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(54) **DEVICE AND METHOD FOR PRODUCING, DOSING AND PACKAGING MEDICAMENTS**

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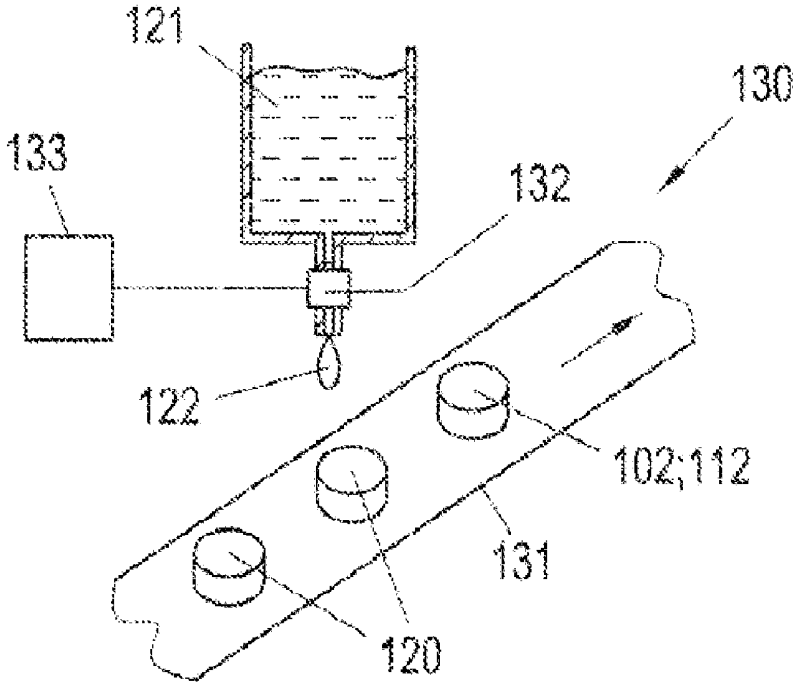
(57) **ABSTRACT**

A method produces a number of medicaments with a predetermined active substance and for simultaneously making an active substance value indicating the active substance quantity contained in the medicament available. A standard value is determined for the active substance quantity of the medicaments and a maximum deviation from the standard value is predefined. An active substance value is selected within an interval cN+/−Δc or predefined and an active substance quantity is used as a reference for the preparation of the respective medicament which quantity matches the active substance value. The active substance value established is associated with the medicament and is held available together with the medicament once the medicament is prepared.



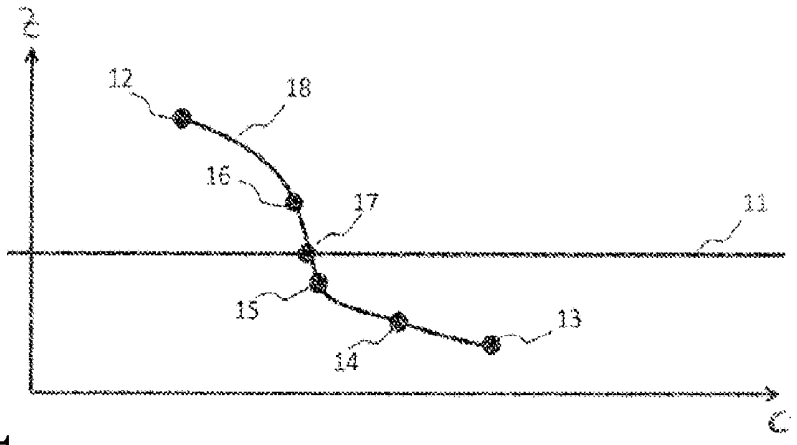


FIG. 1

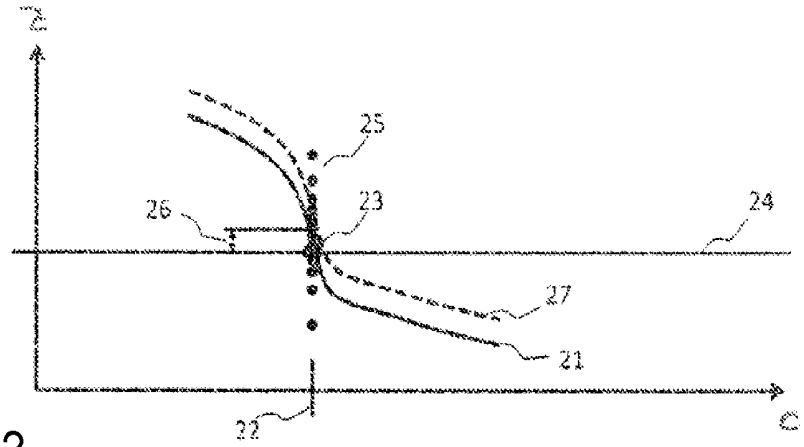


FIG. 2

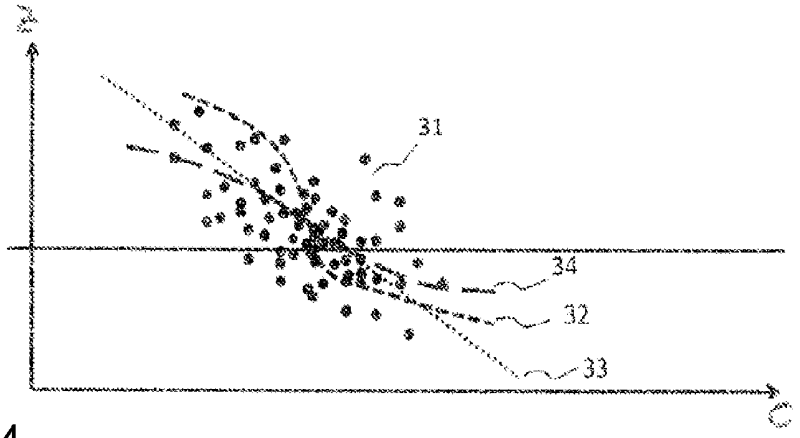


FIG. 4

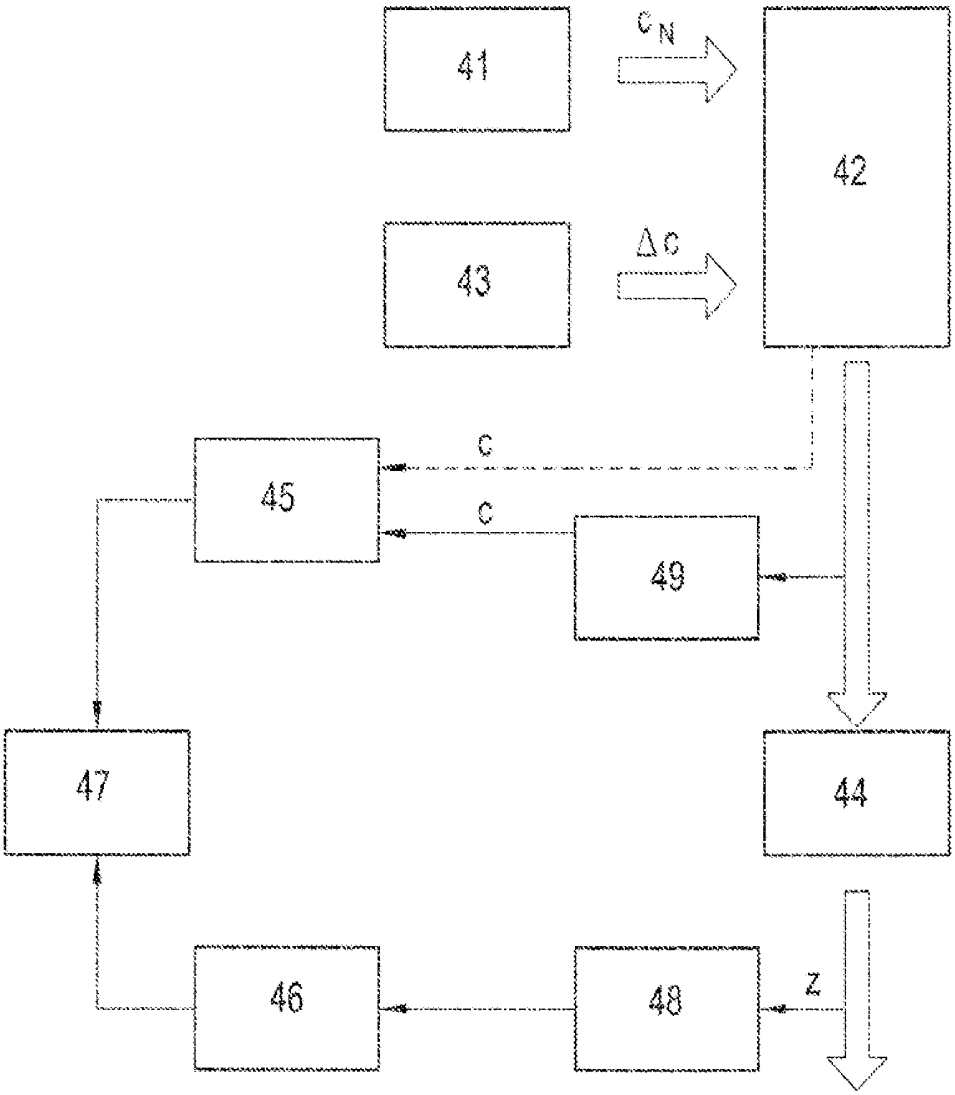


Fig. 3

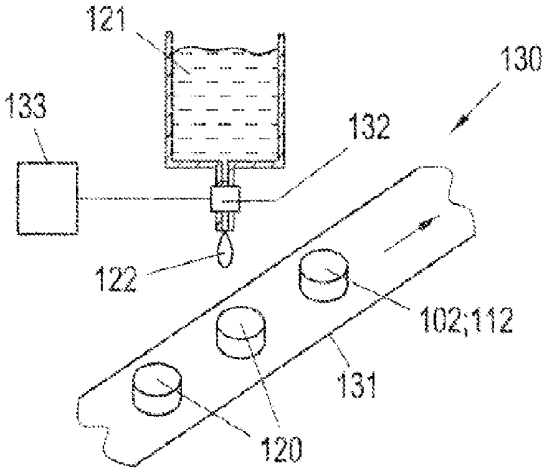


Fig. 5

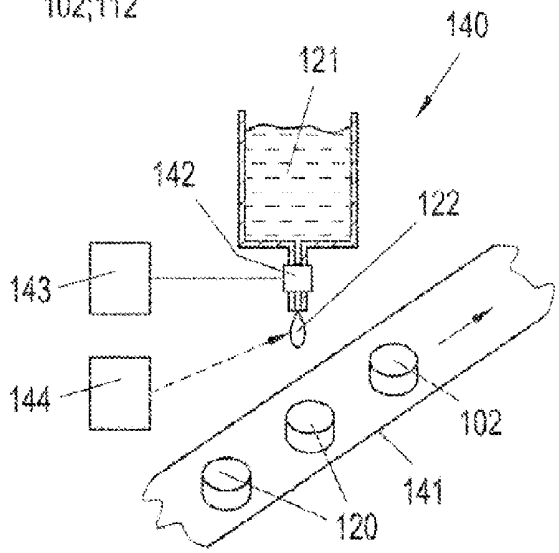


Fig. 6

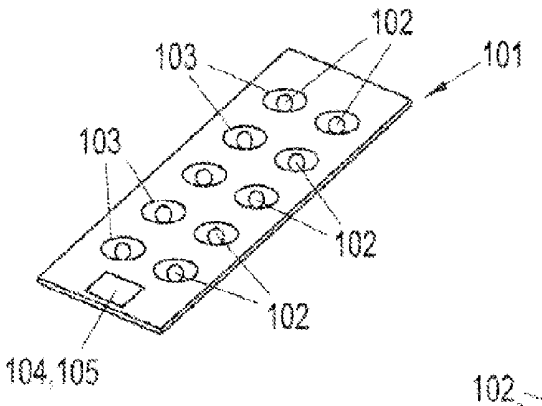


Fig. 7

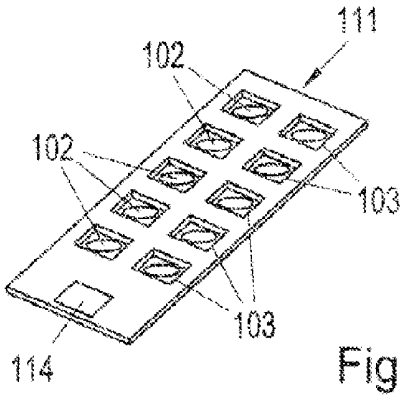


Fig. 8

DEVICE AND METHOD FOR PRODUCING, DOSING AND PACKAGING MEDICAMENTS

[0001] The invention relates to a method for producing medicaments according to the preamble of patent claim **1**. Furthermore, the invention relates to a combination with a medicament blister and storage according to the preamble of patent claim **10**. Finally, the invention relates to a device for producing medicaments according to the preamble of patent claim **15**. The invention also relates to a device for carrying out a therapy according to the preamble of patent claim **21**.

[0002] The invention as well as individual methods, combinations and devices according to the present invention are used in the field of analysis of the effectiveness as well as in the field of compliance- and adherence-measurements of medicaments or treatments.

[0003] The starting point of the invention is a method for determining the sensitivity of a therapeutic measured variable of a person to change of a therapeutic control variable during the therapy. The treatment intensity corresponds—in analogy to control engineering—to the respective control variable, the physiological value to be set, for example, the blood pressure value, corresponds to the measured variable to be controlled.

[0004] In medical therapeutics, it is common, to have an influence on different physiological measured variables of patients with the aid of therapeutic control variables. For example, patients are prescribed medications in a certain doses—this is the control variable with which the blood pressure is influenced—this is the measured variable. The degree of influence of the measured variable can be measured continuously or selectively, invasively or non-invasively with the aid of suitable methods, for example, the systolic and diastolic blood pressure by means of an electronic blood pressure monitor.

[0005] Assuming that all other influencing factors remain constant, it can be assumed, that the relationship between control variable and measured variable m can be represented as a "control variable-measured variable curve." In the pharmaceutical field this relationship is called the dose-response curve. Generalizing, the term treatment intensity also stands for all therapeutic control variables, which are used in this connection.

[0006] The prior art is elucidated in detail by means of two common methods.

[0007] FIG. **1** shows a therapeutic control variable-measured variable curve determined based on a first method.

[0008] FIG. **2** shows a therapeutic control variable-measured variable curve determined based on a second method.

[0009] In FIG. **1** it is shown, for example, how a control variable-measured variable curve can be determined in the course of a treatment. If, for example, a patient is adjusted to a new antihypertensive medication or medicament, a specific target-value of the measured variable z, in the present case a specific blood pressure value, should be achieved. For this purpose, the doctor selects an initial dose of the medication as therapeutic control variable c and measures, if necessary time-delayed after the in-take phase, the blood pressure resulting therefrom as physiological measured variable z. The first point of the control variable-measured variable curve **12** can be derived from this. Depending on the initial value of the measured variable z, the treatment intensity or the control variable c is then adjusted and the measured variable z is measured again. This process is repeated and measured variables z: **14**, **15**, **16** are determined for additional control variables, until that value of the control variable was found, which leads to the desired value of the measured variable. Thus, the dose c of the medication is therefore found, in which the desired blood pressure z is attained for the respective patient. This desired value is also called working point **17** in an analogy to control engineering. By connecting the points, the respective coordinate values of which correspond to control variable c or measured variable z, a graph is obtained, as depicted in FIG. **1**, the control variable-measured variable curve **18**.

[0010] In the course of this adjustment process, individual points of the control variable-measured variable curve are therefore determined. The measured variables z at different control variables are compared with each other and also the sensitivity of the measured variable z to changes in the control variable can be considered. The sensitivity of the measured variable z to changes in the control variable c corresponds to the slope of the control variable-measured variable curve **18**. Each value of the control variable c is set thereby once and by increasing or decreasing the control variable c, with each measurement a new measuring point is found on the control variable-measured variable curve **18**.

[0011] In a scenario in the insulin treatment of diabetics an individual control variable-measured variable curve is determined during the adjustment process. During the therapy, at predetermined times, the patient measures his blood sugar level as measured variable z and subsequently injects that amount c of insulin, which is necessary according to the relationship between control variable and measured variable z obtained from personal experience and medical knowledge, in order to attain the desired value of the measured variable. With each intake of medication and associated blood sugar measurement, thus also even during the ongoing therapy, a point in the control variable-measured variable curve is determined—the curve can thus constantly be adjusted to possible changes.

[0012] However, such an approach can lead to dangerous effects precisely when measuring the sensitivity of a person with respect to changes in the dosage of insulin, since already slight under- and overdoses can cause severe complications.

[0013] It is therefore customary, as depicted in FIG. **2**, no longer to change a medication after the initial setting and to refrain from possible dangers to the patient. As soon as the adequate value of the control variable **22** as well as the associated initial control variable-measured variable curve **21** was found, the medication of the patient is no longer changed for perhaps a long time and the value of the control variable is maintained.

[0014] If the control variable-measured variable curve were temporally invariant and not influenced by other factors, due to the constant control variable **22** at each individual measurement of the measured variable z, one and the same, desired value **24** would be measured and all control variable-measured variable pairs would be located at the working point **23**. However, for several reasons the measured variable z also varies at a constant control variable: in general, disturbance values also influence the measured variable z, for example, time of day, diet, external factors, physical activity, etc. In addition, the measurement is often affected by measurement inaccuracies. As a result, values of the measured variable z deviating from the desired value of the measured variable are therefore measured at the working point at different times and a "one-dimensional point cloud" **25** arises, which has points each with the identical control variable.

[0015] Assuming that the control variable-measured variable curve does not change with time, and that disturbance values and measurement errors are distributed stochastically, the average measured variable of the measured variable z will continue to be the desired value of the measured variable z. However, if the control variable-measured variable curve changes with time—for example, because the body of the patient is accustomed to an administered medication and the effectiveness of the medication diminishes with time—the average value of the measured variable z, which is measured, consequently shifts from the working point.

[0016] If it is found, that, for example, due to this habituation effect the medication of the patient changes and thus the working point must be shifted, as a rule no information is available on this, as to how the control variable-measured variable curve has changed in the meantime.

[0017] In general, no definite statement can be made concerning the changed curve and on how much a slight change in the control variable-measured variable curve—from the working point—could have an impact on the measured variable z, i.e. what slope the control variable-measured variable curve has at the working point.

[0018] The problem addressed by the invention is to provide suitable medicaments or devices, with which a measurement of the individual dose-response curve of a patient is made possible, wherein the dose-response curve can be determined continually at a working point, without disturbing the actual treatment and endangering the patients.

[0019] The invention solves this problem with a method mentioned at the outset with the characterizing features of patent claim **1**. Furthermore, the invention solves the problem with a combination mentioned at the outset of a medicament blister and storage with the characterizing features of patent claim **10**. Further, the invention solves this problem with a device for producing medicaments of the type mentioned at the outset with the characterizing features of patent claim **15**. Finally, the invention solves this problem with a device for producing medicaments of the type mentioned at the outset with the characterizing features of patent claim **21**.

[0020] According to the present invention, with a method is provided for producing a number of medicaments with a predetermined active substance as well as for simultaneously making available an active substance value indicating the respective active substance quantity contained in the medicament, that a standard value to be determined for the active substance quantity of the medicaments and a maximum deviation from this standard value are predefined, wherein an active substance value is selected or predefined within an interval c_N+/−Δc and an active substance quantity is used as a reference for the preparation of the respective medicament, which quantity matches the active substance value, and that active substance value established is associated with the medicament and is kept available together with the medicament once the medicament is prepared.

[0021] With a medicament or medication obtained according to the present invention the respective dose-response curve can be determined. After the administration of the thus-created medications determined physiological measured variables can be put in relation to the active substance values created with the method according to the present invention, whereby a control variable-measured variable curve, particularly a dose-response curve can easily be determined, without changing the basic adjustment of the dosage or the working point of the dosage.

[0022] Advantageously, it can be provided to achieve significant dose-response curves on the basis of the medicament created, that the active substance values of the individual medicaments are predefined as, in particular following a predetermined distribution, in particular uniformly distributed or discretely distributed, random values within a predefined interval c_N+/−Δc.

[0023] For the precise determination of the slope of the control variable-measured variable curve at the working point it can be provided, that the maximum deviation from the standard value is greater than 5%, in particular, greater than 10% of the standard value.

[0024] An especially accurate dosage and handling can be achieved with a medicament available in liquid form. In this connection it is provided that—that an active substance fluid containing the active substance, in particular a solution, emulsion or suspension, as well as a number of excipients, in particular powder tablets, are made available, that a predefined quantity of the active substance fluid is dripped onto the excipient and is received by the excipient substance of the excipient, wherein during the fall of the respective droplet in the direction of the excipient the volume of the respective droplet is determined, and that for the respective medicament the respective size of the droplet is assigned as an active substance value to the medicament created and the medicament is kept available together with the active substance value associated to it.

[0025] In order to make possible a personalization of the medicament to be dispensed or dispensed and a direct statement about the patient, it can be provided, that the medicaments created are assigned to a patient, preferably dispensed to the patient, and the respective active substance value together with the respective dispensing time are stored in a documentation storage assigned to the respective patient.

[0026] In this connection it is also advantageous, that medicaments can be immediately produced and dispensed to a patient.

[0027] In order to make possible the production of the medicaments and a subsequent packaging of the medicament in medicament blisters, it can be provided that—that the medicament created after its production is inserted into a predetermined pocket of a medicament blister, in particular of a medicament blister, that the active substance value associated with the medicament as well as a key characterizing the predetermined respective pocket of the medicament blister are jointly transmitted to a storage located preferably on a controller located on the medicament blister, and that a key characterizing the respective pocket as well as the respective active substance quantity of the medicament located in the respective pocket, are kept available for retrieval, in particular by the controller.

[0028] It can be provided for monitoring the intake, that the pockets of the medicament blister containing the medicaments are closed after insertion of the medicament, and before taking the medicament the respective pocket is opened by the patient, that the opening of the respective pocket is detected by the controller located on the medicament blister, that the respective active substance value of the medicament located in the pocket last opened is kept available separately and/or additionally, in particular by the controller, and that, if necessary, the respective active substance value together with the respective dispensing time is stored in a documentation storage of the documentation server assigned to the respective patent.

[0029] Alternatively, in order to make possible the production of the medicament and a subsequent packaging of the medicament in medicament blisters, it can also be provided,—that the medicament created is inserted into a predetermined pocket of the medicament blister, which has a controller, on which a predetermined identification ($m_1, \ldots, m_n$) characterizing the medicament blister is stored, that the active substance quantity ($c_1, \ldots, c_n$) associated with the medicament, the identification ($m_1, \ldots, m_n$) associated with the respective medicament blister, as well as a key ($k_1, \ldots, k_n$) characterizing the predetermined respective pocket of the medicament blister are transmitted jointly to a server, and that the respective active substance value ($c_1, \ldots, c_n$) of the medicament located in the respective pocket during transmission of the identification ($m_1, \ldots, m_n$) characterizing the medicament blister as well as of the key ($k_1, \ldots, k_n$) characterizing the respective pocket are kept available for retrieval by the server. In this case, it can be provided for monitoring the intake, that—that the pockets of the medicament blister containing the medicament are closed after the insertion of the medicament, and the respective pocket is opened by the patient before taking the medicament, that the respective opened pocket is detected by the controller located on the medicament blister, that the respective key ($k_1, \ldots, k_n$) of the last opened pocket jointly with the identification (m) of the respective medicament blister is transmitted to the server and the server determines and keeps available the active substance quantity ($c_1, \ldots, c_n$) stored on it and associated with the key as well as the identification (m), and that, if necessary, the respective active substance value is transmitted to a control variable storage unit, wherein the respective active substance value together with the respective dispensing time are stored in a storage of the control variable storage unit assigned to the respective patient.

[0030] Furthermore, the invention relates to a combination comprising at least one medicament blister comprising a number of medicaments, in particular, tablets or capsules, which are arranged in pockets formed in the medicament blister, and in particular containing exclusively the respective medicament, wherein the individual medicaments in each case have a different active substance quantity ($c_1, \ldots, c_n$). This combination comprises a storage, which in each case for each of the pockets of the medicament blister has in each case a storage space, in which an active substance value ($c_1, \ldots, c_n$) is stored, which corresponds to the active substance quantity of the medicament located in the respective pocket, wherein the storage keeps available upon request during the transmission of an identification ($m_1, \ldots, m_n$) clearly characterizing the pocket the respective active substance value (c) associated with the medicament in the respective pocket. Such a combination of a medicament blister and its storage can be used advantageously for the determination of dose-response curves. In particular, the respective medication dose as an active substance value is available for each medication taken or to be taken. In order to measure the connection between dosage and effect of the medicament, the respective medicament can be administered to the patient and subsequently the effects can be determined and quantified, for example, by measurement of the blood pressure in the case of an antihypertensive medication. Since the medication dose is available for the respective medication in an easily retrievable manner via the storage, the dose-response curve can be rapidly created and kept available for new therapeutic recommendations.

[0031] In order to detect which of several medicaments was removed from a container and in order to obtain the active substance value to be used for the dose-response curve, it can be provided that a controller is provided on the medicament blister,

a) wherein on the controller an identification ($m_1, \ldots, m_n$) clearly characterizing the medicament blister is stored and/or

b) wherein the controller monitors the opening of pockets formed on the medicament blister and keeps available the identification ($m_1, \ldots, m_n$) clearly characterizing the in each case last opened pocket.

[0032] An easy option of access to the individual active substance values provides, that the storage is integrated into the controller arranged on the medicament blister, wherein in each case a storage area is provided in the storage for each medicament located in the individual pockets, in which the respective active substance quantity ($c_1, \ldots, c_n$) of the medicament is stored, and that upon request the controller indicates the respective active substance quantity ($c_1, \ldots, c_n$) of the medicament located in the respective pocket by specifying a key ($k_1, \ldots, k_n$) characterizing the respective pocket.

[0033] Alternatively, it can be provided for the same purpose, that the controller formed on the medicament blister has an identification storage, on which an identification ($m_1, \ldots, m_n$) clearly characterizing the medicament blister is provided, that the storage is formed on a server, wherein the server, if necessary, has a number of storages, wherein each storage is assigned in each case to a medicament blister, wherein in each case a storage area is provided in the respective storage provided for the medicament blister for each medicament located in the individual pockets of the medicament blister, in which the respective active substance value ($c_1, \ldots, c_n$) of the medicament located in the pocket of the medicament blister is stored, and that the server upon request transmits the respective active substance quantity ($c_1, \ldots, c_n$) of the medicament located in the respective pocket by specifying the identification ($m_1, \ldots, m_n$) characterizing the medicament blister as well as a key ($k_1, \ldots, k_n$) characterizing the respective pocket of the medicament blister.

[0034] Furthermore, this also makes it possible, that the opening of the individual medicament blister can be monitored centrally, as well as makes possible simple central data storage as well as a concomitant increased protection against falsification.

[0035] Advantageously, it can be provided to achieve significant dose-response curves on the basis of the medicament created, that the active substance values (c) of the individual medicaments follow a predetermined distribution within the interval c_N+/−Δc, for example, are uniformly distributed or discretely distributed.

[0036] For the precise determination of the slope of the control variable-measured variable curve at the working point it can be provided that the maximum deviation Δc from the standard value c_N is greater than 5%, in particular, greater than 10% of the standard value.

[0037] Finally, the invention also relates to a device for producing medicaments. According to the present invention, a device is provided for producing medicaments comprising

a) a supply unit for the provision of excipients, in particular powder tablets,

b) a portioning unit for portioning the active substance, in particular an active substance fluid, as well as for applying the active substance, in particular for dripping the active substance fluid the excipient provided by the supply unit: c) a

control unit for controlling the size of the quantity of the active substance supplied by the portioning unit, in particular droplets, wherein the control unit sets a standard value (c_N) for the active substance quantity of the medicament to be set in each case, and the control unit of the portioning unit in each case provides an active substance quantity to be applied within an interval around the standard value (c_N), wherein the control unit keeps available the predetermined active substance quantity or the active substance quantity contained in the medicament as active substance value (c) of the medicament created after its creation and stores it permanently in a storage provided therefor.

[0038] With such a device medicaments can be produced easily and rapidly, the respective active substance value of which is known and can be used for the creation of a dose-response curve.

[0039] In order to obtain medications with a predetermined and in particular adjustable deviation of the dose as well as of the active substance value, it can be provided, that the control unit is designed for controlling the size of the quantity of the active substance supplied by the portioning unit, that the control unit for the active substance quantity of the medicament to be set in each case sets a standard value (c_N) and a maximum deviation Δc from this standard value, that the control unit of the portioning unit provides in each case an active substance quantity to be applied, in particular a random value (c_R) within the interval c_N+/−Δc as active substance value (c), wherein the control unit keeps available the predetermined active substance value (c) after the creation of the medicament.

[0040] In order to use the natural production tolerance of an existing portioning unit, it can be provided that the portioning unit is designed for portioning of active substance fluid as well as for dripping of active substance fluid on the excipients already made available by the supply unit, and the portioning unit dispenses the droplets of the active substance fluid with a predetermined average droplet size (C_N) and a known maximum deviation Δc from the predetermined average droplet size (C_N), and that the control unit is provided a unit for determining the droplet size of droplets applied by the portioning unit on the excipients, which keeps available the size of the respective droplets applied to the excipients as active substance value (c).

[0041] To record a dose-response curve, the invention provides a further method for determining the sensitivity of a patient to a therapy. In this connection, it is provided that the respective medicament is administered to the patient, wherein after taking the medicament in each case a physiological measured variable (z) of the patient is determined and assigned to the active substance value (c), and wherein for all physiological measured variables (z) and active substance values (c) assigned to each other a sensitivity (F) is determined in each case, which corresponds in the range of the standard value (C_N) to the relative increase (dz/dc) of the physiological measured variables (z) in the case of an increase of the respective active substance value (c).

[0042] With this method, not only a generally advantageous treatment can be carried out, it is also still possible, in the case of a setting of the treatment intensity made once, to make the statement, how sensitively the therapeutic measured variable will respond to slight changes in the treatment intensity in the range of a given treatment intensity.

[0043] In order to be able to record the respective effect, it can be provided, that the blood pressure, body weight, ECG parameters, blood values, stress parameters, pain parameters, depression level, flexibility of specific joints as well as the mobility of the patient, measurements for the wellbeing of the patient or combinations thereof are consulted as physiological parameters.

[0044] In order to be able to better record the temporal delay of the effect of a medicament, it can be provided, that the respective parameter is determined a specific time period after dispensing the respective medicament in the body.

[0045] To record a dose-response curve the invention also provides a device for determining the sensitivity of a patient to a therapy. In this connection, it is provided, that a) a therapy administration unit comprising a therapy administration control sets a treatment intensity and, if necessary, a variation of the treatment intensity, wherein the treatment unit performs a treatment on a patient with the predetermined treatment intensity with a variation of the treatment intensity due to its design or predetermined by the therapy administration unit,

b) a control variable storage unit downstream of the therapy administration unit and/or its treatment unit for storage of the respective treatment intensity subject to a variation,

c) a measured variable measuring unit for determining a physiological measured variable by measuring the patient treated,

d) a measured variable storage unit downstream of the measured variable measuring unit for storage of the respective determined physiological measured variable, as well as

e) an evaluation unit downstream of the control variable storage unit and the measured variable storage unit for determining the relationship between the stored treatment intensities and the physiological measured variables, in particular, for determining the effects of changes of the treatment intensity on the physiological measured variables. With this method, not only a generally advantageous treatment can be carried out, it is also still possible, in the case of a setting of the treatment intensity made once, to make the statement, how sensitively the therapeutic measured variable will respond to slight changes in the treatment intensity in the range of a given treatment intensity.

[0046] An advantageous aspect of the invention provides that a control variable measuring unit determines the control variable emitted by the therapy administration control or the treatment unit and keeps it available for storage by the control variable storage unit. Such a device can be easily created and be used for diverse treatments.

[0047] In order to obtain a personal dose-response curve, it can be provided, that the control variable storage unit and the measured variable storage unit keep available for each patient a separate storage area and the downstream evaluation unit in determining the relationship between the stored treatment intensities and the physiological measured variables has access to stored treatment intensities and physiological measured variables of the same person exclusively, which in each case are stored in storage areas which are separate and assigned to this person.

[0048] Some embodiments of the invention are described in more detail by means of the following drawings.

[0049] In FIG. **3** the process of a treatment is depicted schematically. FIG. **4** shows the dose-response curve determined in the method depicted in FIG. **3**. FIGS. **5** and **6** show different embodiments for producing medicaments. FIGS. **7** and **8** show two different medicament blisters produced with a method according to the present invention.

[0050] In FIG. **3** the process of a treatment as well as the evaluation of the individual measured variables are depicted schematically, which forms the starting point of the invention. A doctor **41** determines a treatment intensity, for example, a medicament dose, a radiation dose, training duration for exercises, etc. Through this treatment intensity an initial control point is preset, with which a specific physiological target value shall be achieved. Then the doctor **41** can, for example, with the setting of a dosage of a medication, wish to achieve a reduction of the systolic blood pressure value to a specific standard value. Since, however, different patients **44** respond differently to the respective medication administered, the effect of the medication can be stronger or weaker than expected by doctor **41**, so that after a specific time a correction of the treatment intensity is required. Thus, doctor **41** can, for instance, reduce the daily dosage, in order to prevent a too-low setting of the blood pressure in the case of a too strong response of the patient **44** to the medicament.

[0051] As already mentioned, the doctor **41** at an initial point in time sets both the control variable or the treatment intensity as well as the desired measured variable z. In addition to the control variable c_N and the measured variable z, the doctor also sets a variation Δc of the control variable c. Both the control variable c_N preset by the doctor as a working point setting as well as the variation setting Δc, which is transmitted by a variation unit **43**, are fed to the therapy administration unit **42**. From these values c_N, Δc the therapy administration unit **42** determines a control variable c or treatment intensity c within the interval c_N+/−Δc. A therapy with this treatment intensity is administered to the patient **44** in the context of the respective therapy administration unit **42**.

[0052] The actual value of the control variable c, that is, including the in each case impressed variation, as well as the time of the administration is stored in a control variable storage unit **45**. The information can either be determined indirectly from the setting of the therapy administration unit **42** influenced by the variation unit **43** or directly by measurement of the actual value of the control variable by means of the control variable measuring unit **49**.

[0053] Subsequently, the measured variable z, for example, the blood pressure is measured via a measured variable measuring unit **48** and the value and the measuring time is stored in a measured variable storage unit **46**. From the values for control variable c and measured variable z and the associated times the current working point and the sensitivity of the therapeutic measured variable z of a person can be calculated with regard to change of the therapeutic control variable c in an evaluation unit **47**.

[0054] As a measure for this sensitivity, a sensitivity F of the respective patient to the respective therapy or treatment can be determined at a working point, which in the range of the standard value c_N or of the working point is equal to the relative increase dz/dc of the physiological measured variables z in the case of an increase of the respective active substance value c.

[0055] A more precise setting of the measured variable z can—if the respective dependency of the measured variable z on the control variable at the respective working point is known—be made more easily. In addition, the possibility exists to find out how strongly changes of the control variable c have an impact on the measured variable z. It is thus not only possible in the event of awareness of the dependency of control variable c on the measured variable z at a working point to quantify linear displacements of the control variable-measured variable curve, but rather also to obtain changes of its slope at the working point—and thus to make a statement on how sensitively the measured variable z will respond to slight changes of the control variable c from the working point.

[0056] In order to obtain an up-to-date control variable-measured variable curve at any time, in the event of therapy, or, for example, in the event of any taking of medicaments or treatment, the control variable c or treatment intensity, for example, the dose of a medication, is changed around a working point.

[0057] The respective value of the control variable c is assigned to the respective treatment, for example, the active substance quantity of the medication or medicament located in the medicament blister can already be stored during the production of a medicament blister (FIGS. **5**, **6**). Alternatively, during the administration of the medicament the respective active substance quantity can also be measured and stored (FIGS. **7**, **8**). The storage of the treatment intensity occurs independently of the value of the measured physiological measured variable z, for example, independently of the measured blood pressure. Thus, a point set arises in the control variable-measured variable curve, which reflects both the variation of the control variable as well as the variation of the measured variable z. From this point set depicted in FIG. **4**, through a mathematical procedure, for example, fitting a straight line, the current slope of the curve at the working point, i.e., for the current dosage can be determined, which corresponds to the current sensitivity of the measured variable z to changes in the control variable at the working point.

[0058] The control variable or treatment intensity is not kept completely constant during the therapy, but rather changes with any therapy application, for example, with any taking of medication. The currently administered value in each case of the control variable is stored, even as the value of the current measured variable z. Thus, in the control variable-measured variable curve a two-dimensional point set **31** arises, which reflects both the variation of the control variable as well as the variation of the measured variable z. The measured variable z is now—as described above—still influenced by disturbance values, measurement errors and changes of the original control variable-measured variable curve **32**, but in addition also by the respective value of the control variable. Assuming that disturbance values and measurement errors are distributed stochastically and the control variable-measured variable curve changes only slowly, therefore not only the mean value of the measured variable z, but rather also, for example, by fitting a straight line **33**, the slope dz/dc of the curve at the working point and thus the sensitivity of the measured variable z to changes in the control variable can be determined from the existing point set. If necessary, a further approximation of a known curve **34** can also be made. The more measuring points are available, the less can the influence of the variation of the control variable be in comparison to the influence of the measurement errors and disturbance values and minimal variations of the control variable can also suffice in the case of an appropriately long observation.

[0059] As already mentioned, the control variable c of the treatment is not necessarily the dosage of a medication. The possibility also exists to use other treatment intensities of therapeutic interventions as control variables, which have a controllable or varied control variable. Accordingly, in the case of light therapy the intensity of the light can be changed, in the case of electromagnetic radiation also the intensity or

the wave length, in the case of heat-/cold-therapy the temperature, in the case of all of these therapies the duration of the exposure, etc. Similar adjustable control variables can be found in the acoustics, mechanics, nutrition, etc.

[0060] Also, the measured variable z can in principle be any quantitatively measurable value, which is influenced by the therapy, therefore, for example, blood or urine, blood pressure, ECG parameters, pulse frequency, body temperature, etc.

[0061] During the therapy, pairs (c, z) regularly arise from control variable- and measured variable values. For the fitting of the control variable-measured variable curve all of these previously measured control variable-measured variable pairs can be used. In order to identify changes, it can, however, also make sense to use only the data from a predetermined time period, for example, from the last week or the last month. If it is known that certain parameters as disturbance values also influence the measured variable z—thus the blood pressure depends strongly on the time of day and is often different in the morning than in the evening—only specific value pairs can be included or excluded—depending on the value of the disturbance value. Likewise, value pairs can be excluded, which are obviously statistical outliers, because, for example, the measured variable z is significantly different in the sense of an outlier from the other previously measured variables z.

[0062] The variation of the control variable can follow a specific specification, therefore, consist of a predetermined sequence of values in terms of a deterministic signal, or also be purely accidental, therefore, have the characteristic of a noise. The invention provides that each change of the control variable c is stored and is kept available. Thus, for instance, varying treatment intensities can either be stored in the case of the production of medicaments **102** or in their administration of the medicament **102** or be determined only in the course of the treatment, in order to be able subsequently to determine the control variable-measured variable point clouds.

[0063] The current values of the control variable c are stored separately for each therapy and are available for the later processing. Thus, for instance, the exact, but process-related quantity fluctuating around a statistical average value of an active substance dripped on carrier tablets or excipients **120** in the course of the production and packaging are stored together in a storage unit or a control variable storage unit **45** of a medication dispensing device, for example, a medicament blister **101**, **111**.

[0064] In addition to the value of the control variable c, the time, at which the administration is carried out, therefore, for example, when a medication or medicament **102** is taken, and the time, when the measurement of the measured variable z is made, i.e. either immediately after intake, after hours, or only after days, etc., also influence the measurement result. In order to also take into account these effects, not only the value of the control variable c can be varied, but rather also the time of each individual therapy application and/or the time of the measurement of the measured variable z.

[0065] Additional significance can be conferred to the examination, while after setting a therapeutic intervention a measurement is taken not only once—at one time—, but rather over a longer period of time and repeatedly, if necessary, continuously the course of a measured variable z is observed. If the measurement series is carried out with each application, a statement on the influence of the control variable c on the measured variable z can be determined from the comparison of the signal paths after the individual interventions.

[0066] Furthermore, it can be determined by using a cross-correlation analysis, whether time constants of the influence of the measured variable z are dependent on the value of the control variable or in general a possibly given time lag between the application of the control variable c and the observable changes in the measured variable z are taken into account.

[0067] Generally, in the course of the evaluation a model for the relationship of the control- and the measured variable c; z can be formulated in terms of a transmission system and the structural parameters of this model can be estimated in terms of a system analysis by means of mathematical methods.

[0068] In FIG. **5** a method according to an embodiment of the invention is depicted in detail, which is used to create a number of medicaments **102**, which are provided with a predetermined active substance. The goal of the method is to keep available the respective active substance quantity contained in the medicament **102** in the form of an active substance value c simultaneously with the production of the medicament **102**. In particular, the active substance value c should be kept available for retrieval in a control variable storage unit **45**.

[0069] At the beginning of the process the average target active substance quantity of the medicament **102** in the form of a standard value c_N is prescribed by a doctor or set at a standard value. In addition, a maximum deviation Δc from this standard value c_N is predetermined. The active substance value c is thus within an interval $c_N \pm \Delta c$. The active substance value c can thereby either be selected or the loading of the medicament **102** with the predetermined active substance is undertaken with a certain error tolerance, so that the medicaments **102** ultimately created contain an active substance quantity, which corresponds to an active substance value within the interval $c_N \pm \Delta c$.

[0070] If the active substance value c is predetermined, the active substance c can be assigned to the respective medicament and be stored in the previously mentioned storage **105**.

[0071] If the created active substance value c is subject to a certain variation in that the production of the respective medicament **102** cannot be carried out exactly, the quantity of the active substances located in the medicament **102** is measured in a subsequent step and the measurement result is assigned as active substance value c to the respective medicament **102**. After the creation of the medicament **102** both the medicament **102** as well as the active substance value of the medicament **102** are kept available.

[0072] Depending on the respective medicament or dependent on the respective active substance or active ingredient the maximum deviation Δc from the standard value c_N is between 10% and 20%. In particular, the deviation from the standard value is greater than 5% or greater than 10%.

[0073] Schematic representations of the procedure for the production of medicaments according to two preferred embodiments of the invention as well as two devices **130**, **140** for the creation of medicaments **102** are depicted in FIGS. **5** and **6**. An active substance fluid **121** containing a medicament active substance, for example, an emulsion, solution or suspension, in the present case an active substance solution, is available in a storage container. Both devices **130**, **140** depicted in FIGS. **5** and **6** have in each case a supply unit **131**,

141, with which the excipients **120** in the form of powder tablets are made available. The container filled with the active substance fluid **121** has an outlet at its lower end, which opens into a portioning unit **132**, **142**. The portioning unit **132**, **142** provides droplets **122** of the active substance fluid **121** and lets these drip onto the excipient **120** supplied by the supply unit **131**, **141**.

[0074] Furthermore, the device has a control unit **133**, **143**, which controls the portioning unit **132**, **142** and sets the quantity of the active substance to be dispensed by the portioning unit **132**, **142**. The control unit **133** receives on its part the active substance quantity to be set in each case for the medicament, wherein a standard value of c_N and an interval Δc around this standard value c_N are given.

[0075] If the portioning unit **132** for producing the medicament **102**, depicted in FIG. **5**, operates with sufficient precision, a separate active substance value c in the form of a random value can be predetermined for the creation of medicaments **102** with a certain variance Δc of the individual active substance values c for each individual medicament **102**. This random value is located constantly within the interval $c_N \pm \Delta c$. The distribution of the individual random values follows a specific distribution. In the present embodiment a uniform distribution within the predetermined interval $c_N \pm \Delta c$ is selected as the distribution for the random values.

[0076] If, therefore, the portioning unit **132** supplies medicament **102** with a sufficiently precisely determinable active substance quantity of active substance fluid, the respective active substance value c contained in the medicament **102** can be assigned directly to the respective medicament **102** and can be kept available together with an identification number for this medicament **102**. In this case, the control unit **133** is designed to control the size of the quantity of the active substance fluid **121** dispensed from the portioning unit **132**. The control unit **133** determines the respective active substance quantity contained in the medicament **102** within an interval $c_N \pm \Delta c$ around the standard value c_N, for example, as a random value.

[0077] With a less precise control unit **143** or portioning unit **142**, a statistical distribution of the active substance quantities applied to the individual excipients **120** can already be attained by the production-related tolerances. Such an embodiment of the invention is depicted in FIG. **6**. This embodiment also has a supply unit **141** for excipients **120**, a container for the active substance fluid **121**, a control unit **143**, a portioning unit **142**. In addition, however, this device **140** has a unit **144** for determining the size of the droplets **122** applied by the portioning unit **142** on the excipient **120**. In order to determine the respective active substance quantity assigned to the medicament **102** in the form of an active substance value c, the control signal of the control unit **143** impressed on the portioning unit **132**, **142**, contrary to the embodiment depicted in FIG. **5**, is not consulted, here the impressed signal would be distorted especially by the production-related tolerances. Rather the size of the droplet **122** of the active substance fluid **121** dispensed by the portioning unit **142** is measured separately and directly. The thus determined measured value for the size of the droplet **122** dripped on to the excipient **120** is kept available and stored as active substance value c for the respective medicament **102**.

[0078] After production of the medicament there are now basically two possibilities for dispensing and administering the medicament **102** created to a patient: According to a first embodiment of the invention the individual medicaments are dispensed immediately after their production directly to the patient. The patient receives the medicaments created, wherein the respective active substance value c assigned to the medicament **102** is transmitted directly to a control variable storage unit **45** depicted in FIG. **3**, which is assigned to the respective patient. In this way, for example, a variety of medicaments **102** can be rapidly and cost-effectively created in hospitals or in studies performed, without a complicated packaging process being required.

[0079] Alternatively, a medicament blister **101** depicted in FIG. **7** can be created, in which the medicament **102** thus created can be inserted. The individual medicaments **102** are immediately inserted after their creation in each case into individual pockets **103** of the medicament blister **101**. The active substance value c assigned to the respective medicament **102** as well as a key $k_1, \ldots, k_n$ characterizing the respectively predetermined pocket **103** of the medicament blister **101** is transmitted to a storage **105** and stored in the latter. In the embodiment of the invention depicted in FIG. **5** the storage **105** is located together with a controller **104** on a microchip, which is arranged directly on the medicament blister **101**. The microchip also has RFID functionality and allows the controller **104** to communicate with external data communications units and in particular permits the data transfer of active substance values c to the control variable storage unit **45**. For each medicament **102** in each case a key $k_1, \ldots, k_n$ characterizing the respective pocket **103**, as well as the respective active substance quantity of the medicament **102** located in the respective pocket is stored as digital active substance value c. The controller **104** keeps available the respective active substance quantity as well as the key $k_1, \ldots, k_n$ assigned in each case for joint retrieval.

[0080] After inserting the medicament **102** into the pockets **103** of the medicament blister **101** or container the pockets **103** are closed. The pockets **103** are only opened by the patient **44** immediately for taking the respective medicament **102**. The controller **104** detects the opening of the respective pocket **103** and keeps the key $k_1, \ldots, k_n$ characterizing in each case the last opened pocket **103** available together with the active substance value c of the medicament located in this pocket **103**. It is thus possible to retrieve from the respective medicament blister **101** or from the controller **104** located in it, how high the active substance value c of the medicament **102** located in the last opened pocket **103** is or was. A variety of different methods are available from the prior art for determining when or whether a pocket **103** has been opened. In particular, it is possible to install conducting paths in the area of the foil closing the pockets **103**, which are interrupted during the opening of the pockets **103**. In this way, the controller **104** can determine that the respective pocket **103** is opened and makes available the active substance value c assigned to the respective pocket **103** upon request.

[0081] In determining the dose-response curve it is advantageous that the respective active substance value c of the last opened pocket **103** is transmitted to the control variable storage unit **45**, wherein the respective active substance value c together with the respective dispensing time, that is, the time, at which the patient has opened the pocket **103**, is stored. In addition, a personal identification number of the respective patient **44** is added to the thus stored data set.

[0082] According to a further alternative embodiment of the invention, which otherwise corresponds to the embodiment depicted in FIG. **7**, it can also be provided not to store the individual active substance values in a storage located on the

medicament blister **111**, but rather to keep them available on a storage located on a—not depicted—central server. Such an embodiment of the invention is depicted in detail in FIG. **8**. On the other hand, the individual medicaments are located in a predetermined pocket **103** of a medicament blister or medicament blister **111**. The medicament blister **111** has a controller **114**, on which a predetermined identification $m_1, \ldots, m_n$ characterizing the medicament blister **111** is stored. Moreover, as also in the previous embodiment of the invention, each individual pocket **103** of the medicament blister **111** in each case is assigned a characterizing key $k_1, \ldots, k_n$. In the creation of a medicament **102** in each case a data set is created, which has the active substance quantity c assigned to the medicament **102**, the identification assigned to the medicament blister **111**, as well as a key $k_1, \ldots, k_n$ characterizing the respective pocket **103** of the medicament blister **111**. These data sets are transmitted jointly to the central server, which keeps available the respective active substance value c of the medicament **102** located in the pocket **103** during transmission of the identification $m_1, \ldots, m_n$ characterizing the medicament blister **111** as well as of the key $k_1, \ldots, k_n$ characterizing the respective pocket **103**. As also in the preceding example, the pockets **103** of the medicament blister **111** containing the medicament **102** are closed after the insertion of the medicament **102** and opened only immediately before taking the medicament **102** by the patient **44**. The respective key $k_1, \ldots, k_n$ of the last opened pocket **103** is transmitted together with the identification $m_1, \ldots, m_n$ of the respective medicament blister **111** to the central server and the central server transmits the active substance quantity c stored on it and assigned to the key $k_1, \ldots, k_n$ as well as the identification $m_1, \ldots, m_n$ back to the patient **44**. Finally, the respective active substance value c is transmitted to the control variable storage unit **45**, wherein the respective active substance value c together with the respective dispensing time is stored in a storage of the control variable storage unit **45** assigned to the patient **44**.

1-23. (canceled)

24. A method for producing a number of medicaments with a predetermined active substance and for a simultaneous supply of an active substance value indicating an active substance quantity contained in a medicament, which comprises the steps of:

predetermining a standard value cN and a maximum deviation Δc from the standard value for the active substance quantity to be determined in each case of the medicament, wherein the active substance value being selected or predetermined within an interval cN+/−Δc; and

using the active substance quantity for creating the medicament, which corresponds to the active substance value, and that a created active substance value is assigned to the medicament and after a creation of the medicament the created active substance value is kept available together with the medicament.

25. The method according to claim **24**, which further comprises predefining active substance values of the medicaments as following a predetermined distribution, namely uniformly distributed or discretely distributed, random values within the interval cN+/−Δc.

26. The method according to claim **24**, wherein the maximum deviation from the standard value is greater than 5% of the standard value.

27. The method according to claim **24**, which further comprises:

making available an active substance fluid containing the active substance;

making available a number of excipients; and

dripping a predetermined quantity of the active substance fluid onto an excipient and is received by an excipient substance of the excipient, wherein during a fall of a respective droplet of the active substance fluid in a direction of the excipient a volume of the respective droplet is determined, and that for the medicament a respective size of the respective droplet is assigned as the active substance value to the medicament created and the medicament is kept available together with the active substance value associated with it.

28. The method according to claim **24**, which further comprises:

assigning the medicaments created for a patient and dispensed to the patient; and

storing a respective active substance value together with a respective dispensing time in a documentation memory assigned to the patient.

29. The method according to claim **24**, which further comprises:

inserting the medicament created into a predetermined pocket of a medicament blister; and

transmitting together the active substance value assigned to the medicament as well as a key characterizing the predetermined pocket of the medicament blister to a memory disposed on a controller disposed on the medicament blister, and that the key characterizing the predetermined pocket as well as the active substance quantity of the medicament located in the predetermined pocket are kept available for retrieval from the controller.

30. The method according to claim **29**, which further comprises:

closing pockets of the medicament blister containing the medicament after insertion of the medicament; and

opening one of the pockets by a patient before taking the medicament, that the opening of the pocket is detected by the controller disposed on the medicament blister, that the respective active substance value of the medicament disposed in a last opened pocket is kept available separately and/or additionally, by the controller, and that, if necessary, the respective active substance value is transmitted to a documentation server, wherein the respective active substance value is stored together with a respective dispensing time in a documentation memory of the documentation server assigned to the patient.

31. The method according to claim **24**, which further comprises:

inserting the medicament created into a predetermined pocket of a medicament blister having a controller storing a predetermined identification characterizing the medicament blister; and

transmitting the active substance quantity associated with the medicament, the predetermined identification associated with the medicament blister, and a key characterizing the predetermined pocket of the medicament blister jointly to a server, and the active substance value of the medicament disposed in the predetermined pocket during transmission of the predetermined identification characterizing the medicament blister as well as of the

key characterizing the predetermined pocket are kept available for retrieval from the server.

32. The method according to claim **31**, which further comprises:

closing pockets of the medicament blister containing the medicament after insertion of the medicament, and before taking the medicament a respective pocket is opened by a patient, that each opened pocket is detected by the controller located on the medicament blister, that the key of a last opened pocket together with the predetermined identification of the medicament blister is transmitted to the server and the server determines and keeps available the active substance quantity stored on it and associated with the key as well as the predetermined identification, and that, if necessary, the active substance value is transmitted to a control variable memory unit, wherein the active substance value together with a respective dispensing time are stored in a memory of the control variable storage unit assigned to the respective patient.

33. The method according to claim **24**, wherein the maximum deviation from the standard value is greater than 10% of the standard value.

34. The method according to claim **27**, which further comprises:

providing the active substance fluid as a solution, an emulsion or a suspension; and

providing the excipients as powder tablets.

35. A combination, comprising:

at least one medicament blister having a number of medicaments, being tablets or capsules, being disposed in pockets formed in said medicament blister, wherein the medicaments individually in each case having a different active substance quantity; and

a memory having a storage space in each case for each of said pockets of said medicament blister, said memory storing an active substance value corresponding to an active substance quantity of the medicament disposed in a respective one of said pockets, wherein said memory on request during a transmission of an identification clearly characterizing a pocket keeps available the active substance value associated with the medicament in said respective pocket.

36. The combination according to claim **35**, further comprising a controller disposed on said medicament blister, wherein:

the identification characterizing said medicament blister is stored on said controller; and/or

said controller monitors an opening of said pockets formed on said medicament blister and keeps available the identification characterizing in each case a last opened pocket.

37. The combination according to claim **36**, wherein said memory is integrated into said controller disposed on said medicament blister, wherein in each case a storage area is provided in said memory for each of the medicaments disposed in said pockets individually, in which a respective active substance quantity of the medicament is stored, and that upon request said controller indicates the respective active substance quantity of the medicament disposed in said respective pocket by specifying a key characterizing said respective pocket.

38. The combination according to claim **36**, wherein said controller formed on said medicament blister has an identification memory, in which an identification clearly characterizing said medicament blister is provided, said memory is formed in a server, wherein said server, if necessary, has a number of memories, wherein each of the memories is assigned in each case to said medicament blister, wherein in each case a storage area is provided in a respective memory provided for said medicament blister for each of the medicaments disposed in said pockets of said medicament blister, in which the respective active substance value of the medicament located in said pocket of said medicament blister is stored, and that said server upon request transmits the respective active substance quantity of the medicament located in said respective pocket by specifying the identification characterizing said medicament blister as well as a key characterizing said respective pocket of said medicament blister.

39. The combination according to claim **35**, wherein the active substance values of the medicament are within a predetermined interval $cN+/-\Delta c$, wherein cN represents a standard value and Δc represents a maximum desired deviation of the active substance value from the standard value, wherein:

the active substance values of the medicaments follow a predetermined distribution within the interval $cN+/-\Delta c$, namely are uniformly distributed or discretely distributed; and/or

the maximum deviation from the standard value is greater than 5% of the standard value.

40. A device for producing medicaments, comprising:

a supply unit for supplying excipients;

a portioning unit for portioning an active substance, and for applying the active substance onto the excipient, supplied by said supply unit; and

a control unit for controlling a size of a quantity of the active substance dispensed by said portioning unit, wherein said control unit sets a standard value for an active substance quantity of a medicament to be set in each case, and said control unit for controlling said portioning unit in each case provides the active substance quantity to be applied within an interval around the standard value, wherein said control unit keeps available a predetermined active substance quantity or the active substance quantity contained in the medicament as the active substance value of the medicament created after its creation and stores it permanently in a memory provided therefor.

41. The device according to claim **40**, wherein said control unit is configured for controlling a size of a quantity of the active substance dispensed by said portioning unit, such that said control unit for the active substance quantity of the medicament to be set in each case sets the standard value cN and a maximum deviation Δc from the standard value, said control unit for controlling said portioning unit provides in each case the active substance quantity to be applied, namely, a random value within the interval $cN+/-\Delta c$ as the active substance value, said control unit keeps available the active substance value after a creation of the medicament.

42. The device according to claim **40**, wherein:

said portioning unit is configured for portioning the active substance being an active substance fluid and for dripping the active substance fluid on the excipients already made available by said supply unit, said portioning unit dispensing droplets of the active substance fluid with a predetermined average droplet size and a known maximum deviation from the predetermined average droplet size; and

said control unit has a unit for determining a droplet size of the droplets applied by said portioning unit on the excipients, which keeps available a size of the droplets applied to the excipients as the active substance value.

43. A method for determining a sensitivity of a patient to therapy with a number of medicaments or treatment units, which comprises the steps of:

assigning to the medicaments or the treatment units in each case an active substance value, the active substance value corresponding to an active substance quantity disposed in a medicament or to a treatment intensity of a treatment unit;

predetermining for a respective active substance value, a standard value cN and a maximum deviation Δc from the standard value;

providing the active substance value, namely a random value, within an interval cN+/−Δc and for a creation of a respective medicament or the treatment unit in each case the active substance quantity or the treatment intensity is used, which corresponds to the active substance value;

administering the medicament to the patient; and

determining, after taking the medicament, in each case a physiological measured variable of the patient and the physiological measured variable is assigned to the active substance value, and wherein for all physiological measured variables and active substance values assigned to each other in each case a sensitivity is determined, which corresponds in a range of the standard value to a relative increase of the physiological measured variables in an increase of the respective active substance value.

44. The method according to claim **43**, which further comprises selecting the physiological measured variables from the group consisting of blood pressure, body weight, ECG parameters, blood values, stress parameters, pain parameters, depression level, flexibility of specific joints, mobility of the patient, measurements for a wellbeing of the patient, and combinations thereof.

45. The method according to claim **44**, which further comprises determining the physiological measured variable at a specific time period after dispensing the medicament which corresponds to a time period of a coming into force of the medicament in a body.

46. A device for carrying out therapy, comprising:

a therapy administration unit having a therapy administration controller and a treatment unit, said therapy administration controller sets a treatment intensity and, if necessary, a variation of the treatment intensity, said treatment unit performs a treatment on a patient with a predetermined treatment intensity with a variation of the predetermined treatment intensity due to design or predetermined by said therapy administration unit;

a control variable memory unit disposed downstream of said therapy administration unit and/or said treatment unit for storing a respective treatment intensity subject to a variation;

a measured variable measuring unit for determining a physiological measured variable by measuring the patient treated;

a measured variable memory unit disposed downstream of said measured variable measuring unit for storing of a respective determined physiological measured variable; and

an evaluation unit disposed downstream of said control variable storage unit and said measured variable memory unit for determining a relationship between stored treatment intensities and the physiological measured variables for determining effects of changes of the treatment intensity on the physiological measured variables.

47. The device according to claim **46**, further comprising a control variable measuring unit for determining a control variable dispensed by said therapy administration control or said treatment unit and keeps the control variable available for storage by said control variable memory unit.

48. The device according to claim **46**, wherein said control variable memory unit and said measured variable memory unit keep available a separate storage area for each patient and said evaluation unit in determining a relationship between the stored treatment intensities and the physiological measured variables, has access to stored treatment intensities and the physiological measured variables of a same person exclusively, which in each case are stored in storage areas which are separate and assigned to the person.

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专利名称(译)	用于生产，定量给药和包装药物的装置和方法		
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摘要(译)

一种方法产生许多具有预定活性物质的药物，并且用于同时产生活性物质值，该活性物质值表示可用的药物中含有的活性物质量。确定药物的活性物质量的标准值，并且预定义与标准值的最大偏差。在间隔cN +/-Δc或预定义的范围内选择活性物质值，并且活性物质量用作制备相应药物的参考，其中所述药物的量与活性物质值匹配。所建立的活性物质值与药物相关并且一旦制备药物就与药物一起保持可用。