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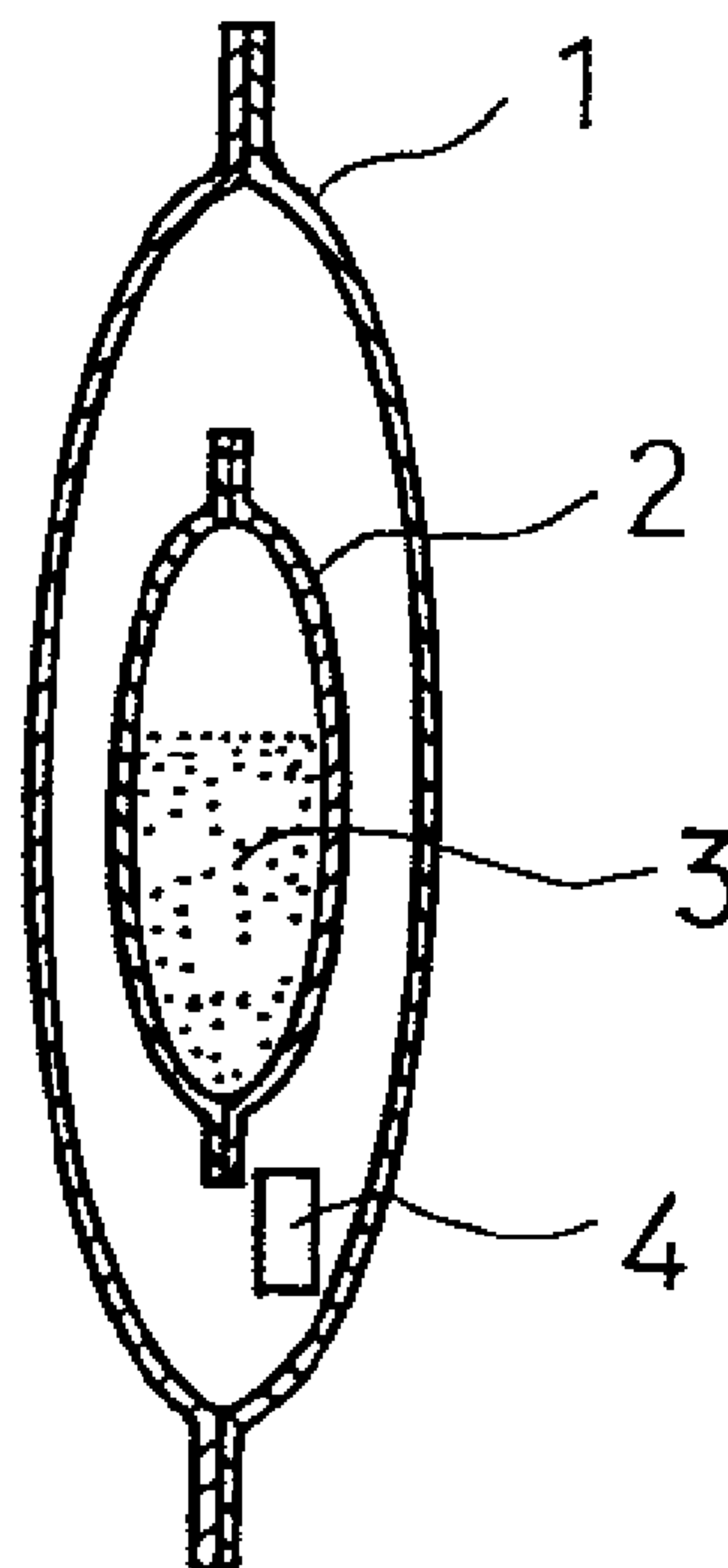
(72) Inventeurs/Inventors:
INOUE, FUJIO, JP;
IZUMI, MASAMITSU, JP;
HAYASHI, SATORU, JP

(73) Propriétaire/Owner:
OTSUKA PHARMACEUTICAL FACTORY, INC., JP

(74) Agent: MARKS & CLERK

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(54) Title: STABILIZING A BICARBONATE-CONTAINING POWDERY PHARMACEUTICAL COMPOSITION



(57) Abrégé/Abstract:

This invention provides a method of stabilizing a bicarbonate-containing powdered medicine by employing the means for packing this powdered medicine in a water- and gas-permeable plastic container, and wrapping this container with a plastic packaging material having a water- and gas-non-permeability with a hollow space between the container and packaging material filled with carbon dioxide or provided therein with a carbon dioxide generating oxygen scavenger or a carbon dioxide saturation adsorbed drying agent: and a container for practicing this method. According to the present invention, its original object of mixing bicarbonate with a powdered material without causing the denaturation and deterioration of a bicarbonate-containing powdered medicine can be achieved.



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ABSTRACT OF THE DISCLOSURE

This invention provides a method of stabilizing a bicarbonate-containing powdered medicine by employing the means for packing this powdered medicine in a water- and gas-permeable plastic container, and wrapping this container with a plastic packaging material having a water- and gas-non-permeability with a hollow space between the container and packaging material filled with carbon dioxide or provided therein with a carbon dioxide generating oxygen scavenger or a carbon dioxide saturation adsorbed drying agent; and a container for practicing this method. According to the present invention, its original object of mixing bicarbonate with a powdered material without causing the denaturation and deterioration of a bicarbonate-containing powdered medicine can be achieved.

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STABILIZING A BICARBONATE-CONTAINING POWDERY
PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

5 The present invention relates to a method of
stabilizing a bicarbonate-containing powdery pharmaceu-
tical composition, particularly a novel method of
stabilizing a bicarbonate-containing powdery pharmaceu-
tical composition which allows the composition in a
10 plastic container to remain wholesome without aging or
degradation and the object of addition of the carbonate
to be accomplished without compromise and to a package
form for such bicarbonate-containing powdery pharma-
ceutical composition.

15 BACKGROUND ART

With very few exceptions such as sodium
chloride, drugs are susceptible to aging loads such as
water, oxygen and light and glass ampules have been in
use for their storage since many years ago. However,
20 with the recent advances in pharmaceutical science,
material engineering, production methodology, production
equipment, etc., these pharmaceutical containers are
being replaced by glass vials and plastic (such as

polyolefins, e.g. polyethylene, polypropylene, etc.,
ethylene-vinyl acetate copolymer, polyethylene
terephthalate, polyvinyl chloride, etc.) containers which
are easy for those engaged in medical practice to handle
5 and easy to dispose of after use and the utilization of
such plastic containers, in particular, is rapidly
spreading of late.

However, unlike glass, plastics are inherently
permeable to gas and moisture and have the disadvantage
10 that containers made thereof cannot be used for all kinds
of drugs. Recently, materials which are almost as
impervious to gas and moisture as glass, such as a
laminate film carrying a vapor-deposited aluminum layer
or an aluminum foil, a laminate film carrying a vapor-
15 deposited silicon monoxide layer, a multi-layer film
consisting of plural materials such as polyethylene
terephthalate, polyvinyl alcohol, polyvinylidene
chloride, ethylene-vinyl alcohol copolymer, etc. have
been developed and today plastics with an oxygen
20 permeability rate of not more than $1.0 \text{ cc/m}^2 \cdot 24 \text{ hrs/1}$
atm. and a moisture permeability rate of not more than
 $1.0 \text{ g/m}^2 \cdot 24 \text{ hrs/1 atm.}$ are available on the market and
finding ever broadening usage and application.

Meanwhile, drugs are generally stable in the
25 bulk form but if they are dissolved and administered to

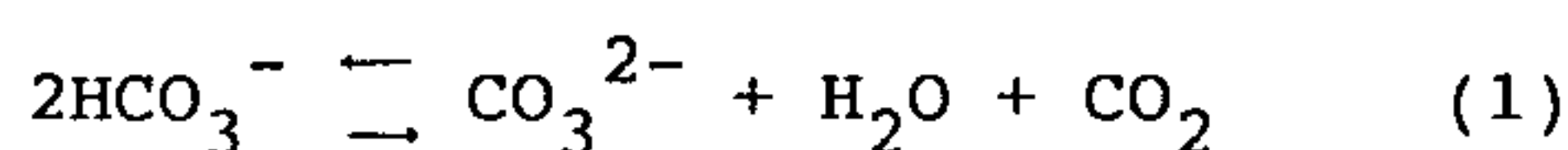
patients, the low pH values of the solutions would not only damage the local tissue at the administration site but also induce systemic disturbances or result in poor absorption. Therefore, a variety of pharmaceutical contrivances has so far been made to avoid the troubles. By way of illustration, assuming that the pharmaceutical composition contains a strongly acidic powdery substance such as the hydrochloride or an acidic powdery drug whose neutral salt would be unstable, it is common practice to formulate the drug with a bicarbonate to insure the proper pH on dissolution or convert it to the neutral salt which is more readily absorbed at the time of administration.

Moreover, drugs which are unstable in solution, for example certain antibiotics, are supplied in the powdery form but since these drugs in general are sparingly soluble in aqueous vehicles, a bicarbonate as a source of carbon dioxide gas, which assists in dissolution, is added as a solubilizer.

On the other hand, sodium hydrogen carbonate is contained as an alkalizing agent in dialysis fluid compositions for artificial kidney use and for the purpose of insuring the ease of handling and reducing the cost of shipment, the recent trend is toward converting such liquid compositions to powdery or granular

preparations (e.g. Japanese Patent Application Kokai H3-38527 and Kokai H3-74331).

The bicarbonate contained in such pharmaceutical compositions liberates water and carbon dioxide gas with time but it is well known that in a closed system there is established an equilibrium among the bicarbonate, carbonate, water and carbon dioxide as indicated by the following relation (1).



However, when a bicarbonate-containing powdery pharmaceutical composition is supplied in a plastic (such as polyolefins, e.g. polyethylene, polypropylene, etc., ethylene-vinyl acetate copolymer, polyvinyl chloride, etc.) container, the carbon dioxide gas and water liberated from the bicarbonate find their way out through the plastic container which is permeable to gas and moisture. As a result, the balance of the above relation (1) is tipped to the right to yield the carbonate so that when the composition is dissolved for administration, the intrinsic objects of adding the bicarbonate, namely supply of HCO_3^- , neutralization of the drug, and assistance in dissolution, cannot be accomplished. Moreover, the solution after reconstitution undergoes increase of pH to affect the stability of the drug solution.

For the protection of a powdery pharmaceutical composition containing a drug liable to decompose on absorption of moisture and a bicarbonate, as supplied in a plastic container, from the decomposition due to moisture, it might be contemplated to dispose a desiccant externally of the plastic container and wrapping the plastic container and desiccant together in a wrapping material with proven performance qualities, e.g. an oxygen permeability rate of not more than $1.0 \text{ cc/m}^2 \cdot 24$ hrs/ 1 atm. and a water permeability rate of not more than $1.0 \text{ g/m}^2 \cdot 24 \text{ hrs/1 atm.}$, such as a laminate film carrying a vapor-deposited silicon oxide layer, a composite laminate film comprising a plurality of materials such as polyethylene terephthalate, polyvinyl alcohol, polyvinylidene chloride, ethylene-vinyl alcohol copolymer, etc. or a laminate film having a vapor-deposited aluminum layer or an aluminum foil which is equivalent to glass in barrier performance. In such cases, there still occur events similar to those encountered when a bicarbonate-containing powdery composition is simply filled into a plastic container. Thus, the water and carbon dioxide gas liberated from the bicarbonate are adsorbed on the included desiccant so that the balance of said relation (1) is tipped to the right to cause the formation of carbonate and, hence, an

elevation of pH of the solution after reconstitution.

The present invention provides a new technology which overcomes all the above-mentioned problems associated with the provision of a bicarbonate-containing powdery pharmaceutical preparation in a plastic container which is permeable to moisture and gas by insuring an increased carbon dioxide concentration in the container, allowing the moisture to be dissipated to the extent not affecting the quality of the drug, and inhibiting decomposition of the bicarbonate and formation of the carbonate to suppress the increase of pH after reconstitution and allow the inherent objects of incorporation of the carbonate, namely supply of HCO_3^- , neutralization of the drug and assistance in dissolution, to be accomplished without compromise.

DISCLOSURE OF INVENTION

In accordance with the present invention there is provided a method of stabilizing a bicarbonate-containing powdery composition characterized in that the placement of a bicarbonate-containing powdery pharmaceutical composition in a plastic container permeable to moisture and gas is followed by at least one procedure selected from among the procedure of introducing carbon dioxide gas into a space between the container and a wrapper and the procedure of disposing a carbon dioxide-

liberating deoxygenating agent in said space and the
procedure of disposing a desiccant previously saturated
with carbon dioxide gas by way of adsorption,
particularly such a method of stabilizing a bicarbonate-
5 containing powdery pharmaceutical composition for
dialysis.

The present invention further provides the
above stabilizing method wherein not only a carbon
dioxide-liberating deoxygenating agent but also a
10 desiccant is disposed in said space between the container
and wrapper, which is applicable with particular
advantage to the case in which said bicarbonate-
containing powdery pharmaceutical composition is an
antibiotic-containing composition.

15 The invention further provides a method of
stabilizing a bicarbonate-containing powdery
pharmaceutical composition characterized by filling the
bicarbonate-containing powdery composition into a plastic
container which is impermeable to moisture and gas and
20 introducing carbon dioxide gas into said container, which
method is applicable with particular advantage to the
case in which said bicarbonate-containing powdery
pharmaceutical composition is a powdered dialysate.

Furthermore, the present invention provides a
25 package form contributory to the stabilization of a

bicarbonate-containing powdery pharmaceutical composition which comprises a plastic container permeable to moisture and gas and adapted to contain the bicarbonate-containing powdery pharmaceutical composition and a plastic
5 packaging wrapper as implemented by following at least one procedure selected from the group consisting of the procedure of filling the space between said container and wrapper with carbon dioxide gas, the procedure of
disposing a carbon dioxide gas-liberating deoxygenating
10 agent in said space and the procedure of disposing a desiccant saturated with carbon dioxide gas by way of adsorption in said space.

The moisture- and gas-permeable plastic container used for accommodating a bicarbonate-containing
15 powdery pharmaceutical composition for the use of the present invention may be made of various materials which are permeable to moisture and gas including but not limited to polyolefins such as polyethylene, polypropylene, ethylene- α -olefin copolymers, etc., ethylene-
20 vinyl acetate copolymer, polyvinyl chloride, polyamides, etc., inclusive of multi-layer films comprising such materials in various combinations.

The moisture- and gas-impermeable plastic wrapper for use in the present invention includes, among
25 others, moisture- and gas-impermeable aluminum-laminated

films, laminate films carrying a vapor-deposited aluminum or silicon monoxide layer and multi-layer films comprising such materials as polyethylene terephthalate, polyvinyl alcohol, polyvinylidene chloride, ethylene-
5 vinyl alcohol copolymer, etc. in suitable combinations. Among the various materials mentioned above, transparent materials through which the contents of the container can be visually inspected, such as a laminate film carrying a vapor-deposited silicon monoxide layer or a multi-layer
10 film comprising a combination of polyethylene terephthalate, polyvinyl alcohol, polyvinylidene chloride, ethylene-vinyl alcohol copolymer and/or the like, are preferred.

The bicarbonate for use in the present
15 invention includes sodium hydrogen carbonate, potassium hydrogen carbonate, ammonium hydrogen carbonate and other bicarbonates. As representative examples of said bicarbonate-containing powdery pharmaceutical composition may be mentioned various powdery preparations for
20 dialysis use (powdered dialysate preparations for artificial kidney use and powdery preparations for peritoneal dialysis) and antibiotic preparations.

The antibiotics for use as active ingredients of said antibiotic-containing pharmaceutical compositions
25 may be any known antibiotics such as cephalosporins

antibiotics, e.g. cefazolin sodium, ceftizoxime sodium,
cefotiam hydrochloride, cefmenoxime hydrochloride,
cefacetrile sodium, cefamandole sodium, cefaloridine,
cefotaxime sodium, cefotetan sodium, cefoperazone sodium,
5 cefsulodin sodium, ceftezole sodium, cefpiramide sodium,
cefmetazole sodium, cefuroxime sodium, ceftazidime, etc.,
penicillin antibiotics such as ampicillin sodium,
carbenicillin sodium, sulbenicillin sodium, ticarcillin
sodium, cloxacillin sodium, piperacillin sodium, etc.,
10 monobactam antibiotics such as carumonam sodium, and
carbapenem antibiotics such as imipenem and so on.

In the present invention which comprises intro-
ducing carbon dioxide gas into the space between said
container accommodating a bicarbonate-containing powdery
15 pharmaceutical composition and said wrapper, disposing a
carbon dioxide gas-liberating deoxygenating agent in said
space or disposing a desiccant saturated with carbon
dioxide gas by way of adsorption in said space, the
concentration of carbon dioxide gas in the container can
20 be maintained at the proper level. For stabilizing a
hygroscopic pharmaceutical composition, a desiccant can
be further disposed in said space to attain a more
satisfactory stabilizing effect.

The present invention may also be carried into
25 practice by using a moisture- and gas-impermeable plastic

container and filling a powdery pharmaceutical composition, such as a powdered dialysate composition, directly into the container. In this mode, the object of the invention can be accomplished by filling carbon dioxide
5 gas in the container. However, the carbon dioxide gas-liberating deoxygenating agent and the desiccant adsorptively saturated with carbon dioxide gas cannot be disposed in the container because it would result in a direct contact of them with the bicarbonate-containing
10 powdery composition.

Filling of the container with carbon dioxide gas can be carried out by any of the conventional methods. For example, when said wrapper is employed, the space between the wrapper and the plastic container can
15 be filled with carbon dioxide gas or a mixture gas of carbon dioxide and nitrogen. When a container impermeable to moisture and gas is employed, the container may be filled with carbon dioxide gas or said mixture gas in the same manner. In either procedure, it is preferable
20 to evacuate the air from the container beforehand, i.e. preceding said filling with carbon dioxide gas.

The carbon dioxide gas-liberating deoxygenating agent which can be used in the present invention can be any substance having both deoxygenating and carbon
25 dioxide gas-liberating activities but is preferably a

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substance which is capable of removing oxygen from said space and insuring a high output of carbon dioxide gas. Such deoxygenating agent includes those which contain, as the principal active ingredient, at least one member

5. selected from the group consisting of iron powder; reducing inorganic salts such as dithionites, sulfites, ferrous salts, etc.; polyphenols such as hydroquinone, catechol, etc., reducing polyhydric alcohols such as ascorbic acid, erythorbic acid and their salts. The

10 dithionites absorb oxygen in the presence of water and, at the same time, react with a bicarbonate or carbonate to yield carbon dioxide gas. The agents comprising sodium ascorbate and ferrous sulfate as main ingredients absorb oxygen and generate carbon dioxide gas in the

15 presence of water. Commercial products among such carbon dioxide gas-liberating deoxygenating agents include Ageless G (registered trademark, Mitsubishi Gas Chemical) and Sendo-Hojizai (Keep-Fresh) Type CTM (Toppan Printing), among others.

20 The desiccant saturated with carbon dioxide gas for use in the present invention includes silica gel, various aluminum silicates, crystalline hydrated alkali metal or alkaline earth metal aluminosilicates and zeolites which have been saturated with carbon dioxide

25 gas by way of adsorption. To let said desiccant adsorb

carbon dioxide gas to saturation, the desiccant is allowed to stand in a carbon dioxide atmosphere at room temperature or a lower temperature, preferably not higher than about 15°C, for several hours. For example, when
5 the commercial product Zeolum (registered trademark) A4 (Tosoh), is subjected to the above procedure, the desired desiccant saturated with carbon dioxide gas is easily obtained. Zeolum (registered trademark) A3RG (Tosoh), which is comparatively low in carbon dioxide adsorption
10 potential, can also be saturated with carbon dioxide gas in the same manner. When the desiccant saturated with carbon dioxide gas is disposed in the space between the plastic container and wrapper, carbon dioxide gas is liberated from the desiccant saturated with carbon
15 dioxide gas so that a carbon dioxide atmosphere is established within the space. Moreover, since such desiccant has a high adsorptive affinity for water vapor than carbon dioxide gas, it adsorbs not only moisture and adherent water from the powdery pharmaceutical
20 composition within the plastic container but, depending on conditions, the water which may be liberated by decomposition of the bicarbonate for some cause or other to release carbon dioxide gas so that the carbon dioxide partial pressure within the container is elevated to
25 inhibit decomposition of the bicarbonate.

It should be understood that when the relative humidity in the container is to be maintained at a level not exceeding 1% at 25°C in the present invention, zeolites having high dehydrating agents are preferably
5 employed.

In the present invention, a desiccant saturated with carbon dioxide gas and a deoxygenating agent which absorbs oxygen by way of oxidation reaction, such as said iron powder, dithionites, sulfites, ferrous salts, etc.,
10 can be used in combination. In this mode, when a moisture-containing self-reacting type deoxygenating agent (e.g. Ageless Z from Mitsubishi Gas Chemical) is used as said deoxygenating agent, the carbon dioxide concentration and moisture level within the container can
15 be adequately maintained without causing degradation of the bicarbonate-containing powdery pharmaceutical composition.

In the present invention, a carbon dioxide gas-liberating deoxygenating agent and a desiccant can be
20 used in combination. In this mode, the use of a moisture-containing carbon dioxide gas-liberating deoxygenating agent is particularly preferred. Thus, when such a moisture-containing carbon dioxide gas-liberating deoxygenating agent is used in combination
25 with a desiccant, the deoxygenating agent releases traces

of water and the desiccant is prevented from adsorbing carbon dioxide gas owing to the preferential adsorption of such traces of water so that the carbon dioxide gas in the space is maintained at a suitable concentration level. The use of said carbon dioxide gas-liberating deoxygenating agent is also beneficial when the bicarbonate-containing powdery pharmaceutical composition is a composition susceptible to oxidative decomposition.

Thus, in accordance with the present invention, the bicarbonate-containing powdery pharmaceutical composition can be preserved in a plastic container without aging and degradation and, at the same time, the object of addition of the bicarbonate can be accomplished without compromise.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a schematic sectional view showing a typical package form of the invention as obtained in Example 1 which appears hereinafter.

In the view, (1) stands for a plastic wrapper, (2) for a plastic container, (3) for a bicarbonate-containing powdery pharmaceutical composition, and (4) for a carbon dioxide gas-liberating deoxygenating agent.

BEST MODE OF PRACTICING THE INVENTION

The following examples are intended to illustrate the invention in further detail. The

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materials used in the examples are referred to by the following abbreviations.

L-LDPE Linear low-density polyethylene

KPET Polyvinylidene chloride-coated
polyethylene terephthalate

PVDC Polyvinylidene chloride

Example 1

A bag (175 μ m thick, 50 x 50 mm) made of L-LDPE (density 0.920) was filled with 20 mg of sodium hydrogen carbonate and 100 mg of sodium chloride. Then, this filled bag and one piece of the carbon dioxide gas-liberating deoxygenating agent (Ageless G15, Mitsubishi Gas Chemical) were placed in a laminate-film wrapping bag of KPET (15 μ m)/PVDC (25 μ m)/L-LDPE (30 μ m) (sized 70 x 70 mm), followed by heat sealing to provide a container of the invention as illustrated in Fig. 1. This product is used for a carbon dioxide gas-liberating deoxygenating agent group.

Similarly an L-LDPE bag containing said drugs was prepared and placed in the same wrapping bag as above. This was followed by filling with a mixture gas of 5%, 10% or 20% of carbon dioxide gas and the balance of air and the wrapping bag was heat-sealed. This was used for a carbon dioxide-filled group. As a control, the same L-DPE bag containing the drugs, not packaged in

the wrapping bag, was tested. This was used for a control group.

The samples in the above CO₂-liberating deoxy-
genating agent group, CO₂ gas-filled group and control
group were stored at 40°C and 75% RH. The samples
immediately after manufacture and after storage periods
of 1, 2 and 3 months were respectively dissolved in 100
ml of physiological saline and the pH of each solution
was measured. The results are shown in Table 1.

Table 1

Sample groups	Immediately after manufacture	Storage at 40°C and 75% RH		
		1 Month	2 Months	3 Months
CO ₂ gas-liberating deoxygenerator group	8.02	8.05	8.02	8.03
CO ₂ gas-filled group				
CO ₂ concentration 5%	8.02	8.05	8.07	8.04
CO ₂ concentration 10%	8.02	8.03	8.02	8.05
CO ₂ concentration 20%	8.04	8.03	8.05	8.02
Control	8.03	8.23	8.47	8.69

Each value is the mean of n=3

It is apparent from Table 1 that the solutions
from the carbon dioxide-liberating deoxygenator group and
carbon dioxide gas-filled group showed no pH elevation,
indicating that the use of a carbon dioxide gas-
liberating deoxygenating agent and the procedure of
filling with carbon dioxide gas, both according to the
invention, arrested decomposition of the bicarbonate in

the plastic container.

While a mixed powder of sodium hydrogen carbonate and sodium chloride was used as the bicarbonate-containing powdery pharmaceutical composition in this example, the method described in this example of the invention can be applied with advantage to any other powdery composition comprising a varying type of electrolyte other than sodium chloride in combination with sodium hydrogen carbonate, for example a powdered dialysate composition.

Example 2

A laminate film bag of KPET (15 μ m)/PVDC (25 μ m)/L-LDPE (30 μ m) (sized 90 x 90 mm) was filled with 20 mg of sodium hydrogen carbonate and 100 mg of sodium chloride. The bag was then filled with a mixture gas of 5%, 10% or 20% of carbon dioxide gas and the balance of air and heat-sealed to provide a package form of the invention.

The above package form was stored at 40°C/75% RH and samples immediately after manufacture and after storage periods of 1, 2 and 3 months were respectively dissolved in 100 ml of physiological saline and the pH of each solution was measured.

As a result, the solution from the above package form was as stable as that in the CO₂ gas-filled

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group of Example 1. Moreover, the method and package form described in this example were suited for powdered dialysate compositions.

Example 3

5 Using a pharmaceutical composition (hereinafter referred to as Drug A) comprising one gram (potency) of a crystalline powder of cefalexin (hereinafter referred to as CEX), a cephem antibiotic, and 20 mg of sodium hydrogen carbonate, the following experiment was carried
10 out.

Thus, Drug A was filled into a glass vial ($\varnothing$ 26 mm, Nichiden Rika Glass Co., Ltd.), stoppered with a butyl rubber stopper and clinched with an aluminum band (Sample 1, control).

15 Then, Drug A was filled into a bag (175 μ m thick, 50 x 50 mm) made of L-LDPE (density 0.920) and the filled bag was placed in a laminate-film wrapping bag of KPET (15 μ m)/PVDC (50 μ m)/L-LDPE (50 μ m) (sized 70 x 70 mm) and heat-sealed (Sample 2, comparative example).

20 Samples were prepared in the same manner except that 6 g of silica gel (Fuji Gel Industry) was inserted before said heat-sealing (Sample 3, comparative example), 2 g of a zeolite (Zeolum A4, Tosoh) was placed before said heat-sealing (Sample 4, comparative example), 2g of a zeolite
25 (Zeolum A3RG, Tosoh) previously saturated with carbon

dioxide gas was inserted (Sample 5, this invention), 2 g of a zeolite (Zeolum A3RG, Tosoh) and one piece of a CO₂ gas-liberating deoxygenating agent (Ageless G20, Mitsubishi Gas Chemical) were inserted (Sample 6, this invention), and 2 g of a zeolite (Zeolum A4, Tosoh) and one piece of a CO₂ gas-liberating deoxygenating agent were inserted (Ageless G20, ditto) (Sample 7, this invention).

The above samples were stored at 40°C and 75% RH.

In a preliminary experiment in which the respective samples were stored at 40°C and 75% RH, elevations of pH were observed after 2 months of storage at 40°C/75% RH. Based on this result, the samples prior to the beginning of storage and those after 3 months of storage were examined for the pH of Drug A (as dissolved in 100 ml of physiological saline), water content, potency (calculated on the anhydrous basis), carbon dioxide concentration in the bag, and appearance (color).

The results are shown in Table 2.

Table 2

				CO ₂ -liberating deoxygenator
No.	Container	Desiccant		
5	1 Glass vial + rubber stopper	-		-
	2 Plastic bag + lamine film wrapper	-		-
10	3 Plastic bag + lamine film wrapper	Silica gel, 6g		-
	4 Plastic bag + lamine film wrapper	Zeolum A4, 2g		-
15	5 Plastic bag + lamine film wrapper	Zeolum A3RG*, 2g		-
	6 Plastic bag + lamine film wrapper	Zeolum A3RG, 2g	Ageless G20	
20	7 Plastic bag + lamine film wrapper	Zeolum A4, 2g	Ageless G20	

Zeolum A3RG* in Sample No. 5 in Table 2 was previously saturated with carbon dioxide gas.

Table 2 (continued)

25	----- Before storage -----					
	No.	pH	Moisture content (%)	Potency of antibiotic (µg(potency)/mg)	CO ₂ con- centration (ppm)	Appearance
30	-----					
	1	7.24	4.35	994	291	White
	2	7.28	4.27	1018	275	White
	3	7.32	4.11	1001	230	White
	4	7.30	4.24	1031	0	White
35	5	7.31	4.18	992	254	White
	6	7.26	4.20	1007	2825	White
	7	7.25	4.21	1012	0	White

----- After 3 months of storage at 40°C/75% RH -----					
	No.	pH	Moisture content (%)	Potency of antibiotic (μ g(potency)/mg)	CO ₂ con- centration (ppm) Appearance

5	1	7.26	4.34	998	2141 White
	2	6.35	5.15	723	2180 Pale
10	3	7.80	4.15	1009	824 yellow
	4	8.02	4.18	1002	0 White
	5	7.43	4.14	1015	1521 White
	6	7.18	4.22	999	9891 White
15	7	7.23	4.15	1002	7368 White

Referring to the combination of an L-LDPE con-
tainer and a laminate film wrapper, Sample 2 (comparative
example) which contained neither of the desiccant and
carbon dioxide gas-liberating deoxygenating agent was
affected by external moisture to show a decrease in
potency of the antibiotic and a change in appearance.
The pH was also fairly depressed and it was considered
attributable to decomposition products of CEX.

Sample 3 (comparative example) which contained
a silica gel having no high desiccating power showed no
loss of potency or an increase in moisture content
because CEX is not so hygroscopic. However, the pH of
its solution showed an increase of about 0.5 from the
value prior to storage. The cause of this increase is
that because the desiccant adsorbed moisture, the sodium
hydrogen carbonate was partially decomposed to sodium

carbonate.

Sample 4 (comparative example) in which Zeolum A4, a potent desiccant, was used, there was no decrease in potency but because of the marked adsorption of carbon dioxide gas on the desiccant, the pH exceeded 8 at 3 months of storage, an increase of about 0.7. This result suggested that the use of a potent desiccant alone is not effective enough for the stabilization of powdery antibiotic products.

On the other hand, Sample 5, Sample 6 and Sample 7 (all of the invention) showed findings comparable to those of Sample 1 (control) employing the glass vial which is the ordinary container for antibiotics, in potency, moisture level and pH.

Sample 5, in which the low CO₂-adsorbing Zeolum A3RG was previously saturated with carbon dioxide gas, showed a lesser change of pH and no remarkable difference in carbon dioxide concentration as compared with Sample 1.

On the other hand, Sample 6 and Sample 7, in which a CO₂-liberating deoxygenating agent was employed, showed somewhat higher CO₂ concentrations than Sample 1 and Sample 5 but no changes of significance in potency, moisture level and pH.

Thus, the bicarbonate-containing pharmaceutical

composition in a plastic container could be well maintained by means of a moisture- and gas-impermeable wrapper, a desiccant and a carbon dioxide gas-liberating deoxygenating agent without causing the aging and
5 degradation of the active ingredient(s) and without inducing the formation of carbonate from bicarbonate.

INDUSTRIAL APPLICABILITY

The method of the present invention for stabilizing a bicarbonate-containing powdery pharmaceutical
10 composition insures an increased carbon dioxide gas concentration in the container, prevents aging and degradation of the drug over a long period of time with great effectiveness and helps accomplish the objectives of incorporation of the bicarbonate, namely the supply of
15 HCO_3^- , neutralization of the drug, and assistance in dissolution.

Furthermore, the invention enables the supply of containers for such stabilized bicarbonate-containing powdery pharmaceutical compositions.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method of stabilizing a bicarbonate-containing powdery pharmaceutical composition, the method comprising:

filling a moisture- and gas-permeable plastic container with the bicarbonate-containing powdery pharmaceutical composition;

wrapping the so-filled container in a moisture- and gas-impermeable plastic wrapper; and

carrying out at least one procedure selected from the group consisting of:

a procedure of introducing carbon dioxide into a space between the container and wrapper;

a procedure of introducing a carbon dioxide-liberating deoxygenating agent in the space; and

a procedure of introducing a desiccant, previously saturated with carbon dioxide by way of adsorption, into the space.

2. The method defined in claim 1, wherein the carbon dioxide-liberating deoxygenating agent and desiccant are introduced together in the space between the container and wrapper.

3. The method defined in claim 1 or 2, wherein the bicarbonate-containing powdery pharmaceutical composition is a powdered dialysate composition.

4. The method defined in claim 1 or 2, wherein the bicarbonate-containing powdery pharmaceutical composition is an antibiotic-containing composition.

5. A package form for ensuring a stabilized bicarbonate-containing pharmaceutical composition, wherein the package form comprises:

(1) a moisture- and gas-permeable plastic container accommodating the bicarbonate-containing pharmaceutical composition;

(2) a moisture- and gas-impermeable plastic wrapper covering the container; and

(3) at least one member selected from the group consisting of:

carbon dioxide;

a carbon dioxide-liberating deoxygenating agent; and

a desiccant previously saturated with carbon dioxide by way of adsorption, the member being introduced in a space between the container and wrapper.

6. The package form defined in claim 5, wherein the carbon dioxide-liberating deoxygenating agent and desiccant are introduced together in the space between the container and wrapper.

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FIG.1

