylic copolymer, polyethylene sulphone, polysulphone, cellulose, cellulose derivatives, cellulose esters and regenerated cellulose. Membranes made of a hydrophobic filter material are not suitable.

The membrane is further characterised in that it has a maximum thickness of 100µm, preferably 80µm. Moreover, the membrane is characterised in that it does not cause any inherent turbidity in an aqueous medium. In particular, the membrane

is characterised in that no fibre fragments become detached from the membrane. By the property of "creating turbidity in an aqueous medium" is meant that there is a reduction in the light passing through water which has been in intensive contact with the filter material.

Surprisingly, it has been found that in addition to filter materials (membrane) consisting of a hydrophobic material, filter materials which constitute a glass fibre membrane are also unsuitable.

It has been found that filter materials are not suitable if they have been made from glass fibres, Teflon (PTFE) and polyvinylidene fluoride.

Suitable membranes are characterised in that they have a gas permeability of 80 litres per minute.

According to the invention, the membranes can be used on the one hand for the depositing of the particles in the cascade impactor and on the other hand for use directly in the air-liquid model system. The membrane is characterised in that the particles are not only deposited on the surface of the membrane but are immobilised in the filter membrane. The presence of the particles in immobilised form in the membrane is apparent from the fact that the filter membrane can be placed directly in the air-liquid model system without any further treatment.

Preferably, the material used for the membrane is cellulose and cellulose derivatives, particularly cellulose and regenerated cellulose, particularly regenerated cellulose, and it is arranged on the filter plate of the cascade impactor instead of a filter which would normally be provided. This cellulose material ensures virtually total immobilisation of the particles filtered out.

Moreover, the cascade impactor is operated to correspond to human breathing, for example with an air flow of 39 litres per minute over a period of 6.15 seconds, in order to simulate, as closely as possible, the quantity of air breathed in during actual inhalation, with the active substances dispersed from the inhaler.

For this purpose, in an advantageous embodiment, the membrane is such that it allows an air flow of at least 20 litres per minute, particularly 30 litres per minute,

more preferably 39 litres per minute. The membrane has a pore size which allows the trapping of particles preferably with a pore diameter of 0.45µm. A membrane material of this kind can easily be wetted with an aqueous solution and is chemically inert in aqueous solutions and does not normally enter into any interactions with a formulation.

According to a further feature, a two-chamber system is used as the air-liquid model system, preferably a Franz diffusion cell. A lower compartment is filled with a release medium which can be freely selected and the membrane is placed on the surface of the medium, ensuring that no air is still trapped between the release medium and the membrane. The upper part of the cell closes off the system and forms an air compartment.

In this embodiment the lower compartment is connected to a pump by tubes that carry the medium to a device for measurement data acquisition, for example a UV detector or a fluorescence detector. An active substance can be quantitatively detected using detectors of this kind. It goes without saying that the entire apparatus is preferably electronically controlled.

Moreover, the air-liquid model system is preferably designed to be temperature-controlled in order to simulate the body temperature inside the lungs.

Finally, the release medium is mixed with a stirrer system such as a magnetic stirrer in order to distribute an active substance taken up in the release medium more evenly inside the chamber.

It will be understood that the features mentioned above and described hereinafter may be used not only in the particular combination specified but also in other combinations. The scope of the invention is defined purely by the claims.

The invention is hereinafter explained in more detail by reference to an embodiment which refers to the associated drawings, wherein:

Fig. 1 shows an inhaler with a cascade impactor of the apparatus according to the invention,

Fig. 2 shows a Franz cell of the apparatus,

Fig. 3 shows two measurement diagrams.

The apparatus 100 for determining the solution rate and release kinetics of aerosol formulations comprises an inhaler 1, which is commercially available under the trade mark HandiHaler, the mouthpiece of which is inserted in a corresponding socket or adaptor 2 of a cascade impactor 3. The various dotted lines 4 indicate the nozzles and the solid lines 5 indicate the nozzle plates of the successive stages of the cascade impactor 3. On the bottom stage of the cascade impactor 3, any particles that have not yet been filtered out are deposited or immobilised by means of a membrane 6, preferably consisting of regenerated cellulose. Of course, a corresponding vacuum is generated through a vacuum connection 7 in order to operate the cascade impactor 3 or inhaler 1 with, as far as possible, the same volume of breath as a person.

The membrane 6 is then arranged in a Franz diffusion cell 13 as shown in Fig. 2, which is part of the apparatus 100, while underneath the membrane 6 is disposed a first compartment 11 for receiving a liquid release medium free from air bubbles, which reacts continuously, as indicated by the connectors 8 and the throughflow arrow D, and a device for measurement data acquisition, such as a UV or fluorescence detector. Above the membrane 6 an air chamber is formed as the second compartment 12, and the entire diffusion cell 13 (Franz cell) is surrounded by thermal insulation 9 and can be temperature controlled in the desired manner by means of a hotplate 10. The release medium is mixed by means of a magnetic stirrer 14.

In order to characterise the system, first of all salbutamol sulphate, as the sample active substance, was added directly in the form of a dilute solution to the release medium (PBS, phosphate buffered saline) and measured at 225 nm in the photometer. The left hand diagram in Fig. 3 shows that after about four minutes' incubation the active substance concentration reaches a plateau. Salbutamol sulphate applied to the membrane 6 reaches the maximum concentration after about ten minutes. This means that the membrane 6 forms a diffusion barrier for about six minutes. The total system has a reaction time of about ten minutes, i.e. changes in concentration caused by the release of active substance are detected with a ten

minute delay. On the timescale of a typical release test over 24 hours this delay can be disregarded.

Then, spray-dried delayed-release powder particles of salbutamol sulphate are dispersed as a test formulation on a membrane 6, without an additional cascade impactor stage, and the release of the active substance in the release system is investigated.

As can be seen from the right hand diagram in Fig. 3, in an investigation of a total fraction, a burst drug release of 50% was measured and delayed release was observed over 24 hours. By inserting suitable cascade impactor plates it was then possible to investigate particles <2µm and <5.8µm for controlled release, as illustrated in the right hand diagram. The result obtained is a significant size dependency in the release kinetics: the smaller particles release the active substance faster. As the method of particle manufacture with the spray dryer used excludes particles less than 1µm by the use of the cyclone, the fraction <5.8µm can be equated to the fine fraction of the population.

To summarise, the results show that this measuring set-up is suitable for online measurement over at least 24 hours, dispersed particles are immobilised on the membrane 6 and particle mixtures of different aerodynamic diameter can be distinguished.

For acquiring the measurement data, first of all the inhaler is connected by means of the adaptor 2 to the cascade impactor 3 and an aerosol to be investigated is immobilised on the membrane 6 in the cascade impactor 3. The membrane 6 is placed in the Franz diffusion cell 13 which is surrounded by the thermal insulation 9. The connectors 9 configured as inlets and outlets serve to deliver a release medium passing through them to the apparatus for measurement data acquisition, such as a UV detector.

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CLAIMS:

1. Test system for determining the solution rate and release kinetics of aerosol formulations, comprising an inhaler, which is connected to a cascade impactor, while a hydrophilic membrane is disposed on a filter plate of the cascade impactor and after being charged with particles in the cascade impactor the membrane is placed in a Franz diffusion cell, wherein a first compartment for receiving a liquid release medium is disposed underneath the membrane,

so that the membrane is in contact with a release medium,

and wherein an air chamber is formed as a second compartment above the membrane,

and wherein medium from the first compartment is carried to a device for measurement data acquisition, the membrane consisting of a material selected from among acrylic copolymer, polyethylene sulphone, polysulphone, cellulose, cellulose derivatives, cellulose esters and regenerated cellulose, and the membrane has a maximum thickness of 100µm.

2. The test system according to Claim 1, wherein the membrane is made of cellulose.

3. The test system according to Claim 1 or 2, wherein the cascade impactor can be operated to correspond to human breathing.

4. The test system according to any one of Claims 1 to 3, wherein the membrane has a permeability of at least 20 litres per minute, particularly 39 litres per minute, and/or a pore size of 0.45µm.

5. The test system according to any one of Claims 1 to 4, wherein the device for measurement data acquisition is a UV detector or a fluorescence detector.

6. The test system according to any one of Claims 1 to 5, wherein the Franz diffusion cell can be temperature controlled.

7. The test system according to any one of Claims 1 to 6, wherein a stirrer system, particularly a magnetic stirrer, is associated with the Franz diffusion cell.

8. Process for determining the solution rate and release kinetics of aerosol formulations, comprising the steps of

(i) releasing an aerosol that is to be measured from an inhaler by means of a cascade impactor, wherein a membrane is disposed on a filter plate in the cascade impactor and

(ii) measuring particles immobilised on the membrane by means of a Franz diffusion cell, wherein in the Franz diffusion cell a first compartment for receiving a liquid release medium is disposed underneath the membrane and an air chamber is formed as a second compartment above the membrane, and with a device for measurement data acquisition, using a hydrophilic membrane made of a material selected from along acrylic copolymer, polyethylene sulphone, polysulphone, cellulose, cellulose derivatives, cellulose esters and regenerated cellulose, and the membrane having a maximum thickness of 100µm.

9. The process according to Claim 8, wherein the membrane made of cellulose is used.

10. The process according to Claim 8 or 9, wherein the cascade impactor is operated to correspond to human breathing.

11. The process according to Claim 10, wherein the cascade impactor is operated with an airflow of 39 litres per minute over a period of 6.15 seconds.

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12. The process according to any one of Claims 8 to 11, wherein the membrane is used with a minimum permeability of 20 litres per minute, particularly 30 litres per minute and/or with a pore size of 0.45µm.

13. The process according to any one of Claims 8 to 12, wherein a UV detector or a fluorescence detector is used as the device for measurement data acquisition.

14. The process according to any one of Claims 8 to 13, wherein the Franz diffusion cell is temperature controlled.

15. The process according to any one of Claims 8 to 14, wherein a stirring system, particularly a magnetic stirrer, is used to mix the liquid release medium.

16. The process according to any one of Claims 8 to 15 wherein a pump is used to carry the medium from the first compartment by tubes to the device for measurement data acquisition.

17. The test system according to any one of Claims 1 to 7 wherein the first compartment is connected to a pump by tubes that carry the medium to the device for measurement data acquisition.

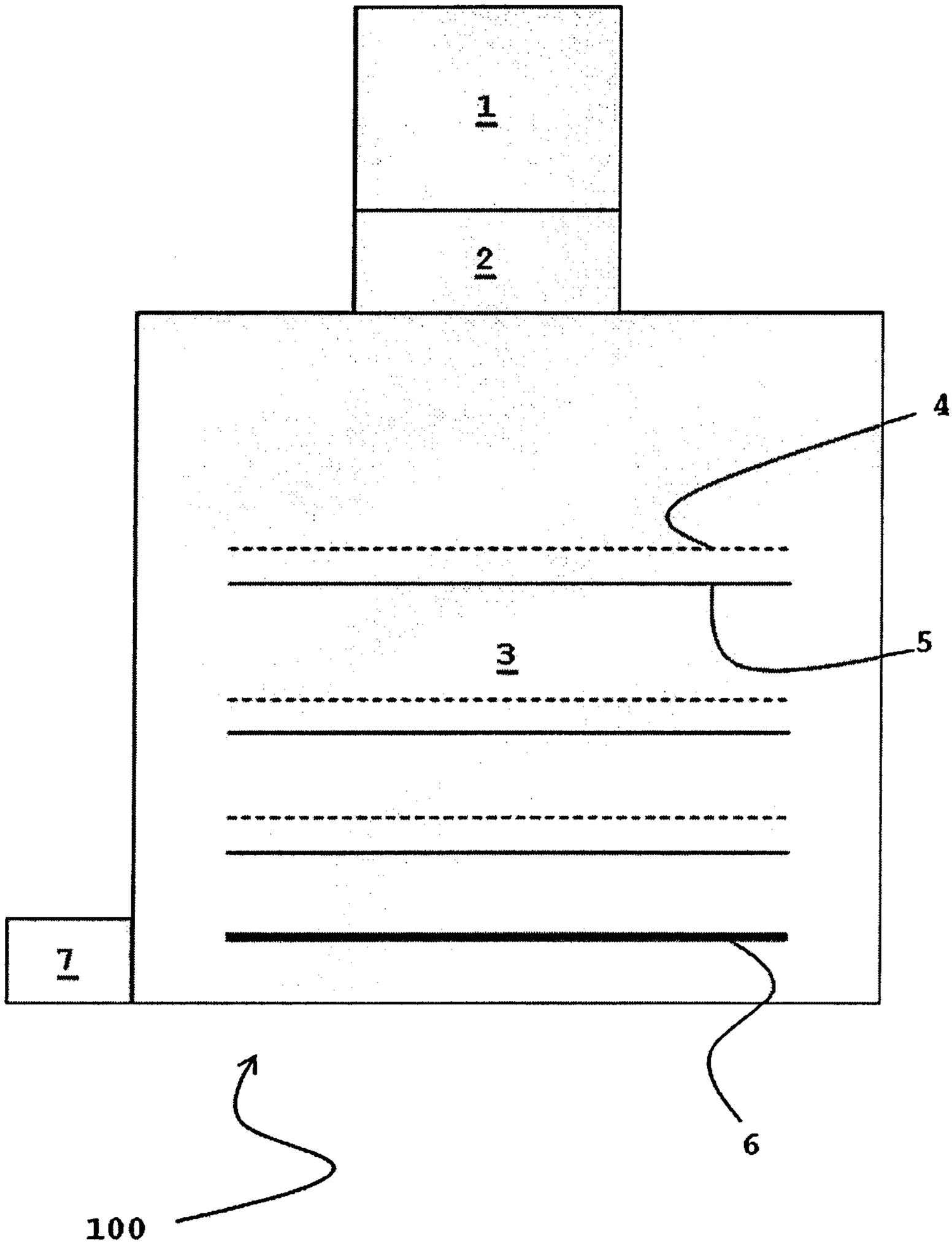


Fig. 1

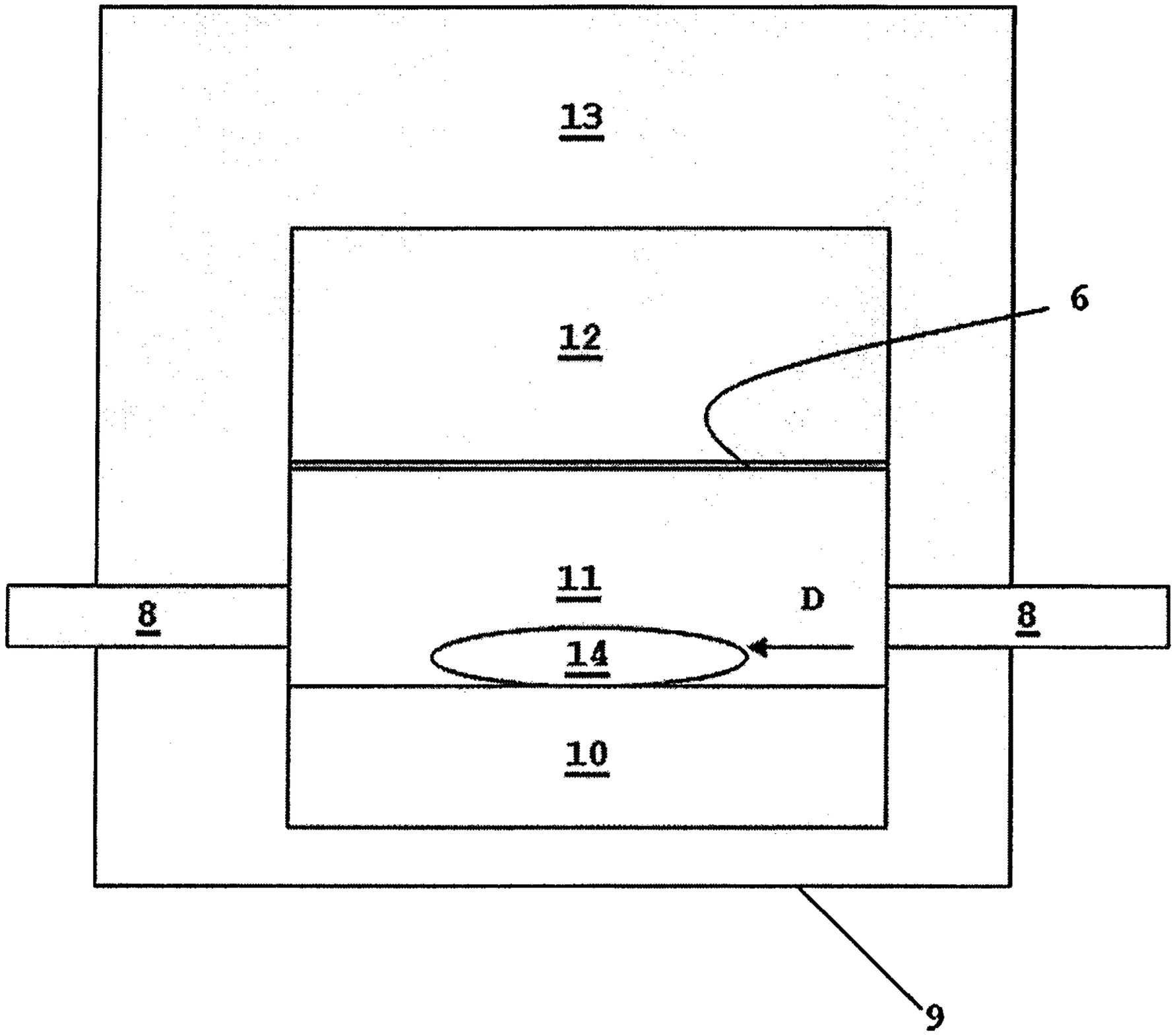
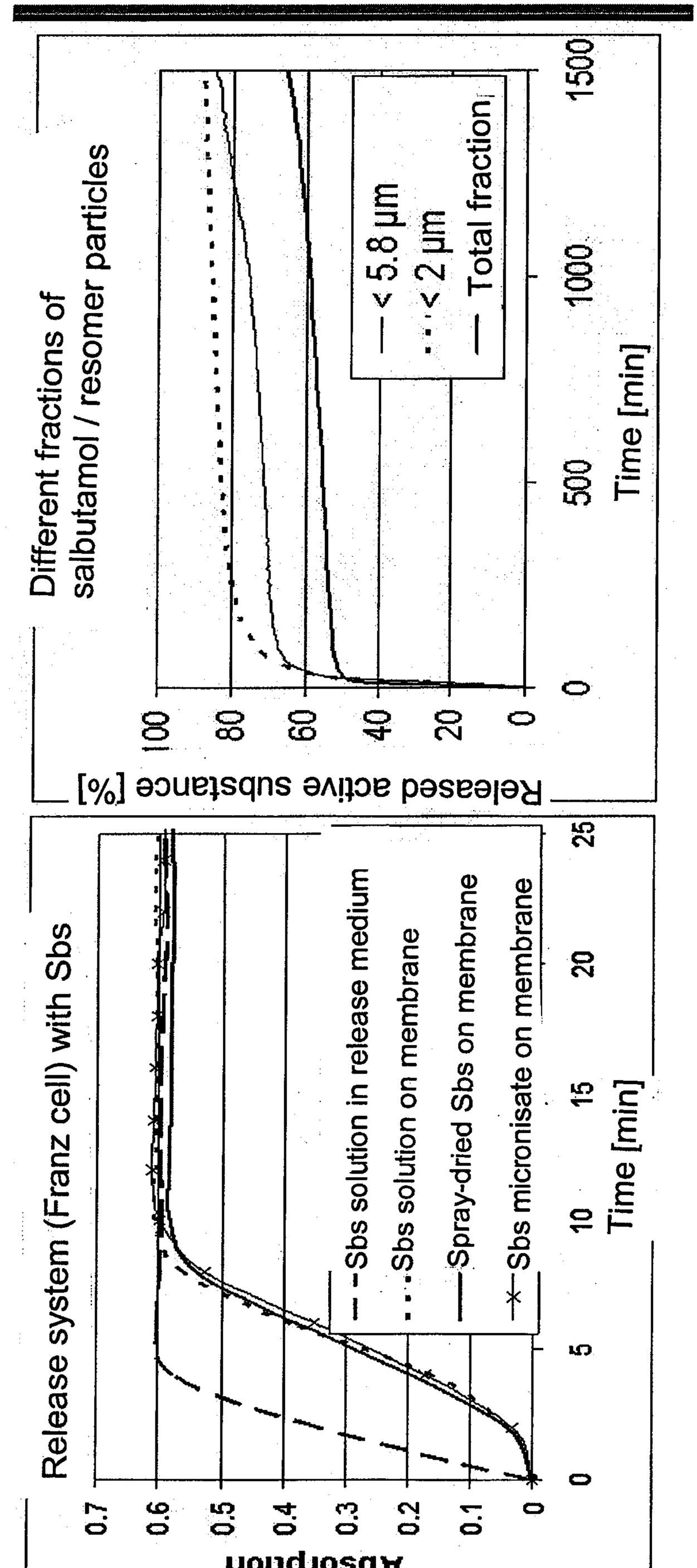


Fig. 2

Fig. 3


Different fractions of salbutamol / resomer particles
Released active substance [%]
100
80
60
40
20
0
0
500
1000
1500
Time [min]
< 5.8 µm
< 2 µm
Total fraction
Release system (Franz cell) with Sbs
Absorption
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
Time [min]
Sbs solution in release medium
Sbs solution on membrane
Spray-dried Sbs on membrane
Sbs micronisate on membrane