Description

The present invention relates to a slow-releasing medical preparation to be administered by adhering to the wet mucous surface of a mucous membrane and skin of men or animals. More particularly, this invention relates to a slow-release medical preparation, which has improved handleability and adhesiveness, comprising a layer which displays adhesiveness to the wet mucous surface and a layer which has no adhesiveness, at least one of said layers contains a medicament.

Several suggestions have hitherto been made as to slow-release medical preparations from which a medicament contained therein is gradually released to maintain the efficacy of the medicament over a long period of time after they are administered to men or animals by adhering to their mucous membrane.

For instance, Japanese Laid-Open Patent Publication No. 38412/76 (U.S. Patent No. 4,059,686, patented November 22, 1977) disclosed a buccal preparation which is to be used by adhering to the buccal mucous membrane, being composed of a medicament, a sodium salt of polyacrylate, and an excipient (i.e., crystalline cellulose, mannitol, lactose, sorbitol, anhydrous calcium phosphate, amilose, etc.). Japanese Laid-Open Patent Publication No. 130421/78 discloses a preparation for treatment of uterine cancer, to be used by adhering to the uterus mucous membrane, comprising hydroxypropyl cellulose, polyacrylic acid or its salt, and a carcino-static agent.

However, these slow-release preparations, when they are prepared in the form of a tablet, have adhesiveness on both the upper and the reverse surfaces and this presents some disadvantages, for instance making handling inconvenient and often causing the tablets to adhere to places not desired at the time of administration. In order to lessen the touchy discomfort occurring at places where a slow-releasing preparation is adhered, it is preferable to make the preparation as thin as possible; however, this presents a problem in that it is virtually impossible to make the thickness of conventional slow-release preparations less than about 1 mm. from the viewpoint of mechanical strength.

The present inventors have developed an improved slow-release preparation to be used by adhering to the wet surface of mucous membrane, etc., which does not possess faults found with the preparations of the prior art.

Disclosure of Invention

The present invention relates to a slow-release medical preparation comprising a polymer which is swellable upon moistening and capable of adhering to a wet mucous surface, and a medicament, characterised in that said preparation is in the form of a two layer tablet comprising an adhesive layer containing said polymer and a layer which does not adhere to a wet mucous surface and is water soluble or disintegrable, said non-adhesive layer having a thickness of at least 0.1 mm and said adhesive layer having a thickness not exceeding 2.0 mm.

In the present invention, a slow-release preparation which is administered by adhering to the wet mucous surface consists of two layers, an adhesive layer and a nonadhesive layer, speaking from the structural viewpoint. And the adhesive layer is a layer which has to adhere to the wet mucous surface of mucous membrane and skin of men or animals and is composed of a polymer which adheres to the wet mucous surface and the property of swelling upon moistening or a combination of said polymer and a medicament.

The adhesive layer comprises a polymer, which displays adhesiveness towards the wet mucous surface and has the property of swelling when moistened, to work as an adhesive component. It is the purpose to administer the preparation fixed to the mucous membrane of the body cavity such as the oral cavity, and the adhesiveness required for fixing the preparation differs depending upon the place of administration in the body cavity. Generally speaking, comparatively greater adhesiveness is required for the place like an oral cavity where larger quantity of motion is common. On the other hand not so much adhesiveness is required for the place where only a small quantity of motion is usual since the strength required for peeling off the preparation is small in such a place. In most cases, the adhesiveness of more than about 40 g/cm^2 adhesion area measured according to a measuring method described later is enough to fix the preparation to the wet mucous surface. When the administration of the preparation by continued fixation is intended for the place where the quantity of motion is especially large, it is desirable to increase the adhesiveness to about 150 g/cm^2 adhesion area. The property to swell upon moistening possessed by the polymer used for the adhesive layer, when medicated, is necessary for the gradual release of the medicament, which, however, is also a desirable property for the nonadhesive layer, when medicated.

As polymers to be used for an adhesive layer, for instance, such homopolymer of acrylic acid monomer as polyacrylic acid, polyacrylic acid sodium salt, polyacrylic acid potassium salt, polyacrylic acid ammonium salt or their pharmaceutically acceptable nontoxic salts; copolymers or acrylic acid obtained by copolymerization of acrylic acid as a main component and methacrylic acid, styrene, or vinyl ethers such as methyl vinyl ether as a comonomer, or their pharmaceutically acceptable nontoxic salts; such hydrophilic vinyl polymers as polyhydroxyethyl acrylate, polyhydroxyethyl methacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, such hydrophilic cellulose derivatives as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose

or their salts; such polysaccharides as hydroxypropyl starch, alginic acid, sodium alginate, and tragacanth gum or their derivatives; and further such derivatives having improved swellability as collagen, gelatine or radiobridged gelatine, chemically modified gelatine (for instance, gelatine denatured by phthalic anhydride or succinic acid) may be mentioned.

These polymers can be used as an adhesive layer either singly or in the form of a mixture of two or more. In addition to a medicament, the adhesive layer may further contain other ingredients, for instance, such as publicly known excipient, binder, disintegrator, coloring agent, corrigent, lubricant, provided that the layer maintains said adhesiveness to the wet mucous surface.

Another of the layers which constitute the slow-release preparation of the present invention is a nonadhesive layer which has no adhesiveness to the wet mucous surface (the adhesiveness is less than about 10 g/cm^2 adhesion area) and this layer is required to be water soluble and water disintegrable. This layer may contain a medicament.

Water soluble or water disintegrable ingredients which compose the abovementioned non-adhesive layer may be any of ingredients so far as they have such required properties and are pharmaceutically acceptable. Choice may be made of them depending upon the place of administration. As ingredients to compose such a nonadhesive layer, for instance, lactose, glucose, sucrose, starch, crystalline cellulose, dextrin, cyclodextrin, silicic acid anhydride, aluminum silicate, talc, calcium stearate, magnesium stearate, beeswax, polyethylene glycol, polyphosphate, may be mentioned. These materials can be used for preparing a nonadhesive layer singly or in the form of a mixture consisting of two or more. In addition to a medicament, other materials, for instance, such as publicly known excipient, binder, disintegrator, coloring agent, corrigent, lubricant, may be contained in the nonadhesive layer.

In case where the adhesive layer of the slow release preparation is medicated in the present invention, it adheres to the wet mucous surface of a body cavity upon administration and the non-adhesive layer dissolves or disintegrates in the presence of the body cavity secretion to expose the adhesive layer in the body cavity. Then the adhesive layer starts swelling due to the body cavity secretion and, as its swells, it slowly releases the medicament. In case where the nonadhesive layer contains a medicament, when the preparation is adhered to the wet mucous surface of the body cavity, the nonadhesive layer gradually dissolves or disintegrates due to the presence of the body cavity secretion, thus slowly releasing the medicament. In this case, the adhesive layer which contains no medicament remains struck to the body cavity after the disappearance of the nonadhesive layer or disappearance of the medicament. This adhesive layer, having the property to swell in the presence of water, may gradually disintegrate and disappear, when left struck to the oral cavity, etc. However, it can be removed with force from where it adheres, if necessary. When it swells up enough, it can be removed easily with the tip of a finger or anything like a spatula. It can be understood from the above fact that the swelling property of the adhesive layer is not only a property necessary when the adhesive layer contains a medicament but also a property desirable when the nonadhesive layer contains a medicament.

When a comparison is made between a case where the adhesive layer is contains a medicament and a case where the nonadhesive layer contains a medicament, the former has the property of releasing the medicament much slower than the latter as the above case shows. Therefore, it is advisable to make a choice depending upon the condition of a disease or the nature of a medicament making the best use of such difference of properties. Therefore, utilizing the different properties of the adhesive layer and the nonadhesive layer as mentioned above, both the two layers may contain a medicament and the two layers may contain a different medicament, thus both cases representing a desirable mode of medical care, as circumstances require.

As it is understood clearly from the above, in the slow-release preparation of the present invention, irrespective of which layer contains the medicament, the nonadhesive layer dissolves or disintegrates to disappear sooner or later after administration while the adhesive layer remains stuck to the wet mucous surface. A feeling of touchy irritancy caused by the adhering preparation differs in degree depending upon the sensibility of the patent and the place of administration. Since, however, if the thickness of the adhesive layer is 0.1 mm or more, the layer can maintain sufficient slow-releasing property, it is preferred that the thickness of the adhesive layer be in the range of approx. 0.1 to 1.0mm. It is also preferred that the thickness of the nonadhesive layer be at least approx. 0.1mm. This provides a preparation which, though giving rise to some touchy irritancy, is quite bearable.

As mentioned, the slow-release preparation of the present invention comprises two kinds of layer. When the preparation is made of two layers, the nonadhesive layer and the adhesive layer cooperate together to increase each other's efficiency. Thus it is possible to make the adhesive layer thinner when compared with conventional slow-release preparations which comprise an adhesive layer only. For instance, if an adhesive layer having a thickness of 0.1 to 1.0mm presents a problem in terms of mechanical strength, the preparation as a whole can be made to have a thickness, e.g. of 1.0mm or more, such as to overcome the problem of mechanical strength by properly selecting the thickness of the nonadhesive layer. A preparation having an adhesive layer of such small thickness has a characteristic of giving no feeling of touchy discomfort when used, for instance, stuck to the oral cavity.

The slow-release preparation of the present invention can be prepared, for instance, according to

the following method. Polymer powder which is used as an adhesive ingredient and a desired medicament together with other ingredients which are added as required are thoroughly mixed to obtain an intimate powdery mixture. This powder may also be made into slag and further into granule. A proper amount of thus obtained powder or granule is compressed with the punch, dice, and press to obtain an adhesive layer. Then a mixture of ingredients which is expected to form a nonadhesive layer is placed on the adhesive layer and again compressed to prepare a two-layer tablet with ease. At the time of pressing, if the latter pressing is effected with higher pressure than the former pressing, the separation of the nonadhesive layer from the adhesive layer hardly occurs, thus offering a higher yield rate in general. The pressure for each pressing may be decided by making a proper selection of balanced pressure. What is referred to as an intimate powdery mixture in the above means a state of mixture in which the respective ingredients contained in the preparation are mixed most uniformly and free from the slightest maldistribution.

As for the medicaments to be used intimately mixed in either the adhesive layer or the non-adhesive layer or both the layers of the preparation of the present invention, general or local therapeutic or preventive remedy and zoopharmaceutical, which are expected to obtain much more success in treatment by way of slow-releasing administration, may be mentioned. For concrete examples, they are analgesics and antiphlogistics such as acetaminophen, phenacetin, Aspirin®, aminopyrine, sulpyrine, phenylbutazone, mefenamic acid, flufenamic acid, Ibufenac, Ibuprofen, indomethacin, colchicine, and Probenecid; anti-inflammatory enzymes such as α-chymotrypsin anti-inflammatory steroids such as hydrocortisone, prednison, prednisolone, triamcinolone acetonide, dexamethasone, betamethasone; antihistamines such as diphenhydramine hydrochloride, chlorpheniramine maleate; antibiotics or antimicrophytes such as tetracycline hydrochloride, leucomycin, fradiomycin, penicillin and its derivatives, cephalosporin derivatives, erythromycin; chemotherapeutics such as sulfathiazole, nitrofurazone; local anesthetics such as benzocaine; cardiac tonics such as digitalis, digoxin; vasodilators such as nitroglycerin, papaverine hydrochloride; antitussives and expectorants such as codeine phosphate, isoproterenol hydrochloride; oral antiseptics such as chlorhexidine hydrochloride, hexylresorcin, dequalinium chloride, cetylpyridinium chloride, ethacridine; drugs for the digestive organs such as pepstatin, azalene, phenovalin, vitamin U; enzymes such as lysozyme chloride, dextranase; hypoglycemics such as insulin; and other drugs including hemostats, sex hormones, hypotensives, sedatives, antitumor agents, antacids. These drugs can be used either singly or as a mixture of two or more which are not therapeutically incompatible to each other. The amount of the drugs to be used in the preparation is the therapeutically effective amount required for the disease to which the preparation of the present invention is to be applied.

As for the lubricants which are used as occasion demands in the present invention, talc, stearic acid, stearate salts, and waxes may be mentioned. The binders include, for instance, starch, dextrin, tragacanth, gelatine, polyvinyl pyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, crystalline cellulose, hydroxypropylmethyl cellulose, ethyl cellulose, carboxymethyl cellulose. The disintegrators include starch, crystalline cellulose, calcium carboxymethyl cellulose. The excipients include starch, crystalline cellulose, dextrin, lactose, mannitol, sorbitol, calcium phosphoric acid anhydride. The corrigents include citric acid, fumaric acid, tartaric acid, menthol citrus perfumes.

The following examples illustrate the present invention in greater detail. Parts cited in the examples indicates parts by weight.

Example 1

50 parts of polyacrylic copolymer (copolymer mainly comprising acrylic acid and allysucrose, manufactured by B. F. Goodrich Chemical Co., Carbopol® 934), 50 parts of hydroxypropyl cellulose and 0.5 parts of magnesium stearate were measured as an adhesive layer matrix and 0.125 part of triamcinolone acetonide, anti-inflammatory drug, was measured as a medicament. The medicament was mixed with the matrix to obtain an intimate powder mixture for the adhesive layer use. On the other hand, 81 parts of lactose, 9 parts of hydroxypropyl cellulose, 10 parts of calcium carboxymethyl cellulose and 0.5 part of magnesium stearate were measured and mixed intimately to obtain a powder mixture for the non adhesive layer use.

With the use of the adhesive layer powder mixture as a lower layer material and the nonadhesive layer powder mixture as an upper layer material, two-layer tablets having a diameter of about 7 mm, with a lower layer weighing about 40 mg and having a thickness of about 1.1 mm and an upper layer weighing about 20 mg and having a thickness of about 0.4 mm, were obtained by use of an ordinary multilayer tablet machine. Following approximately the same procedures as above, two-layer tablets, which had the similar weight, thickness and content of the medicament, respectively comprising the combined components as shown in Table 1 mentioned below, were obtained.

TABLE 1
The number in parentheses indicates parts

No.	Adhesive layer	Nonadhesive layer
1	Polyacrylic acid (50) Methyl cellulose (50)	Lactose (95) Hydroxypropyl cellulose (5)
2	Hydroxypropylmethyl cellulose (100)	Crystalline cellulose (50) Starch (50)
3	Sodium polyacrylate (50) Hydroxyethyl cellulose (50)	Lactose (75) Starch (25)
4	Carboxymethyl cellulose (50) Hydroxypropyl cellulose (50)	Lactose (75), Starch (20), Hydroxypropyl cellulose (50)
5	Hydroxypropylmethyl cellulose (75) Hydroxypropyl starch (25)	Lactose (75) Starch (25)
6	Polyvinyl pyrrolidone (50) Carboxymethyl cellulose (50)	Hydroxypropyl starch (5) Crystalline cellulose (85) Aluminum silicate (10)
7	Gum arabic (30) Methyl cellulose (70)	Lactose (95) Hydroxypropyl cellulose (50)
8	Gelatine (40) Polyacrylic acid (50) Lactose (10)	Ditto
9	Sodium carboxymethyl cellulose (40) Hydroxypropyl cellulose (50) Glucose (10)	Lactose (75) Starch (25)
10	Sodium alginate (40) Methyl cellulose (60)	Ditto
11	Tragacanth gum (40) Hydroxypropylmethyl cellulose (40) Methyl cellulose (20)	Ditto

(13)

All of these two-layer tables had enough adhesiveness to the mucous membrane of the oral cavity and their adhesive layers has a nature to swell gradually after the nonadhesive layer had dissolved or disintegrated.

Example 2

This example is given to make it clear that the medicament is released slowly from the preparation of the present invention.

Predetermined amount of cellulose ether and polyacrylic acid shown in Table 2 below, a total of about 200 mg of a dye (amaranth), which corresponds to 4 mg per tablet, and 1 mg of magnesium stearate were mixed in a mixer. Discs having a weight of about 200 mg, a thickness of about 1.4 mm and a diameter of about 10.0 mm were press-formed from thus obtained intimate mixture. The discs were placed on agar gel at 37°C and the amount of the dye which was released into the agar with time was determined by measuring the absorbance at 520 to obtain the release rate (%) of the dye. The results are shown in Table 2.

For comparison, discs were prepared in the same way as above using sucrose and lactose and subjected to the same test as above. The results are shown in Table 2.

TABLE 2

Component	Hydroxypropyl cellulose/polyacrylic acid					Methyl cellulose/ polyacrylic acid	Hydroxyethyl cellulose/ polyacrylic acid	Hydroxypropyl-methyl cellulose/ polyacrylic acid	Sucrose	Lactose
Weight ratio	90/10	75/25	65/35	50/50	25/75	85/15	85/15	85/15		
Standing time (hour)										
6	22.5	24.1	22.0	21.6	23.1	23.9	28.9	22.8	100	75.0
30	72.0	70.1	70.2	69.0	62.6	72.8	78.2	74.2	–	100
48	74.9	74.1	74.5	72.0	68.0	75.1	84.3	78.3	–	–
96	82.2	81.9	80.3	81.1	86.5	84.4	–	86.2	–	–

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It is clearly seen from the results shown in the above that the releasing of the dye was constant and much slower in the preparation of the present invention than in the discs containing sucrose and lactose which are found with ordinary troches.

Example 3

Two-layer tablets having the same components and combination as Example 1 were obtained, wherein 5 parts of cetylpyridinium chloride oral antiseptic was added to the nonadhesive layer in the place of triamcinolone acetonide which was used in Example 1 and the tablets were made to have a lower layer, or adhesive layer, having a weight of about 20 mg and a thickness of about 0.5 mm and an upper layer, or nonadhesive layer, having a weight of about 40 mg and a thickness of about 0.7 mm.

The two layer tablets thus prepared also showed enough adhesiveness to the mucous membrane of the oral cavity and it was made clear that their nonadhesive layer had a nature to release the medicament as it dissolved in the oral cavity.

Example 4

20 parts of polyacrylic acid, 80 parts of hydroxypropyl cellulose and 0.5 part of magnesium stearate were measured as an adhesive layer matrix and 0.125 part or 0.33 part of dexamethasone antiinflammatory drug was measured as a medicament to be contained in the adhesive layer. The medicament and the matrix were mixed intimately to obtain a powder mixture for adhesive layer use. On the other hand, 90 parts of lactose, 10 parts of hydroxypropyl starch, and 0.5 part of magnesium stearate were mixed uniformly to obtain a powder mixture for nonadhesive layer use.

With the use of the adhesive layer powder mixture as a lower layer material and the nonadhesive layer powder mixture as an upper layer material, two-layer tablets were obtained with an ordinary multi-layer tablet machine. At this time, tablets under one group prepared with the adhesive layer powder mixture containing 0.125 part of dexamethasone were made to have an adhesive layer with varied weights of 40 mg, 80 mg, and 120 mg per tablet respectively and tablets under another group prepared with the adhesive layer powder mixture containing 0.33 part of dexamethasone were made to have an adhesive layer with varied weights of 15 mg and 10 mg per tablet respectively. The weight of a nonadhesive layer was 30 mg (about 0.5 mm thick) and the tablet diameter was 7 mm.

Tests were made with 30 panelists to see the adhesiveness of thus obtained two-layer tablets to the wet mucous surface (inside the lower lip of the mouth and the tip of the tongue) and the feeling of touchness caused around the place where the tablets were adhered. The results are shown in Table 3, in which "excellent" is given to cases where 30 to 25 panelists answered that the two-layer tablets showed satisfactory adhesiveness and caused no feeling of touchiness, "good" when 24 to 15 panelists answered to the same effect, and "fair" when 14 to 5 panelists were obtained.

TABLE 3

Weight of adhesive layer (mg)	Thickness of adhesive layer (mm)	Adhesiveness		Feeling of touchiness
		Inside lower lip of mouth	Tip of tongue	
120	2.9	Excellent	Fair	Fair
* 80	2.0	Excellent	Fair	Good
* 40	1.0	Excellent	Good	Excellent
* 15	0.4	Excellent	Excellent	Excellent
* 10	0.25	Excellent	Excellent	Excellent

* Tablets according to the invention.

It is seen from Table 3 that the slow-release preparation of this invention can be made to cause less feeling of touchiness by decreasing the thickness of the adhesive layer and also that the preparation can be made to have enough adhesiveness even to the place of vigorous movement such as the tip of the tongue.

Example 5

Tests were made with 30 panelists to see the easiness of administration by adhering the tablets

(18)

to the mucous membrane inside the lower lip of the mouth and the upper palate anterior and the occurrence of shifted adherence (displacement) to the facing mucous membrane (the gum) after the administration using the two-layer tablets prepared according to Example 1 and single-layer tablets composed solely of the lower layer of said two-layer tablets. Administration was effected by lightly placing the respective tablets on the mucous membrane inside the lower lip of the mouth with a pincette. To the upper palate anterior, each tablet was administered by carrying it on the tip of a clean finger and being pressed lightly. The results are shown in Table 4.

TABLE 4

	Frequency of failed administration / frequency of tests		Shifting to facing mucous membrane
	Inside lower lip of mouth	Upper palate anterior	Inside lower lip of mouth
Two-layer tablet (according to this invention)	0/90	1/90	0/90
Single-layer tablet (comparison)	3/90	48/90	48/90

It is seen from Table 4 that the slow-releasing preparation (two-layer tablet) of the present invention is highly superior to publicly known conventional single-layer tablet in handling to make administration much easier.

Example 6

The hardness was compared between the two-layer tablets comprising an adhesive layer whose weight was 15 mg and a nonadhesive layer whose weight was 30 mg according to Example 4 and the single-layer tablets prepared solely with the lower layer corresponding to the adhesive layer of said two-layer tablets. The results are shown in Table 5.

TABLE 5

	Average hardness ± standard deviation
Two-layer tablet (according to this invention)	3.5 ± 0.5
Single-layer tablet (comparison)	0.3 ± 0.1

It has been confirmed that the hardness of the tablets is improved by preparing them in the form of a two-layer tablet and no damage is caused to the tablets at the time of their manufacture, packaging, and handling. It has also been confirmed that the nonadhesive layer of the two-layer tablet dissolves or disintegrates gradually and thereafter both the two-layer tablet and the single-layer tablet shown in Table 5 have the similar degree of feeling of touchiness.

Example7

This example is given to show the adhesiveness of the adhesive layer of the slow-release preparation of this invention to the wet surface.

Discs, about 90 mg in weight, about 2 mm in thickness, and about 7 mm is diameter, were obtained by press-forming from respective mixtures mainly consisting of adhesive and swellable polymers as shown in Table 6. These discs were placed on a smooth surfaced wood block which was slightly moistened with water and one side of the disks was adhered to the wood block under a load of 100 g. A rubber sheet lined with a steel plate equipped with a hook was slightly moistened with water and placed on said fixed discs. A load of 100 g was exerted for 30 seconds to adhere the discs to the rubber sheet. Then the wood block was held upon a stand with the wood block above the rubber sheet. Water was filled between the wood block and the rubber sheet. A load was exerted on the hook attached to the rubber sheet to measure the load required for peeling off the rubber sheet from the discs to determine the adhesiveness of the discs under the wet condition. The results are shown in Table 6.

It is seen from Table 6 that the adhesive layer of the slow-releasing preparation of the present invention has enough adhesiveness to the wet surface.

TABLE 6

No.	Adhesive layer	Adhesiveness (g/cm²)
1	Polyacrylic acid (50) Methyl cellulose (50)	600
2	Hydroxypropylmethyl cellulose (100)	750
3	Sodium polyacrylate (50) Hydroxyethyl cellulose (50)	450
4	Carboxymethyl cellulose (50) Hydroxypropyl cellulose (50)	300
5	Hydroxypropylmethyl cellulose (75) Hydroxypropyl starch (25)	450
6	Polyvinyl pyrrolidone (50) Carboxymethyl cellulose (50)	750
7	Gum arabic (30) Methyl cellulose (70)	250
8	Gelatine (40) Polyacrylic acid (50) Lactose (10)	200
9	Sodium carboxymethyl cellulose (40) Hydroxypropyl cellulose (50) Glucose (10)	150
10	Sodium alginate (40) Methyl cellulose (60)	200
11	Tragacanth gum (40) Hydroxypropylmethyl cellulose (40) Methyl cellulose (20)	600
12	Hydroxypropyl cellulose (100)	300
13	Alginic acid (80) Lactose (20)	50
14	Methyl cellulose (100)	150
15	Carboxymethyl cellulose (100)	150

Industrial Application

The slow-release preparation offered by the present invention is a novel pharmaceutical tablet consisting of two layers, an adhesive layer and a nonadhesive layer, and displays an excellent efficacy not attained by any publicly known prior arts. It can be conveniently handled and securely adhered to a desired location of administration. As the thickness of its adhesive layer can be made very thin, it causes the smallest possible feeling of touchy irritancy while in use. The slow-release preparation of the present invention can be used for curing or preventing general or local diseases wherein the slow-releasing method is expected to have increased efficacy than the conventional methods, especially for the diseases in the body cavity such as oral, auricular, nasal, opthalmic, urinary, genital and anal diseases, or can also be applied to the wet mucous surface resulting from operation, cut, and wound.

Claims

1. A slow-release medical preparation comprising a polymer which is swellable upon moistening and capable of adhering to a wet mucous surface, and a medicament, characterised in that said preparation is in the form of a two layer tablet comprising an adhesive layer containing said polymer and a layer which does not adhere to a wet mucous surface and is water soluble or disintegrable, said non-adhesive layer having a thickness of at least 0.1 mm and said adhesive layer having a thickness not exceeding 2.0 mm.

2. A preparation according to claim 1, characterised in that the medicament is contained in the adhesive layer as an intimate mixture.

3. A preparation according to claim 1 or 2, characterised in that the adhesive layer has an adhesiveness of at least about 40 g/cm^2.

4. A preparation according to any of claims 1 to 3, characterised in that the polymer of the adhesive layer is at least one polymer selected from a group comprising acrylic acids and their pharmaceutically acceptable nontoxic salts, copolymers of acrylic acid and their pharmaceutically acceptable nontoxic salts, hydrophilic vinyl copolymers not copolymerized with acrylic acid as a main component, hydrophilic cellulose derivatives, polysaccharides and their derivatives and gelatine or collagen and their derivatives with improved swellability.

5. A preparation according to any of claims 1 to 3, characterised in that the polymer of the adhesive layer is a mixture of cellulose ether and polyacrylic acid (or its salt) or a copolymer of acrylic acid (or its salt).

6. A preparation according to any of claims 1 to 5, characterised in that the nonadhesive layer comprises lactose or glucose or their mixture.

7. A preparation according to claim 5, characterised in that the cellulose ether is methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or their mixture.

Revendications

1. Préparation médicale à libération lente comportant un polymère pouvant gonfler à l'humectage et capable d'adhérer à une surface muqueuse humide, et un médicament, caractérisée en ce qu'elle est sous la forme d'une tablette à deux couches comportant une couche adhésive contenant ledit polymère et une couche qui n'adhère pas à la surface muqueuse humide et es soluble ou désagrégeable dans l'eau, ladite couche non adhésive ayant une épaisseur d'au moins 0,1 mm et ladite couche adhésive ayant une épaisseur ne dépassant las 2,0 mm.

2. Préparation selon la revendication 1, caractérisée en ce que le médicament est contenu dans la couche adhésive sous forme de mélange intime.

3. Préparation selon l'une des revendications 1 ou 2, caractérisée en ce que la couche adhésive a une adhésivité d'au moins 40 g/cm^2.

4. Préparation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le polymère de la couche adhésive est au moins un polymère choisi parmi le groupe comprenant les acides acryliques et leurs sels non toxiques pharmaceutiquement acceptables, les copolymères d'acide acrylique et leurs sels non toxiques pharmaceutiquement acceptables, les copolymères de vinyle hydrophiles non copolymérisés avec l'acide acrylique en trant que constituant principal, les dérivés cellulosiques hydrophiles, les polysaccharides et leurs dérivés et la gélatine ou le collagène et leurs dérivés à pouvoir gonflant amélioré.

5. Préparation selon l'une quelconque des revendications 1 à 3 caractérisée en ce que le polymère de la couche adhésive est un mélange d'éther cellulosique et d'acide polyacrylique (ou de son sel) ou un copolymère d'acide acrylique (ou de son sel).

6. Préparation selon l'une quelconque des revendications 1 à 5, caractérisée en ce que la couche non adhésive est constituée par du lactose ou du glucose ou leur mélange.

7. Préparation selon la revendication 5, caractérisée en ce que l'éther cellulosique est la méthyl-cellulose, l'hydroxypropyl-cellulose, l'hydroxypropylméthyl-cellulose ou leur mélange.

* C L M S *

Industrial Application

The slow-release preparation offered by the present invention is a novel pharmaceutical tablet consisting of two layers, an adhesive layer and a nonadhesive layer, and displays an excellent efficacy not attained by any publicly known prior'arts. It can be conveniently handled and securely adhered to a desired location of administration. As the thickness of its adhesive layer can be made very thin, it causes the smallest possible feeling of touchy irritancy while in use. The slow-release preparation of the present invention can be used for curing or preventing general or local diseases wherein the slow-releasing method is expected to have increased efficacy than the conventional methods, especially for the diseases in the body cavity such as oral, auricular, nasal, opthalmic, urinary, genital and anal diseases, or can also be applied to the wet mucous surface resulting from operation, cut, and wound.

Claims

1. A slow-release medical preparation comprising a polymer which is swellable upon moistening and capable of adhering to a wet mucous surface, and a medicament, characterised in that said preparation is in the form of a two layer tablet comprising an adhesive layer containing said polymer and a layer which does not adhere to a wet mucous surface and is water soluble or disintegrable, said non-adhesive layer having a thickness of at least 0.1 mm and said adhesive layer having a thickness not exceeding 2.0 mm.

2. A preparation according to claim 1, characterised in that the medicament is contained in the adhesive layer as an intimate mixture.

3. A preparation according to claim 1 or 2, characterised in that the adhesive layer has an adhesiveness of at least about 40 g/cm^2.

4. A preparation according to any of claims 1 to 3, characterised in that the polymer of the adhesive layer is at least one polymer selected from a group comprising acrylic acids and their pharmaceutically acceptable nontoxic salts, copolymers of acrylic acid and their pharmaceutically acceptable nontoxic salts, hydrophilic vinyl copolymers not copolymerized with acrylic acid as a main component, hydrophilic cellulose derivatives, polysaccharides and their derivatives and gelatine or collagen and their derivatives with improved swellability.

5. A preparation according to any of claims 1 to 3, characterised in that the polymer of the adhesive layer is a mixture of cellulose ether and polyacrylic acid (or its salt) or a copolymer of acrylic acid (or its salt).

6. A preparation according to any of claims 1 to 5, characterised in that the nonadhesive layer comprises lactose or glucose or their mixture.

7. A preparation according to claim 5, characterised in that the cellulose ether is methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or their mixture.

Revendications

1. Préparation médicale à libération lente comportant un polymère pouvant gonfler à l'humectage et capable d'adhérer à une surface muqueuse humide, et un médicament, caractérisée en ce qu'elle est sous la forme d'une tablette à deux couches comportant une couche adhésive contenant ledit polymère et une couche qui n'adhère pas à la surface muqueuse humide et es soluble ou désagrégeable dans l'eau, ladite couche non adhésive ayant une épaisseur d'au moins 0,1 mm et ladite couche adhésive ayant une épaisseur ne dépassant las 2,0 mm.

2. Préparation selon la revendication 1, caractérisée en ce que le médicament est contenu dans la couche adhésive sous forme de mélange intime.

3. Préparation selon l'une des revendications 1 ou 2, caractérisée en ce que la couche adhésive a une adhésivité d'au moins 40 g/cm^2.

4. Préparation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le polymère de la couche adhésive est au moins un polymère choisi parmi le groupe comprenant les acides acryliques et leurs sels non toxiques pharmaceutiquement acceptables, les copolymères d'acide acrylique et leurs sels non toxiques pharmaceutiquement acceptables, les copolymères de vinyle hydrophiles non copolymérisés avec l'acide acrylique en trant que constituant principal, les dérivés cellulosiques hydrophiles, les polysaccharides et leurs dérivés et la gélatine ou le collagène et leurs dérivés à pouvoir gonflant amélioré.

5. Préparation selon l'une quelconque des revendications 1 à 3 caractérisée en ce que le polymère de la couche adhésive est un mélange d'éther cellulosique et d'acide polyacrylique (ou de son sel) ou un copolymère d'acide acrylique (ou de son sel).

6. Préparation selon l'une quelconque des revendications 1 à 5, caractérisée en ce que la couche non adhésive est constituée par du lactose ou du glucose ou leur mélange.

7. Préparation selon la revendication 5, caractérisée en ce que l'éther cellulosique est la méthyl-cellulose, l'hydroxypropyl-cellulose, l'hydroxypropylméthyl-cellulose ou leur mélange.

* C L M S *

Patentansprüche

1. Ein medizinisches Präparat mit langsamer Freigabe enthaltend ein Polymeres, das nach Befeuchtung quellfähig und dazu befähigt ist, auf einer feuchten, schleimhaltigen Oberfläche zu haften, sowie ein Medikament, dadurch gekennzeichnet, daß dieses Präparat in Form einer zweischichtigen Tablette vorliegt, welche eine Haftschicht aufweist, die dieses Polymere enthält und eine Schicht, die nicht an der feuchten, schleimhaltigen Oberfläche haftet und in Wasser löslich oder zersetzlich ist, wobei diese nicht haftende Schicht eine Dicke von wenigstens 0,1 mm und die Haftschicht eine Dicke von nicht über 2,0 mm aufweist.

2. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß das Medikament in der Haftschichtlage als eine innige Mischung vorliegt.

3. Präparat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Haftschicht eine Haftfestigkeit von wenigstens etwa 40 g pro cm^2 hat.

4. Präparat nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß das Polymere der Haftschicht wenigstens ein Polymeres aus der Gruppe Acrylsäure und deren pharmazeutisch verträgliche, nicht toxische Salze, Copolymer von Acrylsäure und deren pharmazeutisch verträgliche, nicht toxische Salze, hydrophile Vinylcopolymere die nicht mit Acrylsäure als Hauptkomponente copolymerisiert sind, hydrophile, Zellulosederivate, Polysaccharide und ihre Derivate und Gelatine oder Kollagen und deren Derivate mit verbesserter Quellbarkeit ist.

5. Präparat nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß das Polymere der Haftschicht ein Gemisch von Zelluloseäther und Polyacrylsäure (oder einem Salz davon) oder einem Copolymeren von Acrylsäure (oder einem Salz davon) ist.

6. Präparat nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das nicht haftende Schicht Lactose oder Glucose oder ihr Gemisch enthält.

7. Präparat nach Anspruch 5, dadurch gekennzeichnet, daß der Zelluloseäther Methylzellulose, Hydroxypropylzellulose, Hydroxypropylmethylzellulose oder ihr Gemisch ist.