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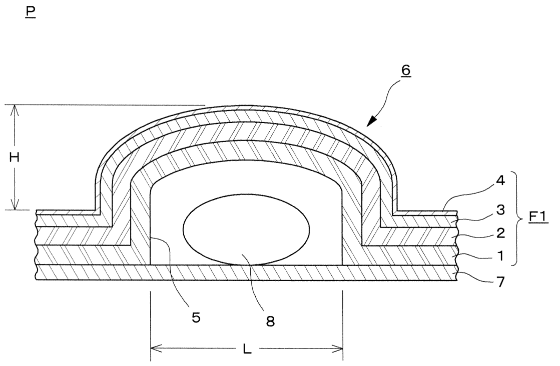
(54) PACKAGE

(57) Provided is a package that exhibits satisfactory moldability as well as moisture adsorption and gas adsorption properties.

A package P includes a container sheet 6 in which a concave receptacle unit 5 that accommodates a solid preparation 8 containing solifenacin succinate or 1-{[a-isobutanoyloxyethoxy]carbonyl}aminomethyl}-1-cyclohexaneacetic acid is formed, and an airtight cover material sheet 7 for sealing the solid preparation 8. The container sheet 6 is formed by a package film F1 in which an adsorption layer 1, at least one or more substrate layers 2 formed by resins, an aluminum foil 3, and a barrier layer 4. The adsorption layer 1 is laminated with the substrate layer 2 while also being disposed on the side where the solid preparation 8 is accommodated, and contains at least zeolite.

FIG. 2



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Description

Technical Field

[0001] The present invention relates to a package, and particularly to a package having moisture adsorption and gas adsorption properties as well as high moldability.

Background Art

[0002] For the packaging of pharmaceutical products, press-through-pack (PTP) packages have been hitherto used in a wide range of applications. A PTP package is a package in a form in which an object to be packaged is accommodated in a container and then is sealed by an easily breakable cover material. When the package is pressed from the container side toward the cover material side, the cover material is broken, and the object to be packaged is taken out. Such a PTP package is excellent in airtightness, handleability, portability and productivity, and also enables saving of resources, it is expected that there will be an ever increasing demand for the PTP package in the future as a package for pharmaceutical products.

[0003] Regarding the material for the container side of the PTP package, a monolayer body of a polypropylene sheet or a polyvinyl chloride sheet, or a laminate formed by plural materials by laminating films and the like on an aluminum foil is generally used. Furthermore, regarding the material for the cover material side, an aluminum foil coated with a resin or the like is used in many cases.

[0004] As such, among the packages which use a variety of materials, if a package should contain a drug substance which is decomposed by moisture, or if the object to be packaged is highly hygroscopic, moisture barrier properties have been increased by sealing the package using polyvinylidene chloride, PCTFE (a trifluorinated chloroethylene resin) or the like, which improves dampproofness, as a material for the package.

[0005] However, there has been a problem that even though an object to be packaged having high hydrolyzability or hygroscopicity is subjected to sealing packaging, moisture permeation occurs through the surface of the pocket (the unit that accommodates the object to be packaged) or the edges of the cover material, and the moisture barrier properties become insufficient, so that the protective effect for the object to be packaged is relatively low.

[0006] In this regard, Patent Document 1 suggests a PTP package having a configuration in which a container using an aluminum foil with high moisture barrier properties and a cover material are pasted together. In the PTP package of Patent Document 1, the aluminum foil that constitutes the container is provided with a stretched polyamide-based resin layer on one surface thereof, and is provided with a thermal adhesive layer on the other surface. Furthermore, when a cover material including at least an aluminum foil, or an aluminum foil of the same configuration as that of the aluminum foil that constitutes the container is heat-sealed with the container, a PTP package having moisture barrier properties can be obtained.

[0007] Furthermore, Patent Document 2 suggests a technology for imparting a desiccant function to a PTP package by providing a moisture adsorptive layer to the container of the PTP package. Since a PTP package imparted with a desiccant function can affect the desiccant function on the object to be packaged, even if the object to be packaged is highly hydrolysable or highly hygroscopic, the object to be packaged can be maintained in a satisfactory state of preservation.

[0008]

Patent Document 1: JP 3983131
Patent Document 2: JP 2006-327690 A

DISCLOSURE OF INVENTION

Problem to be Solved by the Invention

[0009] In regard to the technology disclosed in Patent Document 1, aluminum having high moisture barrier properties is used as the material that constitutes the container, and the cover material is also formed by aluminum. As the container and the cover material are heat-sealed, a PTP package having moisture barrier properties can be thus provided. However, there is a problem that when an object to be packaged is sealed in, the moisture remaining inside the unit where the object to be packaged is sealed in (receptacle unit) cannot be removed, the quality of the solid preparation is impaired. Therefore, there has been a demand for a PTP package having an ability not only to prevent moisture penetration, but also to adsorb moisture. Furthermore, since some of the objects to be packaged have a property that degradation is further accelerated by a gas generated upon degradation, there is a demand for a PTP package having an ability to adsorb moisture as well as gases.

[0010] On the other hand, in regard to the technology disclosed in Patent Document 2, since a moisture adsorbing layer can be provided, a PTP package imparted with a desiccant function for the object to be packaged and the interior where the object to be packaged is sealed in (receptacle unit) can be obtained.

[0011] In regard to the PTP package (blister package) disclosed in Patent Document 2, a film is produced by pasting a moisture-proof barrier layer and a moisture adsorbing layer together, and a PTP package is formed by using this film. At this time, the film that includes a barrier layer and a moisture adsorbing layer is used, in a state of being heated and softened, to form a receptacle unit that accommodates an object to be packaged.

[0012] As such, in a technology of carrying out molding by heating, there is inconvenience that in the case where the various layers have different thermal shrinkage ratios, there is a risk that moldability may deteriorate. Therefore, there is a demand for a technology capable of providing a PTP package which has moisture adsorbability as well as satisfactory moldability.

[0013] Also, in a PTP package, if the receptacle unit (pocket) that accommodates an object to be packaged has insufficient rigidity, not only it is difficult to accommodate an object to be packaged inside the receptacle unit, but also when an external force is applied to the receptacle unit, since the receptacle unit easily collapses, the effect of protecting the sealed object to be packaged is low. Furthermore, if the film that constitutes the package lacks appropriate rigidity, when the receptacle unit of the package is formed, moldability is deteriorated. Therefore, there is a demand for a technology capable of securing moisture barrier properties as well as physically protecting an object to be packaged by attaining appropriate rigidity.

[0014] An object of the present invention is to provide a packages having moisture absorption and gas absorption properties, as well as satisfactory moldability. Another object of the present invention is to provided a package having moisture absorption and gas absorption properties, as well as appropriate rigidity.

Means for Solving Problem

[0015] The above-described problems are solved by a package according to the present invention, the package that accommodate a solid preparation containing solifenacin succinate or 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid, the package including a container, sheet in which a concave (receptacle unit that accommodates the solid preparation is formed, and an airtight cover material sheet that seals in the solid preparation; in which the container sheet is formed by a package film in which an adsorption layer, at least one substrate layer formed by a resin, an aluminum foil, and a barrier layer are laminated, and the adsorption layer is laminated with the substrate layers while also being disposed on the side where the solid preparation is accommodated, and contains at least zeolite.

[0016] As such, since the container sheet that constitutes the package of the present invention includes an adsorption layer containing a zeolite on the side where a solid preparation is accommodated, water or other molecules (gas molecules) inside the receptacle unit can be adsorbed. Furthermore, since the container sheet further includes an aluminum foil having high moisture barrier properties, when the aluminum foil is combined with the adsorption layer, the moisture barrier properties of the package are dramatically enhanced.

Furthermore, since the package film that constitutes the container sheet of the package of the present invention includes at least one or more substrate layers that are laminated on the adsorption layer, appropriate rigidity is imparted to the package film. Therefore, at the time of producing the container sheet provided with a receptacle unit, satisfactory moldability is obtained, and the receptacle unit in which a solid preparation is accommodated also has appropriate rigidity. Therefore, the package film can sufficiently protect the solid preparation that is accommodated inside the package, and also, when a PTP package is fabricated, the solid preparation can be taken out by an appropriate external force.

Particularly, 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid is a hydrolysable substance, and produces acetaldehyde, which causes a odor, through a hydrolysis reaction. Furthermore, a solid preparation containing the aforementioned compound is susceptible to coloration as a result of moisture adsorption. Therefore, a package for the solid preparation is required to have high moisture adsorption and gas adsorption properties.

The package of the present invention can prevent the generation of unpleasant odors or the coloration of solid preparations by adsorbing water, acetaldehyde and the like by means of the adsorption layer. As a result, solid preparations containing the compound can be maintained in a satisfactory state of preservation.

[0017] Furthermore, it is preferable for the substrate layer to be formed by a polyamide-based resin or a polyvinyl chloride resin.

When the materials described above are used in the substrate layers, appropriate rigidity can be imparted to the package film. As a result, when the container sheet that constitutes the package is molded, molding can be carried out easily by press working.

[0018] At this time, it is preferable for the receptacle unit to be molded such that the ratio of the height of the receptacle unit with respect to the diameter of the receptacle unit is adjusted to 0.335 as an upper limit.

In general, it is expected that as the film is stretched more, the occurrence rate of pinholes increases. Therefore, when the receptacle unit that is molded by press working in accordance with the shape or size of the pharmaceutical preparation such as a tablet or a capsule that is accommodated therein is designed, in order to secure a necessary height, the opening of the receptacle may be appropriately enlarged, and thereby the ratio of the height of the receptacle to the diameter of the receptacle (height of receptacle/diameter of receptacle) may be defined to a value less than or equal to the target value that is distinctive of each of various films. Furthermore, in the case of irregularly shaped tablets, design can be carried out on the basis of the height of the receptacle unit relative to the minor axis of the pocket opening.

As such, by adjusting the ratio of the height of the receptacle unit and the diameter of the receptacle to a value less than or equal to the value described above, generation of pinholes can be prevented at the time of molding the container sheet of the package. Generally, when the container sheet is formed by subjecting the package film to press working, as the ratio of the height of the receptacle unit to the diameter of the receptacle unit is larger, more pinholes are generated in the aluminum foil in the package film in the vicinity of the boundary area between the top surface of the receptacle unit and the lateral surfaces (shoulder R section). Particularly, in the case where the container sheet is formed by press working that does not involve heating of the package film, if the ratio of the height of the receptacle unit with respect to the diameter of the diameter of the receptacle unit is larger than the value described above, the probability of the generation of pinholes in the receptacle unit increases; however, when the ratio is adjusted to a value less than or equal to the value described above, the probability of the generation of pinholes can be brought to near zero. Therefore, when the package film is subjected to press working, since pinholes cannot be easily generated in the receptacle unit, a package having excellent moisture barrier properties can be obtained.

[0019] Furthermore, it is preferable for the cover material sheet to include an aluminum foil.

When the cover material sheet is configured to include an aluminum foil, the moisture barrier properties of the receptacle unit for a solid preparation that is formed in the container sheet, and the moisture barrier properties of the cover material sheet can be enhanced. As a result, water and gas molecules inside the receptacle unit are adsorbed by the adsorption layer that has been provided inside the receptacle unit formed in the container sheet, and therefore, the moisture barrier properties are enhanced.

Also, when the cover material sheet is configured to include an aluminum foil, it is preferable because, when the PTP package is produced, the cover material sheet is easily broken by an external force that is applied from the container sheet side, and as a result, the solid preparation inside the receptacle unit can be easily taken out.

[0020] Furthermore, it is preferable for the effective pore diameter of the zeolite to be 3 Å or greater.

Since zeolite has a high rate of adsorption, zeolite can adsorb moisture very rapidly. A molecular sieve, which is an example of zeolite, is a porous particulate material used to separate materials in accordance with the difference in the size of molecules, and has a structure containing uniform pores. A molecular sieve acts as a kind of sieve by adsorbing small molecules that enter into the cavities of the pores. According to the present invention, in the case of using a molecular sieve, the adsorption diameter thereof is preferably 0.3 nm to 1 nm. Conventionally, molecular sieves having pore sizes of 0.3 nm, 0.4 nm, 0.5 nm, and 1 nm are referred to as Molecular Sieve 3A, Molecular Sieve 4A, Molecular Sieve 5A, and Molecular Sieve 13X, respectively. In the present embodiment, Molecular Sieve 3A or Molecular Sieve 4A is used as a preferable desiccating agent. Also, regarding the average particle size of the molecular sieve, for example, a molecular sieve having a particle size of approximately 10 μm is used.

Furthermore, in general, the material to be adsorbed by a zeolite varies depending on the effective pore diameter of the zeolite.

If the effective pore diameter of a zeolite is less than 4 Å, the zeolite can adsorb water but cannot sufficiently adsorb relative large molecules such as carbon dioxide and acetaldehyde. On the contrary, when the effective pore diameter of the zeolite is 4 Å or greater, relatively large molecules such as water, carbon dioxide, acetaldehyde, hydrogen sulfide, ethane and ethanol can also be adsorbed.

Accordingly, in the case where only water affects the state of preservation of a solid preparation, if the effective pore diameter of the zeolite is 3 Å or greater, the solid preparation can be preserved in a satisfactory condition. Furthermore, if the effective pore diameter of the zeolite is 4 Å or greater, a substance which emits a odor, such as hydrogen sulfide, or a substance which has a possibility of affecting the state of preservation of the solid preparation, such as ethanol, is also adsorbed by the adsorption layer, and therefore, the solid preparation can be preserved in a satisfactory state of preservation.

Effect of the Invention

[0021] According to the package of the present invention, an adsorption layer is provided to the package film that constitutes the container sheet, and a substrate layer and an aluminum foil are further provided thereon. Therefore, the package not only has high moisture barrier properties due to the aluminum foil, but also exhibits enhanced moisture adsorption properties as the adsorption layer adsorbs water and gas molecules inside the receptacle unit for a solid preparation, while the substrate layer imparts appropriate rigidity.

Having appropriate rigidity imparted thereto, the package of the present invention can be easily processed by press working that does not involve heating, and thus moldability is dramatically improved. Furthermore, along with an en-

hancement of moldability, the product yield is increased. Moreover, having appropriate rigidity imparted thereto, the package of the present invention can bring a satisfactory state of preservation of a solid preparation.
Furthermore, by adjusting the ratio of the height of the receptacle unit with respect to the diameter of the receptacle unit that accommodates a solid preparation to a predetermined level or lower, the occurrence of pinholes particularly in the vicinity of the receptacle unit can be prevented.
Also, as the cover material sheet includes an aluminum foil, moisture barrier properties are further enhanced.
In addition, when the effective pore diameter of zeolite that is incorporated in the adsorption layer is adjusted to a value greater than or equal to a predetermined value, water as well as other gas molecules and the like can be adsorbed. Therefore, generation of a odor or coloration of solid preparations can also be prevented, and a solid preparation can be preserved in a satisfactory state of preservation.

BRIEF DESCRIPTION OF DRAWINGS

[0022]

Fig. 1 is a schematic cross-sectional diagram of a package film according to an embodiment of the present invention;
Fig. 2 is a schematic cross-sectional diagram of a package according to an embodiment of the present invention;
Fig. 3 is a graph diagram illustrating the results for color difference measurement made in Example 1 of the present invention and Comparative Examples 1 and 2;
Fig. 4 is a graph diagram illustrating the results for color difference measurement made in Example 1 of the present invention and Comparative Examples 1 and 2;
Fig. 5 is a graph diagram illustrating the results for color difference measurement made in Example 1 of the present invention and Comparative Examples 1 and 2;
Fig. 6 is a graph diagram illustrating the results for color difference measurement made in Example 1 of the present invention and Comparative Examples 1 and 2;
Fig. 7 is a graph diagram of the dissolution rates for Example 1 of the present invention and Comparative Examples 1 and 2; and
Fig. 8 is a schematic cross-sectional diagram of a package film according to another embodiment of the present invention.

[0023]

Reference Numerals

P	PACKAGE
F1, F2	PACKAGE FILM
1	ADSORPTION LAYER
2	SUBSTRATE LAYER
2a	PRIMARY SUBSTRATE LAYER
2b	SUB-SUBSTRATE LAYER
3	ALUMINUM FOIL
4	BARRIER LAYER
5	RECEPTACLE UNIT
6	CONTAINER SHEET
7	COVER MATERIAL SHEET
8	SOLID PREPARATION

DETAILED DESCRIPTION OF THE INVENTION

[0024] Hereinafter, an exemplary embodiment of the present invention will be described with reference to the drawings. Meanwhile, the members, arrangement and the like that will be described below are not intended to be limited to the present invention, and various modifications can be definitely made according to the purport of the present invention.
[0025] Figs. 1 to 6 are related to the exemplary embodiment of the present invention. Fig. 1 is a schematic cross-sectional diagram of a package film; Fig. 2 is a schematic cross-sectional diagram of a package; Figs. 3 to 6 are graph diagrams illustrating the results for color difference measurement made in Example 1 of the present invention and Comparative Examples 1 and 2; Fig. 7 is a graph diagram of the dissolution rates in Example 1 of the present invention and Comparative Examples 1 and 2; and Fig. 8 is a schematic cross-sectional diagram of a package film according to

another exemplary embodiment of the present invention.

(Configuration of package film F1)

[0026] A package film F1 according to an exemplary embodiment of the present invention is configured such that, as illustrated in Fig. 1, an adsorption layer 1, at least one or more substrate layers 2, an aluminum foil 3, and a barrier layer 4 are laminated in this order. In addition, an object to be packaged is disposed on the lower side of Fig. 1.

[0027] Regarding the adsorption layer 1, a layer obtained by forming a resin and a zeolite into a film form or a sheet form by an inflation method, a T-die method, co-extrusion or the like, is preferably used.

Furthermore, regarding the thickness of the adsorption layer 1, in order to adsorb sufficient amounts of moisture and gases, the thickness is preferably set to 30 μm to 100 μm.

[0028] Regarding the resin material that constitutes the adsorption layer 1, at least one selected from LDPE (low-density polyethylene), LLDPE (linear low-density polyethylene), PP (polypropylene), chlorinated polypropylene, a saturated polyester, EEA (ethylene-acrylic acid copolymer), EMAA (ethylene-methacrylic acid copolymer), EEA (ethylene-ethyl acrylate copolymer), EMA (ethylene-methyl acrylate copolymer), an ionomer, a carboxylic acid-modified polyethylene, a carboxylic acid-modified polypropylene, a carboxylic acid-modified EVA, PVC (polyvinyl chloride), polystyrene and the like, or combinations of these can be used.

Meanwhile, a skin layer may be disposed on both surfaces of the adsorption layer 1. The material of the skin layer is not particularly limited, as long as it is a material which: (1) prevents the layer containing a zeolite from being exposed to the surface and directly contacted to the preparation; or (2) enhances the laminating properties. As the material for the skin layer, at least one selected from LDPE (low-density polyethylene), LLDPE (linear low-density polyethylene), PP (polypropylene), chlorinated polypropylene, a saturated polyester, EAA (ethylene-acrylic acid copolymer), EMAA (ethylene-methacrylic acid copolymer), EEA (ethylene-ethyl acrylate copolymer), EMA (ethylene-methyl acrylate copolymer), an ionomer, a carboxylic acid-modified polyethylene, a carboxylic acid-modified polypropylene, a carboxylic acid-modified EVA, PVC (polyvinyl chloride), polystyrene and the like, or combinations of these can be used.

[0029] Furthermore, the zeolite that constitutes the adsorption layer 1 contains a molecular sieve, and the molecular sieve preferably has an effective pore diameter of about 3 Å to 10 Å. For the molecular sieve, the effective pore diameter is selected in accordance with the size of the object to be adsorbed. Particularly, when the effective pore diameter is adjusted to 4 Å or greater, not only water but also gas molecules such as carbon dioxide, acetaldehyde, hydrogen sulfide, ethane and ethanol can be adsorbed. Furthermore, also in the case where substances that cause odors, such as acetaldehyde and hydrogen sulfide, are generated when the solid preparation 8 is degraded, these substances are adsorbed to the adsorption layer 1, and therefore, it is preferable.

[0030] Furthermore, artificial zeolites are materials having properties similar to those of natural zeolite, which are formed by various materials by industrial methods. Accordingly, artificial zeolites have improved adsorption properties, ion exchanging properties, and the like. Therefore, the material of the zeolite that constitutes the adsorption layer 1 may be appropriately selected according to the substance to be adsorbed.

[0031] The substrate layer 2 is a layer that is pasted to the adsorption layer 1 and is formed by a resin, and the substrate layer imparts appropriate rigidity and moldability primarily to the package film F1. As the material of the substrate layer 2, at least one selected from polyvinyl chloride, polypropylene, polyvinylidene chloride, polyamides such as Nylon (registered trademark), and the like, or combinations of these can be used. Among these, polyamides such as Nylon (registered trademark) and PVC (polyvinyl chloride) are preferred, and particularly, PVC (polyvinyl chloride) having appropriate extensibility is preferred. When polyvinyl chloride is selected, the moldability and rigidity of the package film F1 can be maintained at a satisfactory level, and when the package P that will be described below is molded by press working, the generation of pinholes can be prevented.

Furthermore, regarding the thickness of the substrate layer 2, in order to secure rigidity of the package film F1 and to maintain satisfactory moldability, the thickness is preferably set to 15 μm to 25 μm.

[0032] The aluminum foil 3 may be any of a pure aluminum foil, or an aluminum alloy foil. Furthermore, a pure aluminum foil coated with a resin such as a PP (polypropylene)-based resin may also be used.

Also, regarding the thickness of the aluminum foil 3, in order to maintain satisfactory moldability, maintain the moisture resistance and light blocking effect of the container, and impart appropriate rigidity and moldability, the thickness is preferably set to 30 μm to 60 μm.

[0033] The barrier layer 4 is formed by a film-like material capable of sealing. As the material that constitutes the barrier layer 4, for example, at least one selected from HDPE (high-density polyethylene), MDPE (medium-density polyethylene), LDPE (low-density polyethylene), polyvinylidene chloride, polychlorotrifluoroethylene, PP (polypropylene), polyethylene terephthalate, polyamides such as Nylon (registered trademark), and the like, or combinations of these can be used. Among them, when a polyamide such as Nylon (registered trademark) is selected, moldability is enhanced, and therefore, it is preferable. Further, in order to maintain sufficient sealability and also to maintain appropriate moldability, the barrier layer 4 is preferably set to 5 μm to 30 μm.

[0034] Furthermore, an adhesive layer (not depicted in the diagram) may be provided respectively between the adsorption layer 1, substrate layer 2, aluminum foil 3, and barrier layer 4. As the adhesive layer (not depicted in the diagram), for example, at least one selected from a urethane-based adhesive, HDPE (high-density polyethylene), MDPE (medium-density polyethylene), LDPE (low-density polyethylene), polypropylene, chlorinated polypropylene, a saturated polyester, EAA (ethylene-acrylic acid copolymer), EMAA (ethylene-methacrylic acid copolymer), EEA (ethylene-ethyl acrylate copolymer), EMAC (ethylene-methyl acrylate copolymer), an ionomer, a carboxylic acid-modified polyethylene, a carboxylic acid-modified polypropylene, a carboxylic acid-modified EVA, PVC (polyvinyl chloride), polystyrene and the like, or combinations of these can be used. Furthermore, the thickness of the adhesive layer (not depicted in the diagram) is preferably set to about 10 μm.

[0035] Furthermore, the respective layers of the adsorption layer 1, substrate layer 2, aluminum foil 3 and barrier layer 4 can be bonded by known methods, and can be bonded by methods such as extrusion lamination, dry lamination, wet lamination, thermal lamination, sandwich lamination and the like.

[0036] As described above, it is preferable that the package film F1 formed by the adsorption layer 1, substrate layer 2, aluminum foil 3 and barrier layer 4 has appropriate rigidity, in order to mold the package P that will be described below. Therefore, the total sum of the thickness of the various layers, that is, the thickness of the package film F1, is preferably set to about 120 μm to 200 μm.

(Configuration of package P)

[0037] The package P according to an exemplary embodiment of the present invention is, as illustrated in Fig. 2, formed by a container sheet 6 that is formed by the package film F1, and a cover material sheet 7 having airtightness, and is intended to package a solid preparation 8 inside a receptacle unit 5. Meanwhile, Fig. 2 displays the thickness of the container sheet 6 in an exaggerated manner for an illustrative purpose.

[0038] The container sheet 6 is formed by a package film F1 in which an adsorption layer 1, at least one or more substrate layers 2, an aluminum foil 3, and a barrier layer 4 are laminated. The container sheet 6 has formed therein one or plural concave receptacle units 5 for accommodating a solid preparation 8, by using the package film F1.

[0039] The container sheet 6 is configured such that as illustrated in Fig. 2, the adsorption layer 1 is disposed on the surface of the side where the solid preparation 8 is accommodated. In this configuration, water contained inside the receptacle unit 5 and in the interior of the solid preparation 8, or any gas generated when the drug substance contained in the solid preparation 8 reacts with water, is adsorbed by the adsorption layer 1. Therefore, the solid preparation 8 that is accommodated in the receptacle unit 5 can be preserved in a preferable state of preservation, without having the components being deteriorated.

[0040] The container sheet 6 having the configuration described above has one or plural receptacle units 5 formed therein by subjecting the package film F1 to a press molding technique or the like. In addition, the shape of the receptacle unit 5 is appropriately designed depending on the shape of the solid preparation 8 that is accommodated inside. The method for press molding is not particularly limited, but known techniques such as bulging and deep-drawing forming are used.

[0041] The cover material sheet 7 is closely adhered to the surface where the adsorption layer 1 of the container sheet 6 is provided, and seals the interior of the receptacle unit 5 where the solid preparation 8 is accommodated. When the adhesiveness between the container sheet 6 and the cover material sheet 7 is low, a heat-sealable resin layer (not depicted in the diagram) may be provided on the surface of the adsorption layer 1 on the side that faces the cover material sheet 7. Regarding the material for the heat-sealable resin layer, the same materials as those used in the adhesive layer described above (not depicted in the diagram) can be used.

[0042] The cover material sheet 7 is formed by a sealable film-like material which has properties that can prevent the inflow and outflow of gases such as water vapor. As the material that constitutes the cover material sheet 7, for example, at least one selected from aluminum, high-density polyethylene, medium-density polyethylene, low-density polyethylene, polyvinylidene chloride, polychlorotrifluoroethylene, polypropylene, and polyamides such as Nylon (registered trademark), or combinations of these can be used. Among them, it is preferable to use aluminum because the moisture resistance and light blocking effect of the container are enhanced. When aluminum is used, it is preferable if an adhesive is applied on the surface of the side that faces the container sheet 6. Regarding the adhesive that is used in this case, an ethylene-vinyl acetate copolymer, polyvinylidene chloride, a vinyl chloride-vinyl acetate copolymer, a chlorinated polypropylene, or the like can be used. Meanwhile, aluminum may be either pure aluminum or an aluminum alloy.

(Test Example 1: Test for rigidity of container sheet 6)

[0043] The strength (anti-collapsibility against an external force) of the receptacle unit 5 of the container sheet 6 in the case where PA or PVC is used in the substrate layer 2, was evaluated, and both the cases exhibited sufficient strength as packages. However, it was found that as compared with the case of using PA (Example 1), the strength of the receptacle unit 5 in the case of using PVC (Example 2) was higher, and the receptacle unit 5 was not easily collapsible. The results are presented in the following Table 1.

[0044]

[Table 1]

		Strength (kgf)	Average strength (kgf)	Strength ratio (times)
Example 1	i	0.21	0.237	1.0
	ii	0.23		
	iii	0.27		
Example 2	i	0.44	0.46	1.9
	ii	0.44		
	iii	0.50		

[0045] From the results described above, it was found that when PVC was used as the substrate layer 2, the strength of the receptacle unit 5 increased about two times, when compared with the case of using PA. The configurations of the package films F1 that constitute the container sheets 6 of Example 1 and Example 2 are described below.

((Example 1))

[Configuration of package film F1]

[0046]

Adsorption layer 1: A two-component three-layer film in which a zeolite (manufactured by Union Showa K.K., trade name: MOLECULAR SIEVE 4A, effective pore diameter: 4 Å)-containing LDPE (manufactured by Tosoh Corp., trade name: PETROTHENE 202, thickness: 50 μm) layer is laminated on both surfaces with a skin layer of LLDPE (manufactured by Prime Polymer Co., Ltd., trade name: EVOLUE (registered trademark) SP2520)
Substrate layer 2: PA (polyamide-based resin) (manufactured by Kohjin Holdings Co., Ltd., trade name: BONYL W, thickness: 15 μm)
Aluminum foil 3: An aluminum alloy foil (manufactured by Toyo Aluminum K.K., trade name: SUPERFOIL, thickness: 40 μm)
Barrier layer 4: PA (polyamide-based resin) (manufactured by Kohjin Holdings Co., Ltd., trade name: BONYL W, thickness: 15 μm)

((Example 2))

[Configuration of package film F1]

[0047] Adsorption layer 1: A two-component three-layer film in which a zeolite (manufactured by Union Showa K.K., trade name: MOLECULAR SIEVE 4A, effective pore diameter: 4 Å)-containing LDPE (manufactured by Tosoh Corp., trade name: PETROTHENE 202, thickness: 50 μm) layer is laminated on both surfaces with a skin layer of LLDPE (manufactured by Prime Polymer Co., Ltd., trade name: EVOLUE (registered trademark) SP2520)
Substrate layer 2: PVC (polyvinyl chloride) (thickness: 60 μm)
Aluminum foil 3: An aluminum alloy foil (manufactured by Sumikei Aluminum Foil Co., Ltd., trade name: BESPAII, thickness: 40 μm)
Barrier layer 4: PA (polyamide-based resin) (manufactured by Toyobo Co., Ltd., trade name: HARDEN N2102, thickness: 15 μm)

(Test Example 2: Test for moldability of container sheet 6)

[0048] In general, under the conditions of defining the diameter of the receptacle unit 5 (pocket diameter) to be constant, the height of the receptacle unit 5 is related to the pinholes generated at the area where the receptacle unit 5 is formed in the package film F1. As the ratio of the height of the receptacle unit 5 with respect to the pocket diameter (ratio of height of receptacle unit 5/pocket diameter) increases, the probability of the occurrence of pinholes increases, and as the ratio of the height of the receptacle unit 5 with respect to the pocket diameter decreases, the probability of the occurrence of pinholes decreases. With regard to the package film F1 (container sheet 6) of Example 3, the probability of the occurrence of pinholes was evaluated by visually inspecting light transmission. The results are presented in Table 2. The configuration of the package film F1 of Example 3 will be described below.

[0049]

[Table 2]

Height of receptacle unit (mm)	4.865	4.935	4.943	4.991	5.002	5.002	5.007	5.032
H/L	0.324	0.329	0.330	0.333	0.333	0.333	0.334	0.335
Rate of occurrence of pinholes (%)	0	0	0	0	0	0	0	0
Height of receptacle unit (mm)	5.045	5.048	5.069	5.072	5.117	5.126	5.151	5.152
H/L	0.336	0.337	0.338	0.338	0.341	0.342	0.343	0.343
Rate of occurrence of pinholes (%)	20	0	10	10	0	20	10	30
Height of receptacle unit (mm)	5.169	5.187	5.188	5.189	5.191	5.198	5.201	5.204
H/L	0.345	0.346	0.346	0.346	0.346	0.347	0.347	0.347
Rate of occurrence of pinholes (%)	20	0	50	0	40	90	30	40
Height of receptacle unit (mm)	5.204	5.222	5.236	5.269	5.273	5.303	-	-
H/L	0.347	0.348	0.349	0.351	0.352	0.354	-	-
Rate of occurrence of pinholes (%)	30	20	80	70	70	100	-	-

[0050] Table 2 presents the results obtained by molding plural receptacle units 5 at different heights, and visually inspecting the light transmittances of the various receptacle units 5. Pockets in which light transmission could be confirmed were counted as pockets having pinholes, and the rates of occurrence of pinholes with respect to the entirety were obtained. Meanwhile, the pocket diameter of the mold used in the molding was 15 mm.

[0051] The rates of occurrence of pinholes in the various receptacle units 5 were measured, and it was found that when the height of the receptacle unit 5 was adjusted to 5.032 mm or less, the rate of occurrence of pinholes would be 0%. Therefore, from the test results described above, it was found that in the case where the diameter of the receptacle unit 5 was 15 mm, when the height of the receptacle unit 5 was adjusted to 5.032 mm or less, the occurrence of pinholes was not recognized, which is preferable. Meanwhile, the "height" of the receptacle unit 5 refers to the distance (H in Fig. 2) from the flat surface (that is, the surface where the receptacle unit 5 is not formed) of the barrier layer 4 of the container sheet 6 to the uppermost surface (top surface) of the pocket. Also, the "diameter of receptacle unit (pocket diameter)" refers to the internal diameter (that is, L in Fig. 2) of the opening of the receptacle unit 5. At this time, the opening of the receptacle unit 5 may not be necessarily perfectly circular. For example, when the opening of the receptacle unit 5 is rectangular or elliptical, the "diameter of receptacle unit 5 (pocket diameter)" refers to the internal diameter of the longitudinal direction.

[0052] Therefore, it was found that the package film F1 including one or more kinds of substrate layers 2 is not subject to the generation of cracks and pinholes at the time of molding of the package P, and is preferable. Furthermore, in the case where the diameter of the receptacle unit 5 was 15 mm, it was found that when the height of the receptacle unit 5 was adjusted to 5.032 mm or less, there was no generation of pinholes, and the package film is preferable.

When a package P which did not include any substrate layer 2 was molded, cracks were generated in the vicinity of the top surface of the receptacle unit 5.

Depending on the shape and size of the solid preparation that is accommodated, the receptacle unit 5 can be molded to have a height of 5.0 mm or greater, by increasing the diameter of the receptacle unit 5. In this case, as can be seen from the test results, it is preferable for the receptacle unit 5 to be molded such that the upper limit of the ratio of the height of the receptacle unit 5 with respect to the diameter of the receptacle unit is 0.335.

In addition, the height of the receptacle unit 5 is appropriately selected in accordance with the shape or size of the pharmaceutical preparation such as a tablet or a capsule, and is not particularly limited. Specifically, for example, (i) when a tablet preparation is an irregularly shaped tablet having a major axis of 15.1 mm, a minor axis of 8.0 mm and a height of 5.7 mm, a receptacle unit having a size of the opening (opening of the receptacle unit 5) with a major axis of 24.0 mm, a minor axis of 22.0 mm, and a height of 6.3 mm (H/L =0.263) may be used; and (ii) when a tablet preparation has a circular shape having a diameter of 9.6 mm and a height of 5.1 mm, a receptacle unit having an opening with a diameter of 19.6 mm and a height of 5.5 mm (H/L = 0.281) may be used.

((Example 3))

[Configuration of package film F1]

[0053] Adsorption layer 1: A two-component three-layer film in which a zeolite (manufactured by Union Showa K.K., trade name: MOLECULAR SIEVE 4A, effective pore diameter: 4 Å)-containing LDPE (manufactured by Tosoh Corp., trade name: PETROTHENE 202, thickness: 130 μm) layer is laminated on both surfaces with a skin layer of LLDPE (manufactured by Prime Polymer Co., Ltd., trade name: EVOLUE (registered trademark) SP2520)
Substrate layer 2: PA (polyamide-based resin) (Manufactured by Kohjin Holdings Co., Ltd., trade name: BONYL W, thickness: 15 μm)
Aluminum foil 3: An aluminum alloy foil (manufactured by Toyo Aluminum K.K., trade name: SUPERFOIL, thickness: 40μ m)
Barrier layer 4: PA (polyamide-based resin) (manufactured by Kohjin Holdings Co., Ltd., trade name: BONYL W, thickness: 15 μm)

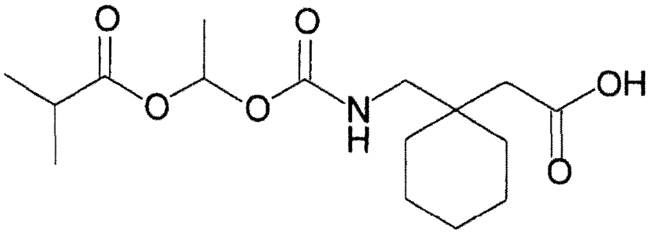
(Test Example 3: Test for moisture barrier property, moisture adsorption property, and gas adsorption property)

[0054] The package P of the present invention is particularly useful for a medicament containing a component which undergoes hydrolysis caused by moisture in the storage environment or moisture contained in the solid preparation 8, and a medicament containing 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid. Hereinafter, the case of applying the package P to a solid preparation 8 containing 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid will be explained.

[0055] The solid preparation 8 is a sustained-release oral medicament formed by a tablet, and contains 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid represented by formula (1) as an active ingredient. 1-{[(α-Isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid is a prodrug of gabapentin (formula (2)), which is a derivative of γ-aminobutyric acid (GABA).

[0056]

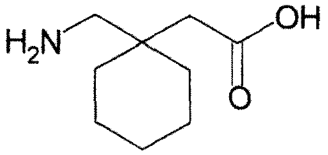
[Chemical Formula 1]



(1)

[0057]

[Chemical Formula 2]



(2)

[0058] A sustained release oral medicament of 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid can be administered to a patient who suffers from any disease or disorder for which gabapentin having a pharmacological action is known to be effective for the treatment, or such effectiveness may be discovered in the future. Examples of the symptoms for which gabapentin is prescribed and the symptoms for which a medicament containing gabapentin is effective, include epilepsy, depression, anxiety, psychosis, dementia, schizophrenia, syncopal attack, hypokinesis, craniopathy, neurodegenerative disorder, panic, pain {particularly, neuropathic pain (for example, postherpetic neuralgia), muscular pain, and skeletal pain}, restless legs syndrome, hot flash, urinary incontinence, inflammatory disorder (namely, arthropathy), insomnia, gastric disorder, addiction to alcohol/cocaine, ethanol withdrawal syndrome, vulval lesion, premature ejaculation, and glutamatergic.

[0059] The relevant medicament can also be administered to a patient as a preventive measurement against the diseases or disorders described above. Therefore, the relevant medicament can be administered as a preventive measurement to a patient having a tendency for epilepsy, depression, anxiety, psychosis, syncopal attack, hypokinesis, craniopathy, neurodegenerative disorder, panic, pain (particularly, neuropathic pain, muscular pain, and skeletal pain), inflammatory disorder (namely, arthropathy), insomnia, gastric disorder, ethanol withdrawal syndrome, premature ejaculation, and vulval lesion.

[0060] Therefore, the relevant medicament can be used so as to prevent certain diseases or disorders, and at the same time, to treat other diseases or disorders (for example, prevention of psychosis, treatment of gastric disorder, prevention of neuropathic pain, and treatment of ethanol withdrawal syndrome). The medicament can be used in combination with other drug substances such as an antiviral drug substance during early viral infection, and can inhibit or alleviate the situation occurring as a result of nervous disorder.

[0061] The dose range preferable for oral administration of gabapentin is usually about 100 mg/day to about 3600 mg/day, and 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof can be regulated so as to provide an equimolar amount of gabapentin. The dose range can be easily determined by methods known to those skilled in the art. According to an aspect, the amount of 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid in a solid preparation is in the range of about 50 mg to about 800 mg; according to another aspect, the amount is in the range of about 100 mg to about 800 mg; and according to still another aspect, the amount is in the range of about 300 mg to about 700 mg. Furthermore, regarding the dosage regimen, the medicament is orally administered once to three times per day. Meanwhile, it is expected that the amount is determined appropriately according to individuals, in consideration of symptoms, age, gender, and the like.

[0062] 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid is hydrolyzed in the presence of water, and from 1 mol each of water and 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid, 1 mol each of acetaldehyde, carbon dioxide, gabapentin, and isobutyl alcohol are generated.

[0063] In the case where the solid preparation 8 is exposed to the atmosphere, or in the case where water remains inside the receptacle unit 5, and in the case where water is included in the interior of the solid preparation 8, as long as water is present in the vicinity or in the interior of the solid preparation 8, 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid produces, as a result of hydrolysis, acetaldehyde, carbon dioxide, gabapentin, and isobutyl alcohol. At this time, since water is produced by a dehydration reaction of gabapentin in an amount equal to the 1 mol of water used in the hydrolysis reaction of 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid, the water produced by this dehydration reaction causes a hydrolysis reaction to newly proceed.

[0064] The solid preparation 8 contains, in addition to the active ingredient 1-{[(α-isobutanoyloxyethoxy)carbonyl] aminomethyl}-1-cyclohexaneacetic acid, a release rate controlling polymer, a filler, a diluent, a fluidizing agent, a lubricating agent, a thickening inhibitor, a surfactant, a buffer solution, a dye, a wetting agent, an emulsifier, a pH buffer, a stabilizer, a thickening agent, a disintegrant, and a colorant as additives. The additives can be added singly or in combination of two or more kinds by an appropriate amount.

[0065] Examples of the release rate controlling polymer include glyceryl esters such as glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macrogol glyceride, stearoyl macrogol glyceride, and combinations of any of the agents described above. According to an aspect, the release rate improving polymer is glyceryl behenate. Other examples of fat and/or wax release rate improving polymers include lauryl alcohol, myristyl alcohol, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, palmitoyl alcohol, ouricury wax, hardened plant oil, candelilla wax, esparto wax, stearic acid, paraffin wax, beeswax, glycol wax, castor wax, and carnauba wax.

[0066] Examples of the filler include starch, sugar, gelatin, malt, rice, wheat flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, glycerol, propylene glycol, water, and ethanol.

The diluent may be added in order to adjust a medicament to a practical size for compression, and can increase the volume. Examples of useful diluents include dibasic calcium phosphate, dibasic calcium phosphate dihydride, calcium sulfate, tribasic calcium phosphate, lactose, cellulose including microcrystalline cellulose, kaolin, mannitol, sodium chloride, dry starch, alpha-starch, compressible sugar, mannitol, and combinations of any of the agents described above. According to an aspect, a single diluent is selected from dibasic calcium phosphate and microcrystalline cellulose. According to an aspect in which the diluent is dibasic calcium phosphate, the medicament can contain the diluent in an amount in the range of about 30% by weight to about 50% by weight, and according to another aspect, the medicament can contain the diluent in an amount in the range of about 35% by weight to about 45% by weight. According to an aspect in which the diluent is microcrystalline cellulose, the medicament can contain the diluent in an amount in the range of about 5% by weight to about 20% by weight, and according to another aspect, the medicament can contain the diluent in an amount in the range caf about 10% by weight to about 16% by weight.

[0067] The fluidizing agent is included in the medicament of the present invention and lowers the wall-attachment affect during production, film formation, and/or drying. Examples of useful fluidizing agents include talc, magnesium stearate, glyceryl monostearate, colloidal silicon dioxide, precipitated silicon dioxide, and combinations of any of the agents described above. According to an aspect, the fluidizing agent is colloidal silicon dioxide. The medicament can contain less than about 2% by weight of a fluidizing agent, and according to an aspect, the medicament can contain less than about 1% by weight of a fluidizing agent.

[0068] A lubricating agent and a thickening inhibitor can be included in the medicament of the present invention so as to be helpful in processing. Examples of useful lubricating agents and/or thickening inhibitors include calcium stearate, glyceryl behenate, glyceryl monostearate, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, sodium lauryl sulfate, sodium dodecyl sulfate, stearic acid, talc, hardened plant oil, zinc stearate, and combinations of any of the agents described above. According to an aspect, the lubricating agent is glyceryl monostearate. According to another aspect, the lubricating agent is magnesium stearate. The medicament can contain a lubricating agent and/or a thickening inhibitor in an amount in the range of about 1% by weight to about 13% by weight, and according to an aspect, the medicament can contain the agents in an amount in the range of about 4% by weight to about 10% by weight.

[0069] Examples of surfactants useful for the medicament of the present invention include pharmaceutically acceptable anionic surfactants, cationic surfactants, amphoteric (amphiphatic/amphiphilic) surfactants, nonionic surfactants, polyethylene glycol esters or ethers, and combinations of any of the agents described above. Preferable examples of pharmaceutically acceptable anionic surfactants include monovalent alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid-polypeptide condensates, sulfuric acid esters, alkyl sulfates such as sodium lauryl sulfate and sodium dodecyl sulfate, ethoxylated alkyl sulfates, ester bond sulfonates such as sodium docusate and dioctyl sodium succinate, α-olefin sulfonates, and phosphorylated ethoxylated alcohols.

The solid preparation 8 of the present embodiment may be a molded tablet, but may also be a capsule.

[0070] For a solid preparation 8 containing 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid, the effect obtainable when the package P of the present invention was applied was evaluated.

((Preparation Example))

[0071] A solid preparation 8 was prepared in the form of a 655-mg tablet containing 1-{[(α-isobutanoyloxyethoxy) carbonyl]aminomethyl}-1-cyclohexaneacetic acid (300 mg) according to the method described in Japanese Translation of PCT International Application No. 2008-518971.

[0072] 1-{[(α-Isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid (active ingredient), calcium hydrogen phosphate (diluent), glycerin fatty acid ester (release controlling polymer), talc (fluidizing agent), anhydrous silicic acid (fluidizing agent), sodium lauryl sulfate (surfactant), and magnesium stearate (lubricating agent) were mixed and compressed, and thus a tablet having a total weight of 655.0 mg was obtained.

The composition per one tablet was 300 mg of 1-{[(α-isobutanoyloxyethoxy)carbonyl]aminomethyl}-1-cyclohexaneacetic acid, 259.1 mg of calcium hydrogen phosphate, 30.05 mg of glycerin fatty acid ester, 40.0 mg of talc, 2.7 mg of anhydrous silicic acid, 12.0 mg of sodium lauryl sulfate, and 11.15 mg of magnesium stearate.

((Example 1))

[0073] The solid preparation 8 obtained in the Preparation Example above was sealed in by bonding a container sheet 6 formed from a package film F1 having the following configuration with a cover material sheet 7 formed by aluminum, and thereby a package P was obtained. Meanwhile, since the configuration of the package film F1 that constitutes the container sheet 6 of Example 1 is the same as the configuration used in Example 1 as described above, further explanation will not be repeated.

((Comparative Example 1))

[0074] The solid preparation 8 obtained in the Preparation Example above was sealed inby bonding a container sheet 6 formed from using a package film F1 having the following configuration that did not include an adsorption layer 1 with a cover material sheet 7 formed by aluminum, and thereby a package P was obtained.

[Configuration of package film]

[0075]

Adsorption layer 1: Absent

Substrate layer 2: PVC (polyvinyl chloride) (thickness: 60 μm)
Aluminum foil 3: Pure aluminum foil (thickness: 45 μm)
Barrier layer 4: Stretched polyamide resin (thickness: 25 μm)

((Comparative Example 2))

[0076] The solid preparation 8 obtained in the Preparation Example above was sealed in by bonding a container sheet 6 formed from using a package film F1 having the following configuration with a cover material sheet 7 formed by aluminum, and thereby a package P was obtained.

[Configuration of package film]

[0077]

Adsorption layer 1: Containing calcium oxide-containing low-density polyethylene
(Amount of calcium oxide relative to polyethylene: 30 wt%) (thickness: 40 μm)
Substrate layer 2: EAA (ethylene-acrylic acid copolymer) (thickness: 10 μm)
Aluminum foil 3: Pure aluminum foil (thickness: 45 μm)
Barrier layer 4: Stretched polyamide resin (thickness: 25 μm)

[0078] In Example 1, Comparative Example 1 and Comparative Example 2 above, in order to investigate the effect of stabilizing the active ingredient contained in the package P for the solid preparation 8, an intercomparison of the external appearance based on color difference measurement was carried out. Graph diagrams illustrating the results of color difference measurement made at various temperatures are presented in Figs. 3 to 6. Meanwhile, ΔE in the graphs represents the value obtained by measuring the color difference ΔE between the solid preparation 8 immediately after production and the solid preparation 8 after storage at a predetermined temperature (Fig. 3: 50°C, Fig. 4: 40°C, Fig. 5: 30°C, and Fig. 6: 25°C) by using a color difference meter.

[0079] In addition, in the present specification, "coloration" means that the external appearance turns from white to a color other than white.

The following various tests were carried out by using as samples the package P for solid preparation 8 obtained in Example 1 and Comparative Examples 1 and 2.

[0080] A solid preparation 8 that had been stored in a cold place after production at a predetermined temperature was used as a control sample, and the various samples of Example 1 and Comparative Examples 1 and 2 that had been respectively stored at 50°C, 40°C, 30°C and 25°C (relative humidity: 75% in all cases) were used as post-storage samples. The solid preparations 8 packaged in the respective packages P were taken out, and the external appearance was evaluated by measuring the color difference ΔE between the control sample and the post-storage samples by using a color difference meter (CM-3500d, manufactured by Konica Minolta Holdings, Inc.).

[0081] In Fig. 3, it is illustrated that when the samples were stored at 50°C, Example 1 had a small degree of coloration of the solid preparation 8 as compared with Comparative Examples 1 and 2. As compared with Comparative Example 1 which did not include an adsorption layer 1, the color difference ΔE of Example 1 was about one-third at the time point after 3 days, and it was found that coloration of the solid preparation 8 was highly suppressed by the package P of Example 1. Furthermore, it was found that Example 1 can suppress coloration of the solid preparation 8 to a larger extent as compared with the package P of Comparative Example 2 containing calcium oxide in the adsorption layer 1.

[0082] In Fig. 4, it is illustrated that even though stored at 40°C, Example 1 exhibited a smaller degree of coloration of the solid preparation 8 as compared with Comparative Examples 1 and 2. In the case of not including an adsorption layer 1 as in Comparative Example 1, ΔE exhibited a high value such as about 32 after one month; however, Comparative Example 2 which contained calcium oxide in the adsorption layer 1, and Example 1 exhibited a value of about 1.

After a lapse of 3 months in which the storage period was further extended, the ΔE value of Example 1 was about 12; however, the ΔE value of Comparative Example 2 was about 22, and after a long-term storage, the difference in ΔE was highly noticeable. Therefore, through this color difference measurement, it was found that the package P of the present invention can effectively suppress coloration.

[0083] In Fig. 5, it is illustrated that when stored at 30°C, Example 1 and Comparative Example 1 have a slight difference, but the value of ΔE of Example 1 is smaller. Furthermore, when the storage temperature was 30°C, Example 1 always exhibited ΔE value of less than 1 throughout the storage period of 6 months. The degree of coloration was very small, and it was found that Example 1 was appropriate for the storage of the solid preparation 8.

[0084] In Fig. 6, it is illustrated that when stored at 25°C, after 6 months, Example 1 maintained a small value of ΔE as compared with Comparative Example 2 that contained calcium oxide in the adsorption layer 1. Also in the case of 25°C, it was confirmed that at the time point that 6 months had passed, the degree of coloration remained small.

[0085] Therefore, from the results of the color difference measurement, it was found that coloration of the solid preparation 8 is effectively prevented by using a package P of the present invention which includes an adsorption layer 1 containing zeolite on the side where the solid preparation 8 is accommodated.

[0086] Meanwhile, in the color difference measurement, the package P of Example 1 (the thickness of the adsorption layer 1 was 50 μm) was evaluated. However, the color difference measurement of the package P of Example 2 (provided that a sample having a thickness of the adsorption layer 1 of 130 μm was evaluated. The layer configuration other than the adsorption layer 1 was the same as the configuration of Example 2 described above), and both exhibited almost the same color difference ΔE values.

[0087] The above-described results suggest that as in the case of Comparative Example 1, the configuration is not a configuration capable of preventing penetration of water and the like from the outside, and the active ingredient can be stabilized by adsorbing the water contained inside the receptacle unit 5 at the time of packaging, by means of the adsorption layer 1.

[0088] Furthermore, it was understood from the results described above that when the configuration of the package P did not include an adsorption layer 1 containing zeolite, it was difficult to promote sufficient stabilization of the active ingredient depending on the storage temperature; however, when the container sheet 6 of the package P is configured to include an adsorption layer 1 containing zeolite on the surface on the side where the solid preparation 8 was accommodated, the active ingredient can be stabilized, and the progress of hydrolysis can be effectively suppressed.
It is speculated that these results are attributable to the fact that as compared with calcium oxide that adsorbs water only, zeolite has an adsorption capacity directed to not only water but also other gas molecules (aldehyde, CO_2 and the like).

(Test Example 4: Dissolution rate of orally disintegrating tablet)

[0089] The effect of the package P of the present invention on an orally disintegrating tablet containing a watersoluble drug substance component was evaluated by using the packages P of Example 1 and Comparative Examples 1 and 2. Meanwhile, since the configurations of the packages P of Example 1 and Comparative Examples 1 and 2 thus evaluated were the same as the configurations described above, further explanation will not be repeated.

((Preparation Example))

[0090] A solid preparation 8 which was a 150-mg orally disintegrating tablet containing solifenacin succinate was prepared according to the method described in WO 2006-070735.

[0091] Particles of crystalline cellulose (particulate) coated with solifenacin succinate were obtained, subsequently mannitol (filler) was added to the particles, and an aqueous solution of maltose (binder) was sprayed onto the particles. Thus, the particles were coated and granulated. The granulation product was mixed with magnesium stearate (lubricating agent), and then tablets were produced by using a rotary tabletting machine. Subsequently, the tablets were subjected to humidified drying by using a humidifying dryer, and thus orally disintegrating tablets which weighed 150 mg per tablet were obtained.

[0092] The orally disintegrating tablets were packaged with the packages P of Example 1 and Comparative Examples 1 and 2, and the tablets were respectively stored for 3 months (Example 1-1, Comparative Example 1-1, and Comparative Example 2-1) and for 6 months (Example 1-2 and Comparative Example 1-2) (storage conditions: 40°C, relative humidity 75%, in the dark).
The degrees of dissolution of the orally disintegrating tablets after predetermined storage periods (the values after the passage of 0 minute, 30 minutes and 45 minutes were measured) are presented in Fig. 7. The dissolution test was carried out by a paddle method using 900 mL of a phosphate buffer solution at pH 6.8, at a speed of 50 rotations per minute.

[0093] As a result, in the samples for which the storage period was set to 3 months, significant differences were observed in the degree of dissolution after a lapse of 30 minutes. The degree of dissolution was 99% in Example 1-1, 81% in Comparative Example 1-1, and 98% in Comparative Example 2-1. It was found that the orally disintegrating tablets packaged in the package P of Example 1 maintained high dissolubility, similarly to the package P of Comparative Example 2-1 containing calcium oxide in the adsorption layer 1.

[0094] Furthermore, also in the samples for which the storage period was set to 6 months, large differences were observed in the degree of dissolution after a lapse of 30 minutes. The degree of dissolution was 92% in Example 1-2, and 82% in Comparative Example 1-2. It was found that the orally disintegrating tablets packaged in the package P of Example 1 maintained high dissolubility.

[0095] Orally disintegrating tablets are tablets that disintegrate in saliva or a small amount of water inside the oral cavity, and it is desired that the tablets rapidly dissolve (disintegrate) in the oral cavity. Generally, orally disintegrating tablets are such that if the state of preservation is not preferable, dissolution is delayed, and it becomes difficult for the tablets to dissolve (disintegrate) in a short time. On the contrary, it was found by the evaluation described above that the delay of dissolution of the orally disintegrating tablets in the oral cavity is suppressed by the package P of the present invention, and the tablets attain high dissolubility in a short time. It is speculated from these results that the adsorption layer 1 provided to the package P of the present invention effectively adsorbs water and the like, and therefore, the adsorption layer 1 contributes to stabilization of the orally disintegrating tablets.

(Another embodiment)

[0096] Furthermore, the package film used in the package P of the present invention is not intended to be limited to the configuration of the package film F1 described above. The package film F1 is configured to include only the substrate layer 2 as the substrate layer. However, as in the case of the package film F2 illustrated in Fig. 8, a configuration including plural substrate layers (main substrate layer 2a and sub-substrate layer 2b) as the substrate layer may also be employed.

[0097] Fig. 8 is a schematic cross-sectional diagram of the package film F2 according to another embodiment of the present invention.

Since the configuration and operation of the adsorption layer 1, aluminum foil 3 and barrier layer 4 are equal to those of the package film F1 described above, further explanation will not be repeated.

The main substrate layer 2a and the sub-substrate layer 2b are provided in order to impart appropriate rigidity and moldability to the package film F2, similarly to the substrate layer 2. Also, the main substrate layer 2a and the sub-substrate layer 2b are formed by the same material as that of the substrate layer 2.

[0098] In addition, the amount of incorporation of the drug substance is not particularly limited as long as it is a pharmaceutically effective amount for prevention or treatment. However, the drug substance is usually administered to a patient at an adult dosage level of from 10 ng to 5000 mg; according to another aspect, at an adult dosage level of from 500 μg to 1000 mg; and according to still another aspect, at an adult dosage level of from 1 mg to about 100 mg, per day. Also, the proportion of incorporation is usually appropriately selected in accordance with the kind of drug substance, use (applicable disease), and age (or body weight), but the proportion of incorporation is not particularly limited as long as it is a therapeutically effective amount or prophylactically effective amount.

Claims

1. A package that accommodates a solid preparation containing solifenacin succinate or 1-{[(α-isobutanoyloxyethoxy) carbonyl]aminomethyl}-1-cyclohexaneacetic acid,
the package comprising:

a container sheet in which a concave receptacle unit that accommodates the solid preparation is formed, and an airtight cover material sheet that seals in the solid preparation,
wherein the container sheet is formed by a package film in which an adsorption layer, at least one substrate layer formed by a resin, an aluminum foil, and a barrier layer are laminated, and
the adsorption layer is laminated with the substrate layer while also being disposed on a side where the solid preparation is accommodated, and contains at least zeolite.

2. The package according to claim 1, wherein the substrate layer is formed by a polyamide-based resin or a polyvinyl chloride resin.

3. The package according to any one of claims 1 and 2, wherein the receptacle unit is molded such that a ratio of a height of the receptacle unit with respect to a diameter of the receptacle unit is adjusted to 0.335 as an upper limit.

4. The package according to any one of claims 1 to 3, wherein the cover material sheet comprises an aluminum foil.

5. The package according to any one of claims 1 to 4, wherein an effective pore diameter of the zeolite is 3 Å or greater.

FIG. 1

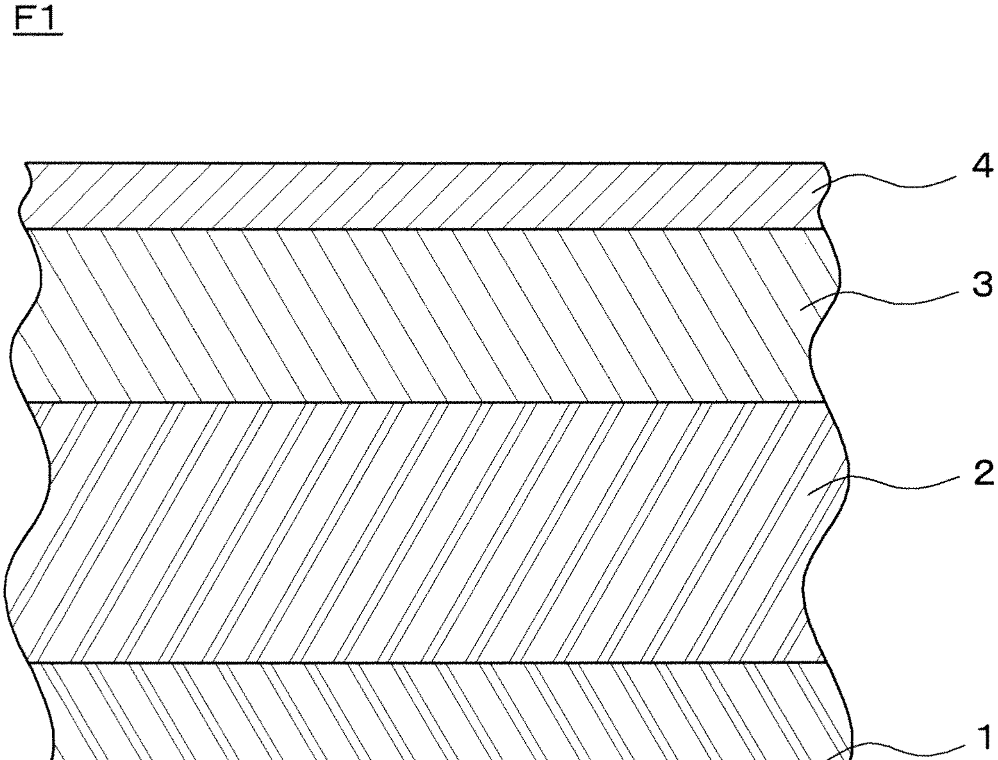


FIG. 2

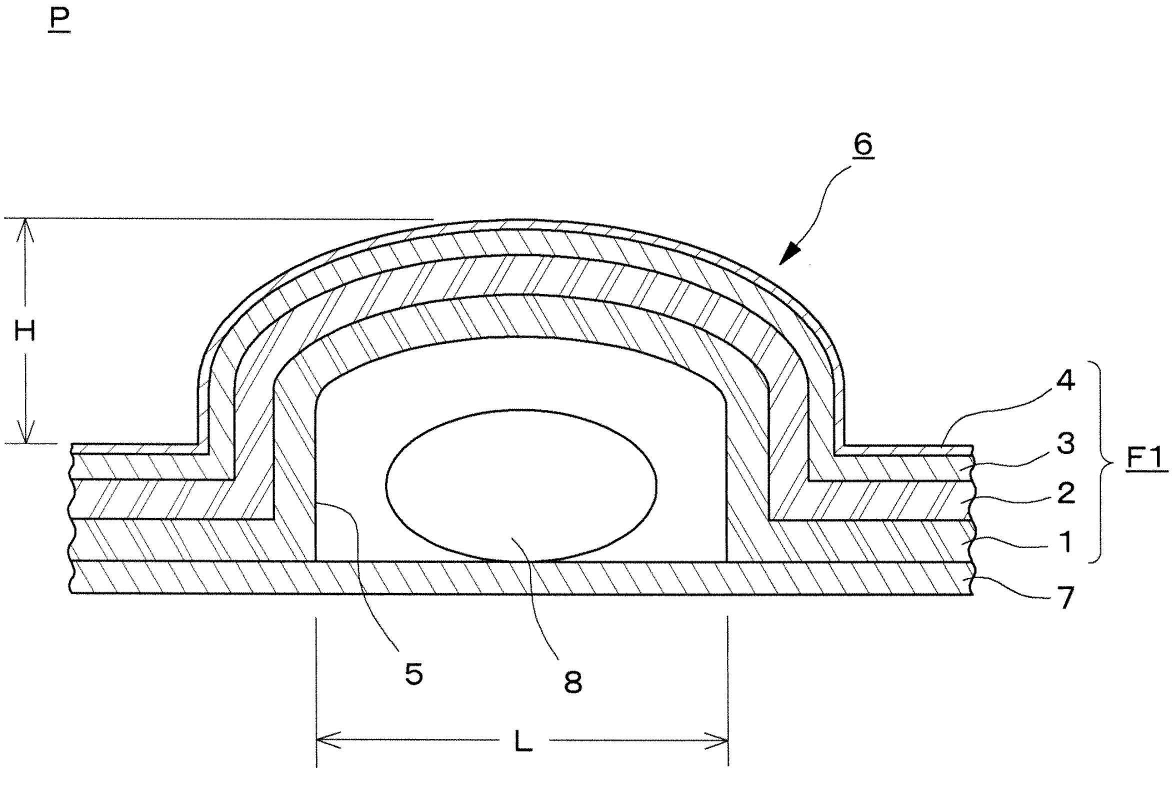


FIG. 3

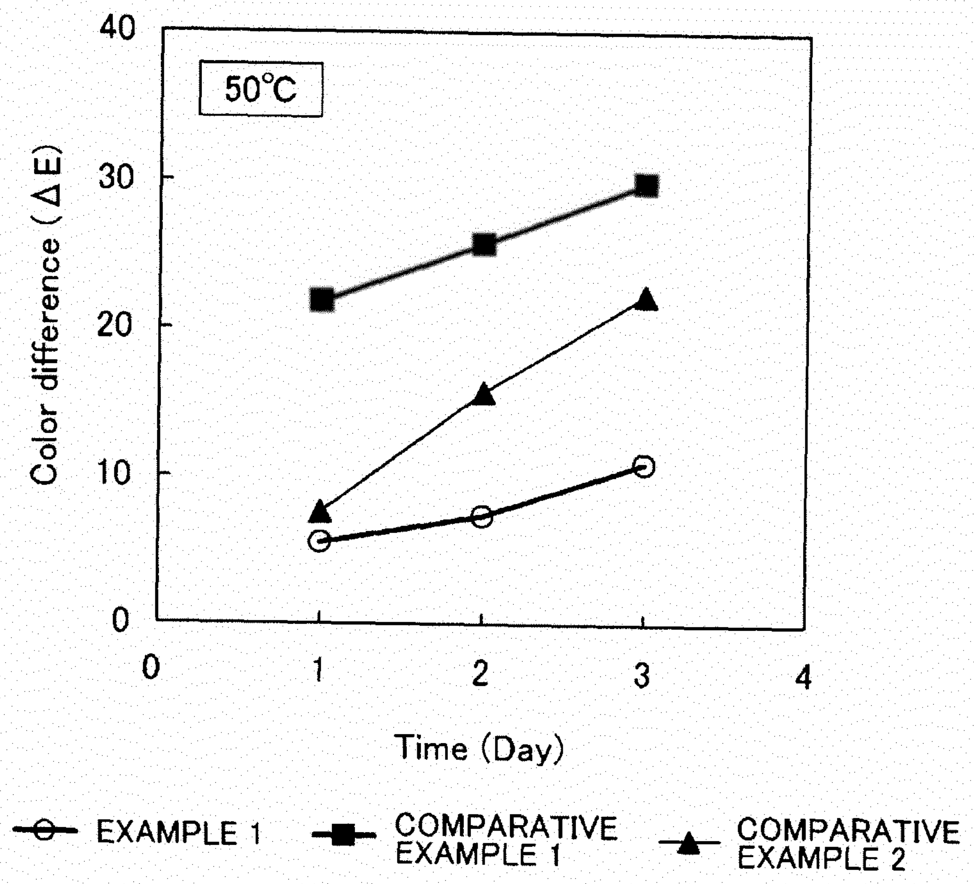

50°C
Color difference (ΔE)
0
10
20
30
40
Time (Day)
0
1
2
3
4
EXAMPLE 1
COMPARATIVE EXAMPLE 1
COMPARATIVE EXAMPLE 2

FIG. 4

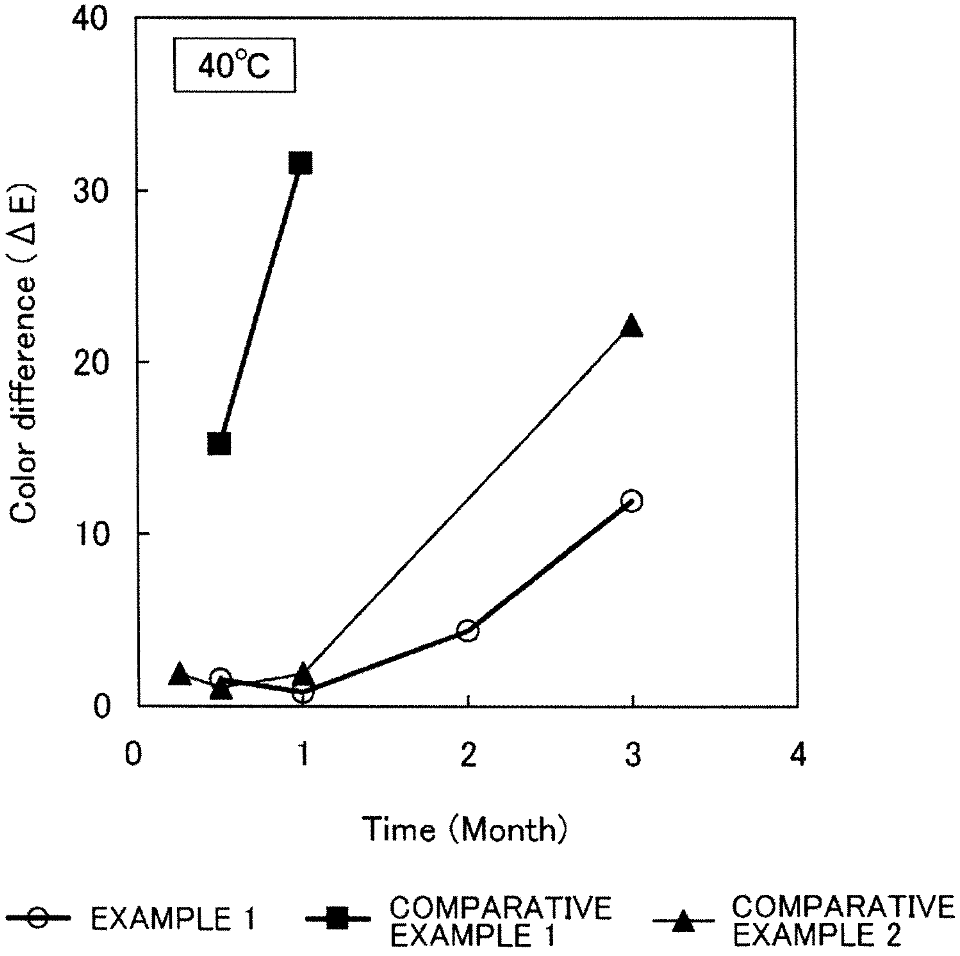

40°C
Color difference (ΔE)
0
10
20
30
40
0
1
2
3
4
Time (Month)
EXAMPLE 1
COMPARATIVE EXAMPLE 1
COMPARATIVE EXAMPLE 2

FIG. 5

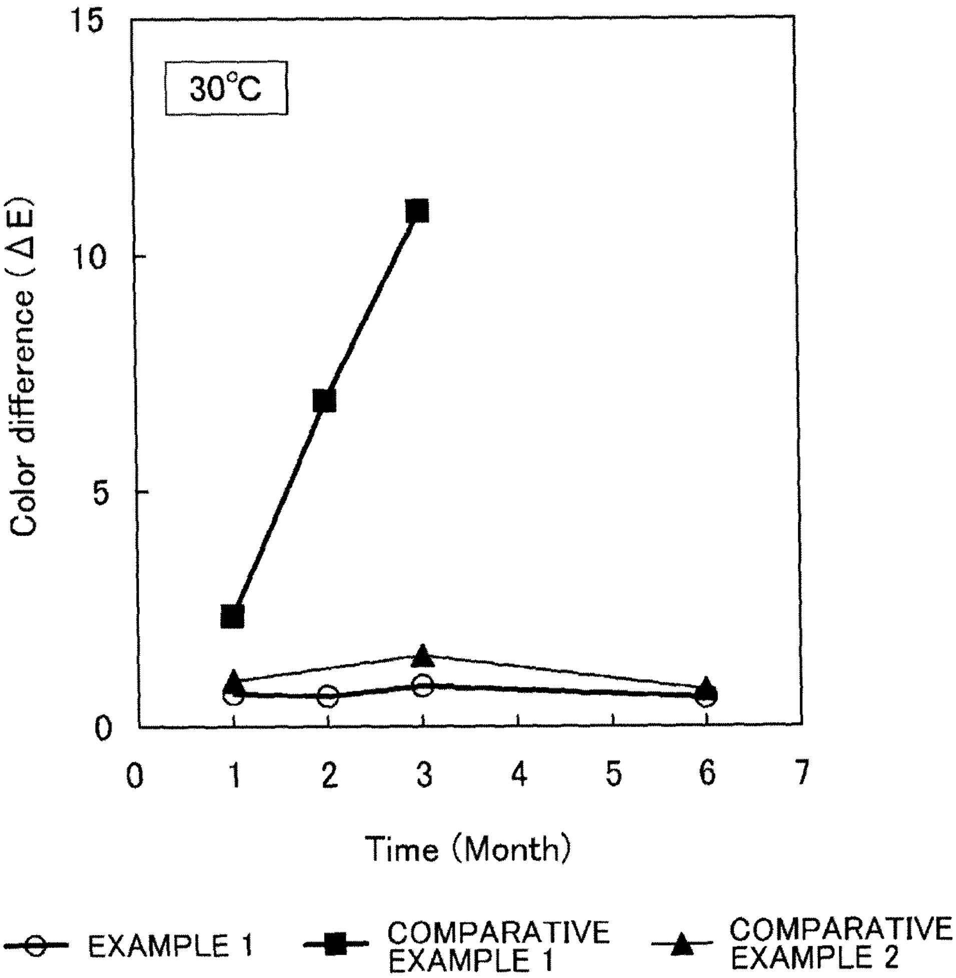

30°C
Color difference (ΔE)
0
5
10
15
0
1
2
3
4
5
6
7
Time (Month)
EXAMPLE 1
COMPARATIVE EXAMPLE 1
COMPARATIVE EXAMPLE 2

FIG. 6

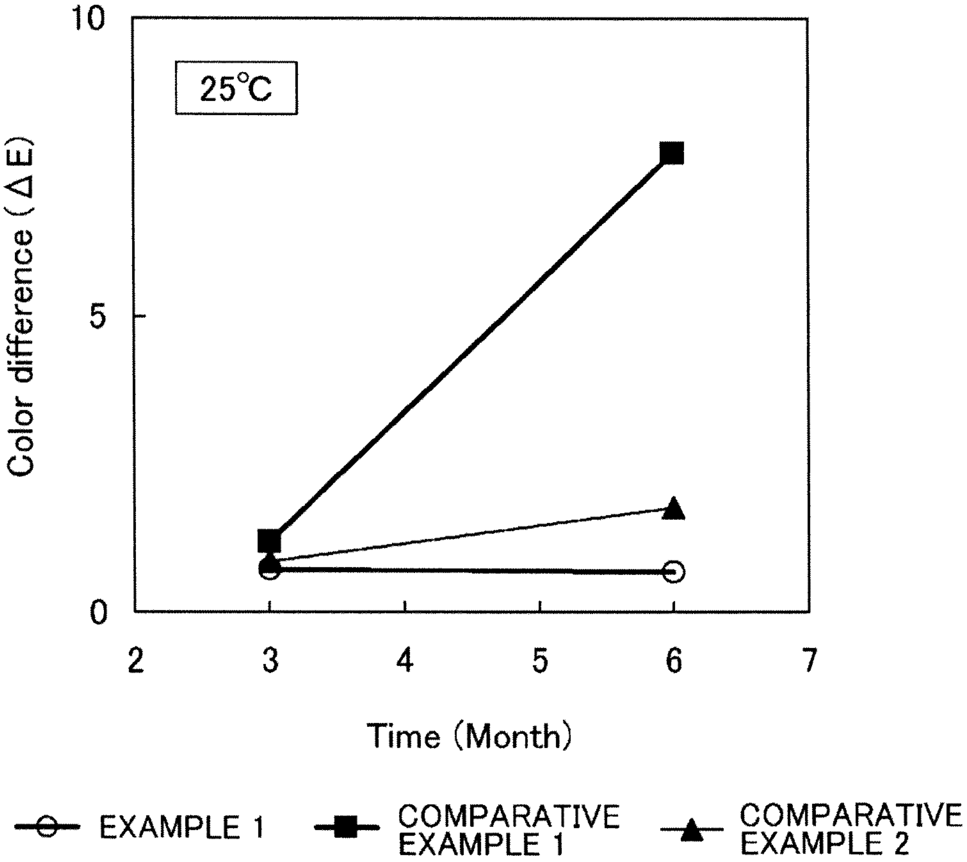

25°C
Color difference (ΔE)
10
5
0
2
3
4
5
6
7
Time (Month)
EXAMPLE 1
COMPARATIVE EXAMPLE 1
COMPARATIVE EXAMPLE 2

FIG. 7

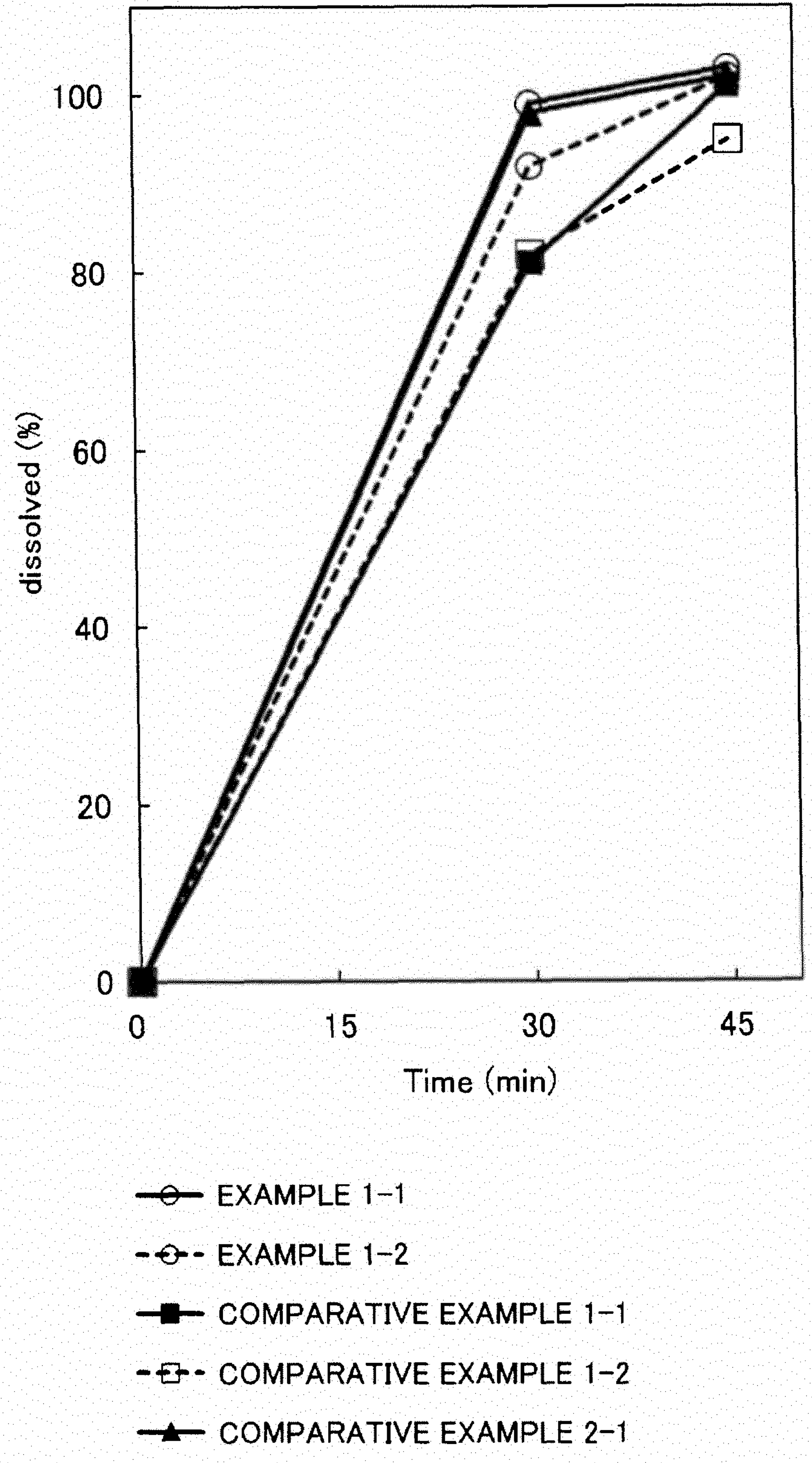
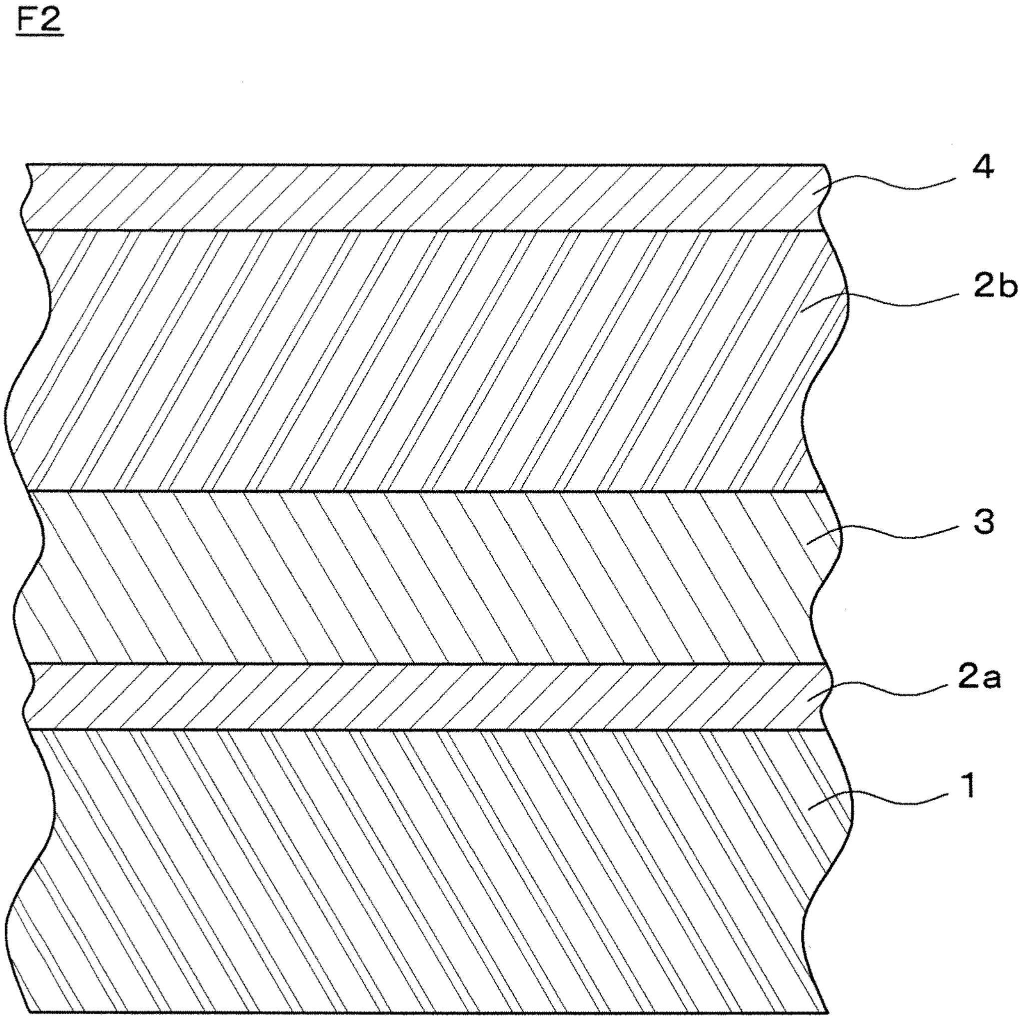

100
80
60
40
20
0
dissolved (%)
0
15
30
45
Time (min)
EXAMPLE 1-1
EXAMPLE 1-2
COMPARATIVE EXAMPLE 1-1
COMPARATIVE EXAMPLE 1-2
COMPARATIVE EXAMPLE 2-1

FIG. 8



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/069881

A. CLASSIFICATION OF SUBJECT MATTER
B65D81/24(2006.01)i, *A61J1/03*(2006.01)i, *B32B1/02*(2006.01)i, *B32B15/08*(2006.01)i, *B65D65/40*(2006.01)i, *B65D75/34*(2006.01)i, *B65D81/26*(2006.01)i, *B65D83/04*(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B65D81/24, A61J1/03, B32B1/02, B32B15/08, B65D65/40, B65D75/34, B65D81/26, B65D83/04

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

Jitsuyo Shinan Koho	1922-1996	Jitsuyo Shinan Toroku Koho	1996-2011
Kokai Jitsuyo Shinan Koho	1971-2011	Toroku Jitsuyo Shinan Koho	1994-2011

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2010-504252 A (Takeda Chemical Industries, Ltd.), 12 February 2010 (12.02.2010), entire text; all drawings & EP 2068812 A & WO 2008/041663 A1 & CA 2664380 A	1-5
X	JP 2006-346888 A (Kyodo Printing Co., Ltd.), 28 December 2006 (28.12.2006), entire text; all drawings (Family: none)	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 November, 2011 (29.11.11)	Date of mailing of the international search report 13 December, 2011 (13.12.11)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 2009)

REFERENCES CITED IN THE DESCRIPTION

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- WO 2006070735 A **[0090]**