

NEW METHOD AND SYSTEM

Technical Field

The present invention relates to a new method for dosing a pharmaceutical product in
5 a packaging machine comprising at least one volumetric dosing unit with a dosing chamber
provided with a first and a second slidable part. The pharmaceutical product comprises at
least a first and a second component, the components typically being a portion of a
pharmaceutical pellets and a portion of a powder, respectively.

The present invention further relates to a system for dosing a pharmaceutical product
10 in a packaging machine comprising at least one volumetric dosing unit with a dosing
chamber provided with a first and a second slidable part. The pharmaceutical product
comprises at least a first and a second component. The system comprises a dosing unit for
metering a volume of the components. The system further comprises means for introducing
the said components into a package and means for weighing the components and the
15 package.

Background of the Invention

In the pharmaceutical industry, the accuracy of the metered doses of medicinal
mixtures is of importance. These mixtures often contain active drug components that are
20 harmful if the given dose is too high. On the other hand, the desired effect of the
medicament is not achieved if the dose is too low.

The majority of pharmaceutical bulk products like powders, granulations and pellets
are dosed volumetrically, due to process speed and cost effectiveness. By individually
metering a volume of each dose before the dose is packaged, an accurate way of ensuring
25 correct dosing is achieved.

Volumetric dosing can be performed by gravimetric feeding of the components to be
dosed, or by forced feeding where, for example, one or more scrapers, rotating augers or
rotating means making use of centrifugal force are used to feed medicament into a dosing

chamber with a predetermined volume. To generate the correct dose, the volumetric dosing chamber is provided with slides opening and closing the dosing chamber during a cycle, for feeding and emptying the dosing chamber, respectively.

In some fields of pharmaceutical manufacturing 100% check-weighing is a common technology, where a filled package is check-weighed and the mean weight of the empty package (tare weight) is subtracted to calculate the fill-weight ("tare-gross-weighing"). This method providing an indirect weighing of the dose of medicament is often used when filling medicament in e.g. capsules. The capsules are weighed empty, then filled with medicament and then weighed again together with the contents. By subtracting the result of the first measurement from the second, an indirect indication of the weight of the medicament will be obtained.

This method of indirect weighing is also applicable for other packages, such as sachets. Thus, the sachet is weighed empty, then filled with the medicament, and then weighed again together with the contents, and the two measurements are subtracted for indirectly obtaining the weight of the medicament.

When the variance of the tare weight is equal to or greater than the target fill weight, the tare weights of the single receptacles have to be determined individually to calculate single fill weights. Further, when the tare weight of the receptacle is a multiple of the fill weight of the dose, the tare-gross-weighing approach is not applicable any more. For those cases, due to the relatively high preload of the receptacles, weighing cells with sensitivity and resolution appropriate for the dose to be weighed cannot be used. Further, this indirect weighing approach is not accurate enough when the weight of an active ingredient is considerably smaller than the weight of the package. The amount of active ingredient in a single dose might weigh as little as 1 mg, while the excipient with which they are to be mixed may weigh much more, in some cases up to a thousand times more, one or more grams.

However, the method of indirect weighing is not sufficient enough if high accuracy is needed since individual packages may vary in weight due to variations in, for example moisture content, surface weight and size.

Usually, medicaments contain one or more active ingredients to be mixed with inactive ingredients. In some cases, mixing of the components prior to filling the mixture in separate doses are not an alternative due to problem with segregation of the mixture during handling. This might be the case for example when mixing components with different
5 properties, such as flow properties, density and/or particle-size. The result of mixing larger volumes before filling in separate doses might in those cases be an unreliable amount of active content in each dose. For those cases, there are methods of volumetrically dosing each and every component separately.

Volumetric dosing is in spite of the issues mentioned above widely used. By using
10 well investigated formulations, balancing different needs it is possible to manage the issues mentioned. For pediatric formulations the issues with accuracy and precision is even more pronounced. These formulations require less active drug and the dosing accuracy requirements from a patient as well as legislative perspectives is as high as for other patient groups.

15 In contrast to dosing, where the dose normally is determined by metering a specific volume, pharmacopoeia requirements refer to mass, uniformity of mass and content uniformity (in % of mass).

When using volumetric dosing systems, mass of the dosed portion and uniformity of mass depend on precision of dose confinement and uniformity of product reservoir.

20 In the case of volumetric dosing of particles or pellets there are more to consider; changes e.g. in density, shape or particle size may lead to deviation in dosed weights, even if the metered volumes are the same.

Further, if the dose to be metered decreases compared to the size of the particles, or the pellets, the contribution from each individual particle or pellet increases. A normal
25 dosing range constitutes 1000 – 10 000 particles or pellets. In formulations with less than 500 particles or pellets the experience is that those will generate an uncertainty of accuracy and precision in dosage content (precision of target weight) and content uniformity (high relative standard deviations).

In those cases, it is therefore appropriate to further control the dosing process, i.e. single weights and dose uniformity, by statistical IPC or by a 100% check-weighing. The weighing results are used to adjust the dosing system, thus minimizing rejects.

An example where indirect weighing is not accurate enough is when a small amount of pellets, in the range of 5mg to 500mg, have to be filled into sachets with tare weight of one to several grams.

The Object of the Invention

The object of the present invention is in a first aspect to provide a method and a system for dosing a pharmaceutical product, overcoming the disadvantages discussed above. To overcome the problems mentioned above, the product to be filled is check-weighed before delivery into a package. The system check-weighs the volumetrically dosed product with appropriate speed and is integrated into a filling or packaging machine.

Summary of the Invention

The present invention relates to a method for dosing a pharmaceutical product. The method is used in a packaging machine comprising at least one volumetric dosing unit with a dosing chamber. The pharmaceutical product comprises at least a first and a second component. The method comprises metering a volume of the first component and weighing the metered volume of the first component. Thus, the confined dose of the first component, for example being pellets, is check-weighed on line. Further, the method comprises introducing the metered and check-weighed volume of the first component into a package, metering a volume of the second component, introducing the metered volume of the second component into the package, weighing of the package into which the components have being introduced.

By weighing the metered volume of the first component, the amount of the first component for each dose is secured with very high accuracy. Thus, one of the advantages with the present invention is that the accuracy and precision of the amount of the weighed

components can be monitored and the result used to secure the quality of the pharmaceutical product.

In one embodiment, the dosing chamber is provided with a first and a second slidable part.

5 In another embodiment, the method comprises sealing the package after introducing the first and second components and before weighing the package. The sealing procedure performed before the weighing of the package with its contents secures that the quantity to be weighed is not affected by any further processing, or that the content in the package, and thus the weight, is affected by environmental factors before weighing, such as
10 mechanical handling or moisture.

In yet another embodiment the method comprises weighing of the second component after metering the volume of the second component and before introducing the second component in the package. The advantage of this is that the accuracy and precision of direct weighing is used and that the weight of the packaging material does not interfere
15 with the weighing of the second component.

In yet another embodiment, in the case that the pharmaceutical product comprises more than two components, the method comprises weighing at least two of the components after metering the volume of said at least two components, and before introducing the components in the package. The advantage of this is that the accuracy and precision of
20 direct weighing is used and that the weight of the packaging material does not interfere with the weighing of any of the components weighed before filling into the package.

In yet another embodiment the method comprises using at least one of the results from the weighing procedures in a feed-back loop regulation of the volume metering of the pharmaceutical components. By the use of a feed-back loop, the volume defined in the
25 volumetric dosing chamber is adjusted to ensure that the weight of the amount of the component filled in the dosing chamber equals the target weight. Thus, the risk that a patient is given a dose with too high, or too low, dose is minimized.

In yet another embodiment, the method comprises intermittent feed-back loop regulation of the volume metering of the pharmaceutical components during operation of
30 said packaging machine. By intermittent use of the feed-back loop, the process is allowed to stabilize between each adjustment and the manufacturing process will be easy to stabilize.

In yet another embodiment, the method comprises continuous feed-back loop regulation of the volume metering of the pharmaceutical components during operation of said packaging machine. With the use of a continuous feed-back loop, regulation will react on quick events and trends and the process will be adjusted quickly to meet the target weight in spite of these. The amount of product that has to be discarded due to dose outside the dose interval is by this procedure minimized.

In yet another embodiment, the method is performed in the case that the weight of the first pharmaceutical component is significantly less than the weight of the second pharmaceutical component. It is possible to accurately determine the weight of the first component when using the invention.

In yet another embodiment, the weight ratio between the first and the second pharmaceutical components is more than 1:10.

In yet another embodiment the weight ratio between the first and the second pharmaceutical components is more than 1:100.

In yet another embodiment, the volume of the first pharmaceutical component is significantly smaller than the volume of the second pharmaceutical component.

In yet another embodiment, the volume ratio between the first and the second pharmaceutical components is more than 1:10.

In yet another embodiment, the volume ratio between the first and the second pharmaceutical components is more than 1:100.

In yet another embodiment, the pharmaceutical product is introduced into sachets. For sachets, the variations in properties, i.e. weight, may vary a lot between individual sachets. By the use of the method, the influence of said variations is minimised.

In yet another embodiment, the said sachets are made of aluminium foil.

In yet another embodiment, the pharmaceutical product is introduced into blister packages.

In yet another embodiment, the pharmaceutical product is introduced into capsules. For capsules, the variations in properties, i.e. weight, may vary between individual capsules. By the use of the method, the influence of said variations is minimised.

In yet another embodiment, the at least one of said components is pellets.

In yet another embodiment, the at least one of said components is powder.

In yet another embodiment, the at least one of said components is granulate.

The invention further relates to a system for dosing a pharmaceutical product in a packaging machine comprising at least one volumetric dosing unit with a dosing chamber provided with a first and a second slidable part. The pharmaceutical product comprises at least a first and a second component. The system for dosing comprises a first dosing unit
5 for metering a volume of the first component, and a second dosing unit for metering a volume of the second component. Further, the system comprises means for introducing the components into a package and means for weighing the package and the components.

The means comprises a first weighing unit for weighing the package and the components, and a second weighing unit for weighing the first component after metering
10 the first component by volume and before introducing the first component into the package.

In another embodiment, the system comprises means for sealing the said package.

In yet another embodiment, the system comprises a third weighing unit for weighing the second component after metering the second component by volume and before
15 introducing the second component into the package.

In yet another embodiment, the system comprises means for feed-back loop regulation of the volume metering of the components. The means for feed-back loop regulation uses at least one of the results from the weighing procedures.

In yet another embodiment, the means for feed-back loop regulation are arranged to perform intermittent regulation of the volume metering of the pharmaceutical components during operation of said packaging machine.
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In yet another embodiment, the means for feed-back loop regulation are arranged to perform continuous regulation of the volume metering of the pharmaceutical components during operation of said packaging machine.

25 The invention further relates to a package containing a pharmaceutical product comprising at least a first and a second component, said components are being dosed by a method according to any of claims 1-22.

The invention still further relates to a method for producing a package containing a pharmaceutical product comprising at least a first and a second component, said method
30 comprising the method for dosing according to any one of claims 1-22.

Brief Description of the Drawings

Fig. 1-9 shows a system for dosing according to the present invention.

Detailed Description of Preferred Embodiments

5 Figure 1 shows part of a system for volumetric dosing according to the present invention. The pharmaceutical product to be dosed comprises at least a first and a second component. The system comprises a first dosing unit comprising an adjustable dosing chamber 11, confined by a first slidable part, the feeding slide 10, and a second slidable part, the discharge slide 12. The dosing unit further comprises an adjustable chamber wall 10 16 and a chamber wall 17 (see Fig. 6a, b) attached to the discharge slide 12. The dosing unit is used for metering a volume of the first component, in the figure shown as pellets.

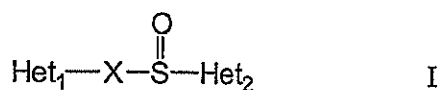
The system comprises a first weighing unit for weighing the package, together with the components, after the components have been introduced into the package. Thus, the final package is check-weighed to control the total fill weight. The system further 15 comprises a second weighing unit for weighing the first component after it has been metered by volume. Every single dose of the first component is check-weighed by the second weighing unit before delivery into a primary package receptacle.

In the system, the dose of the first component, in the figures shown as pellets, is confined by means of a volumetric dosing system, consisting of a pellet feeding unit with a 20 feeding tube 7, having a closure valve 15, a level sensor 8 and an intermediate pellet hopper and the dosing unit described above.

The pharmaceutical formulations used together with the invention can comprise an acid sensitive proton pump inhibitor or an alkaline salt thereof or a single enantiomer or an alkaline salt of its enantiomer as active ingredient. The single enantiomers, racemic 25 mixtures (50% of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to be used with the present invention.

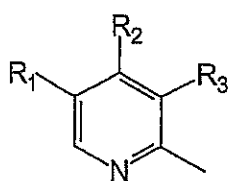
The active ingredient is being comprised optionally together with excipients, in small enteric coated pellets/beads.

Compounds/active ingredients of interest for the pharmaceutical compositions in question are compounds of the general formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers

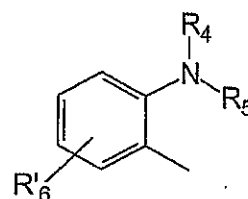


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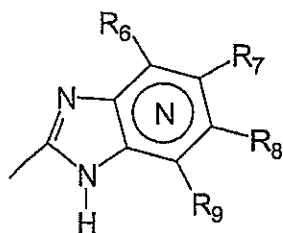
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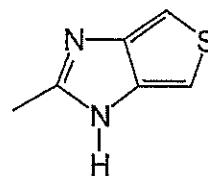
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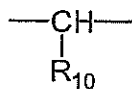
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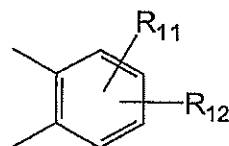
or



X =



or



wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and arylalkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

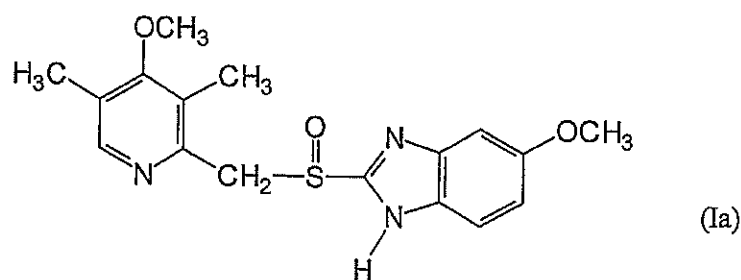
R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazoliny, pyrrolyl and trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

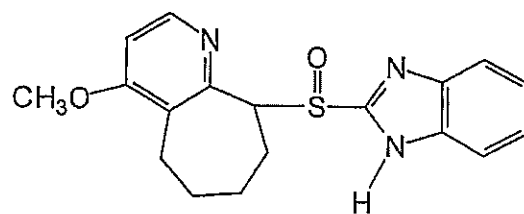
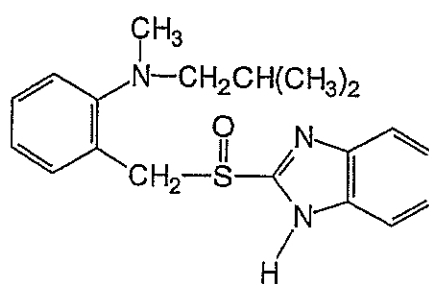
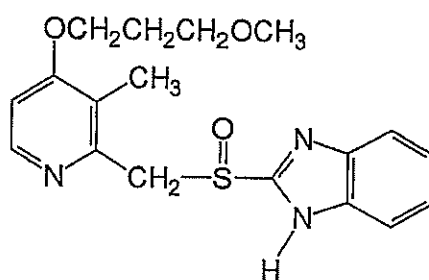
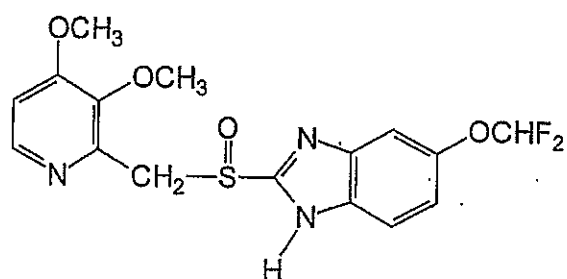
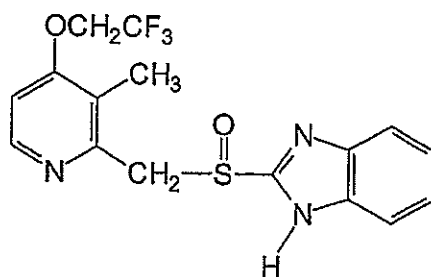
R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen and alkyl.

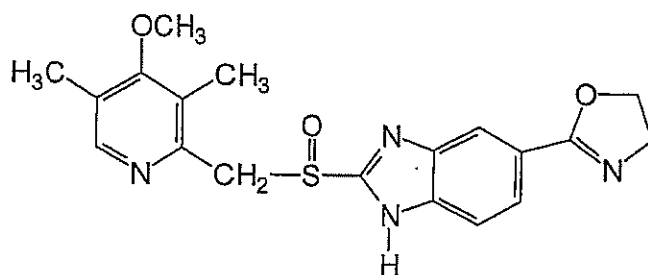
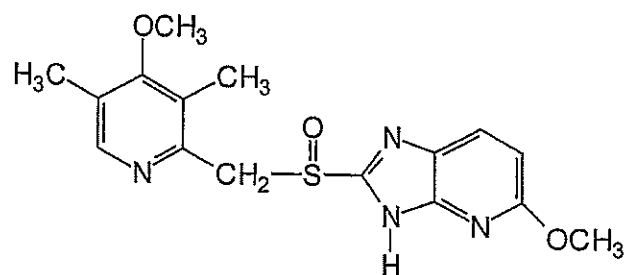
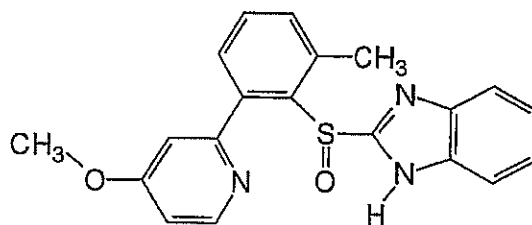
In the above definitions alkyl groups, alkoxy groups and moieties thereof may be branched or straight C₁-C₉-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

Examples of specifically interesting compounds according to formula I are

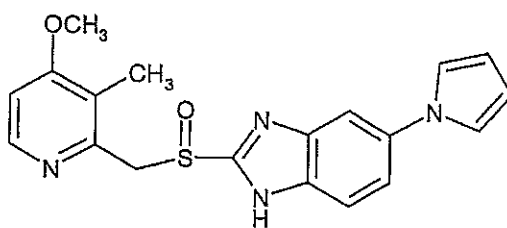




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including tautomeric forms thereof.

Preferred compounds for the pharmaceutical preparation used with the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole. The latter having the generic name esomeprazole.

The active ingredient can for example be esomeprazole magnesium trihydrate, or
5 tenatoprazole or a pharmaceutically acceptable salt thereof, or a single enantiomer of either of them, being the active drug.

As another example, the compound/ active ingredient can be a hydrated form of anyone of the aforementioned compounds/active ingredients.

The amount of active ingredient in the preparation is in the range of 1 mg - 100 mg, 2
10 mg - 80 mg or 5 mg - 50 mg.

A second dosing unit is provided for metering a volume of the second component. Further, means for introducing the components into the package receptacle are provided.

The shown system is to be used with a packaging machine for filling sachets with pellets and at least one additional component, i.e. a recipient in the form of a powder. The
15 shown system allows for 100% determination of net fill weight, independent on tare weights of the primary packaging receptacles, and uses optimized adjustable dosing chamber 11 with feeding and discharge slides 10, 12. The system uses a direct gravimetric mass determination (e.g. a weighing cell). The system is protected against influences by any machine vibrations or air turbulences.

20 The system can be run with production speed appropriate for pharmaceutical industry. The fill weight is determined down to less than 10mg with appropriate accuracy. The system shown in the figures uses gravimetric force to convey pellets through the system. Feed back to the volumetric dosing system permits the system to adjust the dosing volume. Defective packages are identified and rejected.

25 As shown in Figure 1, when the dosing cycle has started, the upper part of the dosing chamber 11 is opened by sliding the first slidable part, the feeding slide 10, to its opened position. The first component, the pellets, are introduced into the dosing chamber 11 by means of gravity through the opening in the feeding slide 10. The first component may be fed into the dosing chamber 11 by gravity, or by force. In the figure, gravimetric feed is
30 shown. The metered dose will depend on the position of the adjustable chamber wall 16.

As shown in Figures 2 and 3, confinement of the dose is achieved by movement of the feeding slide 10, which will close the dosing chamber 11. Simultaneously, the discharge

slide 12 is moved in the direction of the arrow to open the dosing chamber 11 and release the dose into the first discharge tubes 13 connected to the transfer tube 1. The functionality of this pellet dosing system is characterised by the advantage that the feeding slide 10, the discharge slide 12 and the moving chamber wall 17 are fixed to each other and thus can be moved by one single drive only.

In Figure 4, the discharge slide 12 is moved in the other direction to release the dose into the second discharge tube 14.

The pellet feeding can be interrupted by a closure valve 15, e.g. to run empty and disassemble the dosing unit without loss of pellets. The interrupted, closed state of the system is shown in Figure 5.

Figures 6a and 6b are sideviews of the dosing unit. In Figure 6a the dosing chamber 11 has been filled via the pellet hopper 9 and then closed by the feeding slide 10. The volume of the dosing chamber 11 is determined by the position of the adjustable wall 16, movable in the direction of the arrows.

In figure 6b the discharge slide 12 has been moved aligned to one of the discharge tubes 13, 14 to empty the dosing chamber 11.

As shown in Figure 7, the metered dose of pellets is transferred through a transfer tube 1 to a weighing receptacle 3. During the feeding phase of the pellet portion the weighing receptacle 3 is fixed by a lifting device 2. The conical discharge opening of the weighing receptacle 3 is closed by spring force 3a when the pellets are transferred into it.

As shown in Figure 8, when having received the by volume premetered pellet portion, the weighing receptacle 3 moves down on to the load cell 4 where it has no contact with the lifting device 2. In this position the weight (=mass) of the contained pellets is determined by subtracting the tare weight of the weighing receptacle 3, which has been determined very exact before filling.

The following step is shown in Figure 9, where the weighing receptacle 3 is lifted up by the lifting device 2, contracting the spring 3 until the shaft of the discharge cone 5 is brought in contact with the backstop 3b. By this, the discharge cone 5 is pushed downwards to open the weighing receptacle 3 and release the pellet portion. The pellets are transferred by gravity into a transfer funnel 6 which will lead them into the sachets as primary packaging.

The check-weighing cycle is terminated by lowering the weighing receptacle 3 to the feeding position, whereby the weighing receptacle 3 is closed again.

To increase machine output, the pellets are check-weighed alternately by two weighing cells in parallel, which are supplied by a dosing chamber 11 and will discharge
5 the pellets on to the same sachet position.

The weighing cells are protected by a special cover to keep off air turbulences caused by the product and the packaging machine.

Sachets with incorrect fill weight are rejected in the course of the process.

The dosing chamber 11 is readjusted by a feed back loop automatically on basis of the
10 mean fill weight.

CLAIMS

1. A method for dosing a pharmaceutical product in a packaging machine comprising at least one volumetric dosing unit with a dosing chamber, said pharmaceutical product comprising at least a first and a second component, wherein at least one of said components comprises an active ingredient, the said method comprises:
 - metering a volume of the first component,
 - weighing the metered volume of the first component;
 - introducing the metered and weighed volume of the first component into a package,
 - metering a volume of the second component,
 - introducing the metered volume of the second component into the package, and
 - weighing of the package and the components, wherein the volume of the first component is metered and weighed on-line.
2. A method according to claim 1, wherein said dosing chamber is provided with a first and a second slidable part.
3. A method according to claim 1 or 2, wherein the method comprises weighing of the second component after metering the volume of the second component and before introducing the second component in the package.
4. A method according to any one of claims 1, 2 or 3, wherein the method comprises sealing the package after introducing the first and second components and before weighing the package.
5. A method according to any one of claims 1 to 4, the pharmaceutical product comprising more than two components, wherein the method comprises weighing at least two of the components after metering the volume of said at least two components and before introducing the components in the package.
6. A method according to any one of claims 1 to 5, wherein the method comprises using at least one of the results from the weighing procedures in a feed-back loop regulation of the volume metering of the pharmaceutical components.

7. A method according to claim 6, wherein the method comprises intermittent feed-back loop regulation of the volume metering of the pharmaceutical components during operation of said packaging machine.
8. A method according to claim 6, wherein the method comprises continuous feed-back loop regulation of the volume metering of the pharmaceutical components during operation of said packaging machine.
9. A method according to any one of claims 1 to 8, wherein the weight of the first pharmaceutical component is significantly less than the weight of the second pharmaceutical component.
10. A method according to claim 9, wherein the weight ratio between the first and the second pharmaceutical components is more than 1:10.
11. A method according to claim 9, wherein the weight ratio between the first and the second pharmaceutical components is more than 1:100.
12. A method according to any one of claims 1 to 11, wherein the volume of the first pharmaceutical component is significantly smaller than the volume of the second pharmaceutical component.
13. A method according to claim 12, wherein the volume ratio between the first and the second pharmaceutical components is more than 1:10.
14. A method according to claim 12, wherein the volume ratio between the first and the second pharmaceutical components is more than 1:100.
15. A method according to any one of claims 1 to 14, wherein the pharmaceutical product is introduced into sachets.
16. A method according to claim 15, wherein said sachets are made of aluminium foil.
17. A method according to any one of claims 1 to 14, wherein the pharmaceutical product is introduced into blister packages.

18. A method according to any one of claims 1 to 14, wherein the pharmaceutical product is introduced into capsules.
19. A method according to any one of claims 1 to 18, wherein at least one of said components is pellets.
20. A method according to any one of claims 1 to 18, wherein at least one of said components is powder.
21. A method according to any one of claims 1 to 20, wherein at least one of said components is granules.
22. A package containing a pharmaceutical product comprising at least a first and a second component, said components are being dosed by a method according to any of claims 1 to 21.
23. A method for producing a package containing a pharmaceutical product comprising at least a first and a second component, said method comprising the method for dosing according to any one of claims 1 to 21.