Description

The present invention relates to improved pharmaceutical compositions. In particular, the present invention relates to pharmaceutical compositions in tablet form, formulated to provide a controlled and sustained release of a pharmaceutically active ingredient over an extended period of time. The invention also relates to pharmaceutical compositions in the form of buccal tablets or sub-lingual lozenges and to a device for retaining a sustained release or buccal tablet in place in a patient's mouth.

It has been recognised, for more than 10 years, that patients in intensive care units, particularly those who require artifical ventilation, are extremely susceptible to bacterial infection. In many cases, despite good nursing care, patients die from bacterial infection rather than from an original traumatic injury. Gram-negative bacteria are responsible for most of these potentially pathogenic infections. Once a patient has been admitted to hospital, his endogenous aerobic flora are replaced by nosocomial (hospital originating) gram-negative bacteria, such as Pseudomonas, Acinetobacter and, Klebsiella, which may rapidly colonise the oropharynx, stomach and intenstines. Once the digestive tract has been so colonised, subsequent colonisation and infection of major organ systems may occur.

More than 80% of critically ill patients are colonised by nosocomial gram-negative bacteria within 10 days of admission to hospital (Northey et al. (1974), Surgery, Gynaecology, and Obstetrics 139 , 321-5; Sheild, Hammill and Neale (1979), Intensive Care Medicine 5 , 171-81 and; Thorpe, Richards and Telfer (1979) Anaesthesia 34 , 643-50) and these organisms are responsible for the majority of late infections (Rose & Babcok (1975) American Journal of Epidemiology 101 , 495-501 and; Weinstein and Kabins (1981) American Journal of Medicine 70 , 449-54). Considerable success has been achieved in reducing the incidence of such infection by the prophylactic administration of non-absorbable antibiotics to selectively decontaminate the digestive tract. The antibiotics are selected to eliminate the potentially pathogenic aerobic gram-negative micro-organisms from the digestive tract, leaving the mainly endogenous anaerobic flora substantially unaffected. This work was carried out by C. P. Stoutenbeek and H. K. F. Van Saene and co-workers since 1982 and has been reported in:- Journal of Antimicrobial Chemotherapy (1984) 14 , supplement B, 203-211; Journal of Antimicrobial Chemotherapy (1987) 19 , 513-520 and; Intensive Care Medicine (1986) 12 , 419-423. The non-absorbable antibiotics were administered through a nasogastric tube, in the form of an extemporaneously prepared suspension of Polymyxin E (15%), Tobramycin (12%) and, amphotericin (73%), and applied to the buccal mucosa in the form of a commercially available paste (ORABASE^{R} Registered Trade Mark, available from Squibb) containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B. Both preparations were administered to patients every four hours, with gastric suction being applied for the first hour after administration. To prevent infections of the respiratory tract, systemic antibiotic prophylaxis may also be given to multiple trauma patients.

Although prophylactic and selective decontamination of the digestive tract has proven to be very successful, it is difficult and time consuming in application. These difficulties have prevented the method from becoming more widely used.

Buccal tablets, sub-lingual lozenges and conventional pharmaceutical tablets are all formulated to include pharmaceutically active components. The distinction between a buccal tablet and a conventional pharmaceutical tablet arises from the manner in which a buccal tablet is used. In use, a buccal tablet is placed between the lip and the gum and allowed to dissolve, or otherwise release its pharmaceutically active component. With all hitherto known buccal tablets, this active component is then absorbed through the buccal tissues of the mouth. A sub-lingual lozenge is similar, however it is designed to be placed under the tongue to dissolve, or otherwise release its pharmaceutically active component, which, conventionally, is absorbed through the sub-lingual area of the mouth.

Erodible pharmaceutical tablets formulated to provide a sustained and controlled release of a medicament from within the stomach are known and, for example, may be formed by compressing a hydroxypropylmethyl cellulose (available from the Dow Chemical Corporation under the Trade Mark METHOCEL^{R}) in admixture with a pharmaceutically active ingredient and other pharmaceutical excipients. See "Formulating Sustained Released Pharmaceutical Products with Methocel" The Dow Chemical Co., 1982. However, in these tablets the active ingredient is of a type which acts systemically by oral administration into the gastro-intenstinal tract, followed by subsequent absorption into the blood.

Controlled release buccal tablets and sub-lingual lozenges may also be formed from hydroxypropylmethyl cellulose and a suitable medicament. However as suggested above, such tablets and lozenges, conventionally, contain medicaments which are absorbed through the buccal or sub-lingual tissues of the mouth.

Compositions for sustained and controlled release tablets, including buccal tablets and sub-lingual lonzenges, are described in British Patent No. 1583801, Published British Patent Application Nos. 2061950,

2111386 and 2117239, U.S. Patent No. 4226849, Australian Patent No. 452221 and European Patent Application No. 0157695, all in the name of Forest Laboratories Incorporated of 150 East 58th Street, New York, N.Y. United States of America.

U.S. Patent No. 4226849 discloses pharmaceutical tablets and lozenges which have a prolonged and regular release pattern of a therapeutically active medicament incorporated therein. The tablets comprise a carrier base material of hydroxypropylmethyl cellulose, or a mixture thereof with ethyl cellulose or sodium carboxymethyl cellulose, which has been modified by hydrolysis and oxidation. The tablets and lozenges include buccal tablets and sublingual lozenges, however all of the medicaments disclosed act systemically, gaining access to the blood stream via the gastro-intestinal tract or the buccal tissues of the mouth.

Australian Patent No. 452221 discloses buccal tablets and sublingual lozenges, formed by compressing an active agent with moist ethyl and methyl cellulose, optionally together with an adjuvent such as saccharin. All of the active agents discussed in this document are absorbed, to act systemically, either through the tissue of the mouth or in the gastro-intestinal tract.

According to a first aspect of the present invention there is provided a pharmaceutical tablet or lozenge, comprising at least two non-absorbable antibiotic agents in combination with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable, in a substantial quantity, through a normal and untraumatised human or animal digestive tract and the tablet, or lozenge is arranged for providing controlled and sustained release of a prophylactic dose of said antibiotic agents, from a buccal or sub-lingual location and into the mouth and gastro-intestinal tract, for selectively decontaminating a human or animal digestive tract. The term non-absorbable is used herein to describe an antibiotic agent which is not absorbed into the blood, or bodily fluids, in any substantial quantity from a normal and untraumatised human digestive tract.

Preferably, the tablet matrix is formulated so as to be erodible on exposure to the fluid present within the mouth.

An advantage of a pharmaceutical tablet or lozenge in accordance with the present invention is that when placed in a buccal or sub-lingual location in a patient's mouth, the tablet provides a controlled and sustained dose of the antibiotic agents to the entire digestive tract, from the mouth to the large intestine. Since the antibiotic agents are non-absorbable, any systemic side effects that the agents may have are avoided and the likelihood of creating resistance to the agents is reduced. When the tablet matrix is chosen to be erodible, no residue or empty shell remains in a patient's mouth after the active agents have been discharged.

Thus the complexities of the previously practiced method of prophylactic and selective decontamination of the digestive tract, including the use of a nasogastric tube, extemporaneously prepared antibiotic mixtures and gastric suction, may be replaced by the simple and regular administration of a tablet, in accordance with the present invention, to the buccal or sub-lingual area of the patient's mouth.

In a preferred embodiment of the first aspect of the present invention, the table matrix includes a water soluble cellulose derivative, which may be a hydroxypropylmethyl cellulose or a mixture of hydroxypropylmethyl celluloses. In a preferred embodiment, the tablet matrix includes an ethyl cellulose and a salt of carboxymethyl cellulose, preferably the sodium salt.

Hydroxypropylmethyl celluloses are commercially available in several different grades. These include METHOCEL^{R} E,F,J, and K manufactured by the Dow Chemical Co in the United States, HPM^{R}, manufactured by British Celanese, Limited and METALOSE^{R} SH manufactured by Shin-Etsu KK in Japan. The various grades available under each of the aforementioned Trade Marks represent differences in methoxy and hydroxypropyl content as well as molecular weight. The designations of the various hydroxypropylmethyl celluloses are based on the viscosities of 1% aqueous solutions at 20 °C. The viscosities range form 15 mPas (cps) to 30,000 mPas (cps).

The rate at which the antibiotic agents are released from a tablet in accordance with the present invention held in a buccal, or sub-lingual location and the total period over which such a tablet remains active can be determined by altering the total and relative amounts of different grades of hydroxypropylmethyl cellulose in the tablet matrix. Thus, for example, a tablet can be formulated to release its entire dose in a matter of minutes, or to release its dose at an even rate over a period of several hours. Up to eight hours being possible.

Preferably, the antibiotic agents are selected to have a narrow spectrum of activity and to be active only against selected potentially pathogenic organisms.

In a second aspect, the invention provides a pharmaceutical tablet or lozenge, comprising at least two non-absorbable antibiotic agents, in combination with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable in a substantial quantity, through a normal and untraumatised human or animal digestive tract, and are selected from the gourp comprising

non-absorbable aminoglycosides, non-absorbable polymyxins, non-absorbable antifungal polyenes, and non-abosrbable substituted imidazole derivatives, and the tablet or lozenge is arranged for providing controlled release of said antibiotic agents into the mouth and gastro-intestinal tract, from a buccal or sub-lingual location.

In an embodiment of the first aspect of the invention, the non-absorbable antibiotic agent is a non-absorbable aminoglycoside, a non-absorbable polymyxin, a non-absorbable polyene, a non-absorbable substituted imidazole derivative, or a mixture of such agents. Preferably, a tablet in accordance with the present invention includes three such antibiotic agents. More preferably the antibiotic agents belong to different ones of the above classes.

The non-absorbable aminoglycoside may be a non-absorbable form of tobramycin, framycetin, neomycin, netilmicin, gentamicin, or streptomycin. The non- absorbable polymyxin may be colistin sulphate, or sulphur methylated colistin. The antifungal polyene may be nystatin or amphotericin B. The non-absorbable substituted imidazole derivative may be a non-absorbable form of ketoconazole, miconazole or, clotrimazole.

In a further embodiment, the tablet matrix comprises a salivation promotion agent, an inert tablet filler and an inert tablet lubricant. Varying the amount and nature of the fillers and lubricants in a tablet or lozenge, provides a further method of adjusting the rate of release of the antibiotic agents and the period over which the agents are released.

In an alternative embodiment, the non-absorbable antibiotic agents are selected for treating the digestive tract of immuno-compromised patients, such as those with leukaemia or HIV infection or others who have undergone transplant surgery. In a further alternative embodiment one of the non-absorbable antibiotic agents is benzylmetronidazole.

Two buccally administered pharmaceutical preparations are currently available in the United Kingdom. The first is sold under the Trade Mark SUSCARD BUCCAL^{R} by Pharmax Ltd. of Bourne Road, Bexley, Kent. and includes lactose in its formulation, together with glyceryl trinitrate as the active ingredient. The second preparation is sold under the Trade Mark BUCCASTEM^{R} by Reckett and Colman Ltd. of Dansom Lane, Hull, North Humberside. and contains sucrose in its formulation, together with prochloroperazine maleate as the active ingredient.

Since both lactose and sucrose are carigenic it is most likely, in view of their site of administration, that repeated use of buccal tablets or sub-lingual lozenges containing these sugars will cause dental caries. The risk of causing dental caries would be particularly acute with sustained and controlled release buccal tablets or sub-lingual lozenges including sucrose or lactose, because these must reside in a patient's mouth for long periods of time.

Thus, it is preferred that tablets and lozenges in accordance with either aspect of the invention should include a non-carigenic sugar. Preferred non-carigenic sugars include sorbitol, mannitol and, xylitol. Advantageously, prolonged use of a tablet in accordance with the present invention will not promote the formation of dental caries in a patient's teeth.

Surprisingly, the administration of buccal or sub-lingual tablets that include non-carigenic sugars does not cause the gastro-intestinal disturbances, that normally are associated with the use of such sugars. This is believed to be because such disturbances result from an immediate administration of the sugar in gram quantities; whereas a typical buccal tablet includes about 100 mg of sugar and the sugar from the tablet is released more slowly than with a conventional tablet.

Preferably, a buccal tablet or sub-lingual lozenge in accordance with the present invention comprises less than 200 mg of non-carigenic sugar and, more preferably, less than 100 mg of non-carigenic sugar.

Further embodiments of the invention include tablet lubricants, such as magnesium stearate, stearic acid, sodium fumarate and colloidial silicon dioxide plus other components, such as flavourings and artifical sweetners, such as aspartame.

For contracting state ES, the first and second aspects of the invention are set out in claims 1 and 7, in the attached set of claims identified as being for effect in that state. Preferred embodiments of these aspects of the invention are set out in claims 2-6, 8-16 and 27 of this latter set of claims.

A difficulty, which has been encountered during the past and in connection with buccal tablets, is that such a tablet may become dislodged from between a patient's lip and gum, before all of its active ingredient has been released. The risk of this eventuality is more acute with patients in intensive care units, who are often partially or totally unconscious.

Accordingly and in a third aspect, the present invention provides a tablet retaining device, for use with a pharmaceutical tablet or lozenge in accordance with either of the first two aspects of the invention, comprising means engageable to a patient and means for accommodating and retaining the pharmaceutical tablet or lozenge, wherein the device is arranged to hold the tablet or lozenge in a location with a patient's

mouth, from which an active ingredient, from the tablet or lozenge, is releasable by the action of the patient's saliva or other fluid within the mouth.

The device, therefore, can be used in a method of providing a patient with a sustained prophylactic dose of antibiotics, to selectively decontaminate the patient's digestive tract.

In a preferred embodiment, a device according to the third aspect of the invention is arranged to hold a tablet in a buccal location between a patient's gum and lip.

An advantage of devices in accordance with the third aspect of the present invention is that, when one is used to hold a tablet in the mouth of a partially or totally unconscious patient, there is no risk of that patient inadvertantly swallowing or choking upon the tablet.

In a most preferred embodiment, the means engagable to a patient are arranged to be engaged upon one, or a plurality of teeth. Also, the device may be configured to hold a plurality of appropriately located tablets.

For contracting state ES, the third aspect of the invention is set out in claim 17, in the attached set of claims identified as being for effect in that state. Preferred embodiments of this aspect of the invention are set out in claims 18-26 of this latter set of claims.

According to a further aspect of the present invention there is provided the use of a composition comprising at least two non-absorbable antibiotic agents which are not absorbable, in a substantial quantity, through a normal and untraumatized human digestive tract, in combination with a tablet matrix arranged to provide controlled and sustained release of a prophylactic dose of said agents, into the mouth and gastro-intestinal tract, from a buccal or sub-lingual location, in the manufacture of a medicament for the prophylactic and selective decontamination of the human of animal digestive tract.

Preferred, formulations for buccal tablets in accordance with the present invention are given below. The quantities of each constituent are given in terms of milligrams thereof per tablet. Typically, each tablet will weigh in the order of 50-200mg.

Formulation 1	
Ingredient	amount/tablet
Colistin sulphate	2 - 15 mg
Tobramycin sulphate	2 - 15 mg
Amphotericin B	5 - 40 mg
Hydroxypropylmethyl cellulose	5 - 150 mg
Citric acid	2 - 20 mg
Mannitol	0 - 100 mg
Magnesium stearate	2 - 10 mg
Colloidal silicon dioxide	2 - 10mg

Formulation 2	
Ingredient	amount/tablet
Colistin sulphate	2 - 15 mg
Framycetin	5 - 20 mg
Nystatin	5 - 40 mg
Hydroxypropylmethyl cellulose	50 - 150 mg
Citric acid	2 - 20 mg
Mannitol	0 - 100 mg
Magnesium stearate	2 - 10 mg
Colloidal silicon dioxide	2 - 10 mg

Formulation 3	
Ingredient	amount/tablet
Colistin sulphate	2 - 15 mg
Netilmicin	2 - 15 mg
Clotrimazole	5 - 40 mg
Hydroxypropyl cellulose	50 - 150 mg
Citric acid	2 - 20 mg
Xylitol	0 - 100 mg
Stearic acid	2 - 10 mg
Colloidal silicon dioxide	2 - 10 mg

EXAMPLE 1

One thousand 100 mg buccal tablets in accordance with formulation 1 were prepared from the following ingredients:-

Ingredient	amount/g
Colistin sulphate	5
Tobramycin sulphate	4
Amphotericin B	25
Methocel K	40
Citric acid	5
Mannitol	10
Magnesium stearate	5
Colloidal silicon dioxide	6

The colistin sulphate, tobramycin sulphate, amphotericin B and the methocel K were mixed together and the remaining ingredients were then added to the blend which, thereafter, was mixed for a total of 30 minutes. The resulting mixture was then compressed in a conventional tableting machine into 1,000 cylindrical tablets, each weighing 100 mg. The pressure applied by the punch of the tableting machine was 770bar (5 tons per square inch).

EXAMPLE 2

One thousand 150 mg tablets in accordance with formulation 2 were prepared from the following ingredients:-

Ingredients	amount/g
Colistin sulphate	10
Framycetin	12
Nystatin	30
Methocel K	50
Citric acid	8
Mannitol	24
Magnesium stearate	8
Colloidal silicon dioxide	8

The colistin sulphate, framycetin, nystatin and methocel K were first mixed together and the remaining ingredients were then added thereto. The resulting mixture was blended for a total of 30 minutes and then compressed into 1,000 cylindrical tablets in a conventional tableting machine. The tableting machine puch compressed each tablet at a pressure of 308bar (2 tons per square inch).

EXAMPLE 3

One thousand 200 mg tablets in accordance with formulation 3 were prepared from the following ingredients:-

Ingredients	amount/g
Colistin sulphate	5
Netilmicin	10
Clotrimzole	20
Methocel K	140
Citric acid	8
Xylitol	12
Stearic acid	3
Colloidal silicon dioxide	2

The above ingredients were blended together for a total of 45 minutes and, thereafter, compressed into a 1,000 cylindrical tablets of 200 mg in a conventional tableting machine. The tableting machine punch subjected each tablet to a pressure of 1078bar (7 tons per square inch).

A tablet retaining device, in accordance with the third aspect of this invention will now be described, by way of example only, with reference to the following drawings:-

Figure 1 is a front view of a first such device;

Figure 2 is a rear view of the device shown in Figure 1;

Figure 3 is a section A-A'in Figure 1;

Figure 4 is a front view of a second device in accordance with the present invention;

Figure 5 shows a patient's mouth with a device, as shown in Figure 1, engaged therein; and

Figure 6 is a view of the same patient's mouth as shown in Figure 5, but with the top lip raised so that the tablet retaining device is fully visible.

The tablet retaining device illustrated in Figures 1 to 3 is formed from a resilient plastics resin material, such as polystyrene, polycarbonate, or an acrylic plastic resin such as polymethylmethacrylate. The tablet retaining device is integrally formed, preferably by moulding, and includes an elongate leg member 1 which forms a part of and links first and second channel section clip portions 2 and 3.

The elongate leg member 1 has a rectangular cross section, is of substantially uniform thickness along its length and, defines first and second parallel outwardly facing surfaces 5 and 6. A first end portion 7 of the elongate leg member 1, has a greater width than the remainder thereof. The first end portion 7 of the elongate member 1 provides a first rectangular jaw plate 4 for the first clip portion 2. The first clip portion 2 further comprises a second rectangular jaw plate 8, spaced apart from the first jaw plate 4 and parallel thereto. A bridging portion 9, extending from a first margin 10 of the second rectangular jaw plate 8 to meet the first surface 5 of the elongate leg member 1, where the first end portion 7 broadens out from the remainder thereof, completes the first clip portion 2. Both the jaw plates 4 and 8 are substantially square in outline, with facing surfaces of substantially the same area.

The second clip portion 3 comprises a first jaw plate 11, defined by a second end portion 21 of elongate leg member 1, a second rectangular jaw plate 12, spaced apart from the first jaw plate 11 and substantially parallel thereto, and a bridging portion 13. The bridging portion 13 is in the form of an extension to the elongate leg member 1, which curves through approximately 180°, to extend into the second rectangular jaw plate 12 of the second clip portion 3.

The second jaw plate 12 of the second clip portion 3 faces the second surface 6 of the elongate leg member 1; whereas the second jaw plate 8 of the first clip portion 12 faces the first surface 5 of the elongate leg member 1.

The second jaw plate 12 of the second clip portion 3 is of a greater width than the first jaw plate 11 of the second clip portion 3, the remainder of the elongate leg member 1 and the jaw plates 4 and 8 of the first clip portion 2.

The first and second jaw plates 4 and 8 of the first clip portion 2, both define an array of ciruclar cross-section holes 14. The holes 14 defined by the first jaw plate 4 are in register with corresponding holes 14 defined by the second jaw plate 8.

A first ridge 15 is defined along the edge portion of the second jaw plate 12 of the second clip portion 3, remote from the bridging portion 13, and faces the second surface 6 of the elongate leg member 1. A second similar ridge 16 extends across the second surface 6 of the elongate member 1, facing the first

ridge 15.

The same reference numerals as used above to identify parts of the device shown in Figures 1 to 3, are used to identify corresponding parts of the device shown in Figure 4. The difference between the two devices is that the jaw plates 4 and 8 of the first clip portion 2, of the device shown in Figure 4, are of considerably greater width than the remainder of said device and the entire device shown in Figures 1 to 3.

The jaw plates 4 and 8 of the first clip portion 2 in the device shown in Figures 1 to 3 are dimensioned and spaced apart, so as to accommodate a tablet 20, in the manner shown in Figures 1 to 3. The spacing between the jaw plates 4 and 8 is chosen so that the tablet 20 is resiliently gripped therebetween. Likewise, the jaw plates 4 and 8 of the first clip portion 2 in the device shown in Figure 4, are dimensioned to accommodate two tablets 20 in a side-by-side relationship, as shown in Figure 4.

To use the device illustrated in Figures 1 to 3, a tablet 20 is pushed between the jaw plates 4 and 8 of the first clip portion 2, until it is located as shown in Figures 1 to 3 and tightly gripped between the jaw plates 4 and 8. The loaded device is then inserted into a patient's mouth 23 and the second clip portion 3 is engaged on a tooth 24 (see Figures 5 and 6). The tooth is resiliently gripped between the first and second jaw plates 11 and 12 of the second clip portion 3, in such a way that the device cannot be accidentally dislodged. The device is installed in the orientation shown in Figure 6, that is with the first clip portion 2, holding the tablet 20 immediately adjacent to the buccal mucosa 25 and between the latter and the patient's top lip 26 (when the top lip is in the normal relaxed position).

Fluids such as saliva, within the mouth can gain access to the tablet 20 both through the holes 14 and through the gap between the jaw plates 4 and 8 of the first clip portion 2. The holes 14, in the first jaw plate 4, allow matter disolved from the tablet to pass directly into contact with the buccal mucosa 25.

The illustrated devices can be used in conjunction with tablets in accordance with the first or second aspects of the present invention, especially those formulated in accordance with the above formulations and examples. In this regard, a tablet produced in accordance with one of examples 1 to 3 should be placed in a device as shown in Figures 1 to 3 and the device then should be installed in a patient's mouth as shown in Figures 5 and 6. The device and tablet should be left in place until the tablet has completely dissolved and, if necessary, removed, reloaded with a fresh tablet and reinstalled in the patient's mouth. The time taken for a given tablet to dissolve and release its phamaceutically active component(s) is dependent upon the type and relative quantity of the Methocel (or the like) which is used, and can be determined by carrying out appropriate trials.

Most preferably, a device as shown in Figures 1 to 3 is loaded with a tablet made in accordance with one of examples 1 to 3. Such a loaded device can then be installed in a patient's mouth as aforesaid, to selectively decontaminate his mouth and digestive tract.

As suggested above, the rate at which any given tablet dissolves and releases antibiotic can be determined experimentally. Tablets used for selective decontamination treatment are selected to provide the dose judged appropriate for a particualr patient, over an appropriate period. Both the daily dose and the period over which it should be provided depend upon a particular patients dispositon. Thus, for example, a suitable daily dose may be provided by a tablet which dissolves completely within one hour, or at the other extreme may be provided by three, successively administered, tablets that each take eight hours to dissolve.

If the patient's salivary flow is reduced, and during the routine maintenance of oral hygiene, the tablet and device may be sprayed with oral cleansing fluid or an artificial salivary agent to facilitate the dissolution of the tablet.

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. A pharmaceutical tablet or lozenge, comprising at least two non-absorbable antibiotic agents, in combination with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable, in a substantial quantity, through a normal and untraumatised human or animal digestive tract and the tablet or lozenge is arranged for providing controlled and sustained release of a prophylactic dose of said antibiotic agents, from a buccal or sub-lingual location and into the mouth and gastro-intestinal tract, for selectively decontaminating a human or animal digestive tract.

2. A pharmaceutical tablet or lozenge as claimed in claim 1, wherein the non-absorbable antibiotic agents are selected from the group consisting of non-absorbable aminoglycosides, non-absorbable polymyxins, non-absorbable antifungal polyenes and non-absorbable substituted imidazole derivatives.

ridge 15.

The same reference numerals as used above to identify parts of the device shown in Figures 1 to 3, are used to identify corresponding parts of the device shown in Figure 4. The difference between the two devices is that the jaw plates 4 and 8 of the first clip portion 2, of the device shown in Figure 4, are of considerably greater width than the remainder of said device and the entire device shown in Figures 1 to 3.

The jaw plates 4 and 8 of the first clip portion 2 in the device shown in Figures 1 to 3 are dimensioned and spaced apart, so as to accommodate a tablet 20, in the manner shown in Figures 1 to 3. The spacing between the jaw plates 4 and 8 is chosen so that the tablet 20 is resiliently gripped therebetween. Likewise, the jaw plates 4 and 8 of the first clip portion 2 in the device shown in Figure 4, are dimensioned to accommodate two tablets 20 in a side-by-side relationship, as shown in Figure 4.

To use the device illustrated in Figures 1 to 3, a tablet 20 is pushed between the jaw plates 4 and 8 of the first clip portion 2, until it is located as shown in Figures 1 to 3 and tightly gripped between the jaw plates 4 and 8. The loaded device is then inserted into a patient's mouth 23 and the second clip portion 3 is engaged on a tooth 24 (see Figures 5 and 6). The tooth is resiliently gripped between the first and second jaw plates 11 and 12 of the second clip portion 3, in such a way that the device cannot be accidentally dislodged. The device is installed in the orientation shown in Figure 6, that is with the first clip portion 2, holding the tablet 20 immediately adjacent to the buccal mucosa 25 and between the latter and the patient's top lip 26 (when the top lip is in the normal relaxed position).

Fluids such as saliva, within the mouth can gain access to the tablet 20 both through the holes 14 and through the gap between the jaw plates 4 and 8 of the first clip portion 2. The holes 14, in the first jaw plate 4, allow matter disolved from the tablet to pass directly into contact with the buccal mucosa 25.

The illustrated devices can be used in conjunction with tablets in accordance with the first or second aspects of the present invention, especially those formulated in accordance with the above formulations and examples. In this regard, a tablet produced in accordance with one of examples 1 to 3 should be placed in a device as shown in Figures 1 to 3 and the device then should be installed in a patient's mouth as shown in Figures 5 and 6. The device and tablet should be left in place until the tablet has completely dissolved and, if necessary, removed, reloaded with a fresh tablet and reinstalled in the patient's mouth. The time taken for a given tablet to dissolve and release its phamaceutically active component(s) is dependent upon the type and relative quantity of the Methocel (or the like) which is used, and can be determined by carrying out appropriate trials.

Most preferably, a device as shown in Figures 1 to 3 is loaded with a tablet made in accordance with one of examples 1 to 3. Such a loaded device can then be installed in a patient's mouth as aforesaid, to selectively decontaminate his mouth and digestive tract.

As suggested above, the rate at which any given tablet dissolves and releases antibiotic can be determined experimentally. Tablets used for selective decontamination treatment are selected to provide the dose judged appropriate for a particualr patient, over an appropriate period. Both the daily dose and the period over which it should be provided depend upon a particular patients dispositon. Thus, for example, a suitable daily dose may be provided by a tablet which dissolves completely within one hour, or at the other extreme may be provided by three, successively administered, tablets that each take eight hours to dissolve.

If the patient's salivary flow is reduced, and during the routine maintenance of oral hygiene, the tablet and device may be sprayed with oral cleansing fluid or an artificial salivary agent to facilitate the dissolution of the tablet.

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. A pharmaceutical tablet or lozenge, comprising at least two non-absorbable antibiotic agents, in combination with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable, in a substantial quantity, through a normal and untraumatised human or animal digestive tract and the tablet or lozenge is arranged for providing controlled and sustained release of a prophylactic dose of said antibiotic agents, from a buccal or sub-lingual location and into the mouth and gastro-intestinal tract, for selectively decontaminating a human or animal digestive tract.

2. A pharmaceutical tablet or lozenge as claimed in claim 1, wherein the non-absorbable antibiotic agents are selected from the group consisting of non-absorbable aminoglycosides, non-absorbable polymyxins, non-absorbable antifungal polyenes and non-absorbable substituted imidazole derivatives.

3. A pharmaceutical tablet or lozenge as claimed in claim 1 or claim 2, wherein the tablet matrix is formulated so as to be erodible on exposure to fluid present within the mouth.

4. A pharmaceutical tablet or lozenge as claimed in claim 3, wherein the tablet matrix includes a water soluable cellulose derivative, preferably hydroxypropylmethyl cellulose or a mixture of hydroxypropylmethyl celluloses.

5. A pharmaceutical tablet or lozenge as claimed in claim 3, wherein the tablet matrix includes an ethyl cellulose and a salt of carboxymethyl cellulose, preferably the sodium salt.

6. A pharmaceutical tablet or lozenge as claimed in any of the preceding claims, wherein the antibiotic agents are selected to have a narrow spectrum of activity and to be substantially active only against selected potentially pathogenic organisms.

7. A pharmaceutical tablet or lozenge, comprising at least two non-absorbable antibiotic agents, in combination with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable, in a substantial quantity, through a normal and untraumatized human or animal digestive tract, and are selected from the group comprising non-absorbable aminoglycosides, non-absorbable polymyxins, non-absorbable antifungal polyenes, and non-absorbable substituted imidazole derivatives, and the tablet or lozenge is arranged for providing controlled release of said antibiotic agents into the mouth and gastro-intestinal tract, from a buccal or sub-lingual location.

8. A pharmaceutical tablet or lozenge as claimed in claim 2 or claim 7, wherein said tablet or lozenge includes three antibiotic agents, which, preferably, belong to different ones of the classes set out in claims 2 and 7.

9. A pharmaceutical tablet or lozenge as claimed in claim 2, 7 or 8, wherein the non-absorbable aminoglycosides include non-absorbable forms of tobramycin, framycetin, neomycin, netilmicin, gentamicin, and streptomycin; the non-absorbable polymyxins include colistin sulphate and sulphur methylated colistin; the antifungal polyenes include nystatin and amphotricin B and; the non-absorbable substituted imidazole derivatives include non-absorbable forms of ketoconazole, miconazole and clotrimazole.

10. A pharmaceutical tablet or lozenge as claimed in any of the preceding claims, wherein the tablet matrix comprises a salivation promotion agent, an inert tablet filler and an inert tablet lubricant.

11. A pharmaceutical tablet or lozenge as claimed in claim 1, wherein the antibiotic agents are selected for treating the digestive tract of immunocompromised patients, such as those with leukaemia or HIV infection, or others who have undergone transplant surgery.

12. A pharmaceutical tablet or lozenge as claimed in claim 1, wherein one of the antibiotic agents is benzyl- metronidazole.

13. A pharmaceutical tablet or lozenge as claimed in any of the preceding claims, further comprising a tablet lubricant selected from magnesium stearate, stearic acid, sodium fumarate and colloidial silicon dioxide.

14. A pharmaceutical tablet or lozenge as claimed in any of the preceding claims, wherein the tablet matrix includes a non-carigenic sugar, preferably sorbitol, mannitol, xylitol or a mixture thereof.

15. A pharmaceutical tablet or lozenge as claimed in claim 14, wherein the tablet or lozenge comprises less than 100 mg of non-carigenic sugar.

16. A tablet or lozenge as claimed in any of claims 1 to 15, characterised in that the tablet is a buccal tablet.

17. A tablet retaining device for use with a pharmaceutical tablet or lozenge as claimed in any of the preceding claims, comprising means engagable to a patient and means for accommodating and

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retaining a pharmaceutical tablet or lozenge, wherein the device is arranged to hold a tablet or lozenge in a location within a patient's mouth from which an active ingredient, from the tablet or lonzenge, is releasable by the action of the patient's saliva, or other fluid within the mouth.

18. A device as claimed in claim 17, arranged to hold a tablet or lozenge in a buccal location, between a patient's gum and lip.

19. A device as claimed in either of claims 17 and 18 wherein the means engageable to a patient comprise a clip for resiliently gripping a tooth or teeth.

20. A device as claimed in either of claims 18 and 19 wherein the means for accommodating the tablet or lozenge comprises a clip for resiliently gripping the tablet or lozenge.

21. A device as claimed in claim 20, wherein each of said clips comprises a pair of resiliently partable jaw plates.

22. A device as claimed in claim 21, wherein a leg member extends between the clips and provides one jaw plate for each clip.

23. A device as claimed in claim 21 or 22, wherein at least one of the jaw plates of the tablet clip is perforated.

24. A device as claimed in claim 23, wherein the tablet clip is dimensioned to hold a plurality of tablets.

25. A device as claimed in any of claims 17 to 24 wherein said device is moulded from a resilient plastic resin material.

26. A device as claimed in any of claim 17 to 25, further comprising a pharmaceutical tablet or lozenge as claimed in any of claims 1-16.

27. A pharmaceutical tablet or lozenge as claimed in claim 16, arranged for adminstration in a device as claimed in any of claims 17 to 25.

28. Use of a composition comprising at least two non-absorbable antibiotic agents which are not absorbable, in a substantial quantity, through a normal and untraumatized human digestive tract, in combination with a tablet matrix arranged to provide controlled and sustained release of a prophylactic dose of said agents, into the mouth and gastro-intestinal tract, from a buccal or sub-lingual location, in the manufacture of a medicament for the prophilactic and selective decontamination of the human or animal digestive tract.

Claims for the following Contracting State : ES

1. A method of preparing a pharmaceutical tablet or lozenge, comprising admixing at least two non-absorbable antibiotic agents with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable, in a substantial quantity, through a normal and untraumatised human or animal digestive tract and the tablet or lozenge is arranged for providing controlled and sustained release of a prophylactic dose of said antibiotic agents, from a buccal or sub-lingual location and into the mouth and gastro-intestinal tract, for selectively decontaminating a human or animal digestive tract.

2. A method as claimed in claim 1, wherein the non-absorbable antibiotic agents are selected from the group consisting of non-absorbable aminoglycosides, non-absorbable polymyxins, non-absorbable antifungal polyenes and non-absorbable substituted imidazole derivatives.

3. A method as claimed in claim 1 or claim 2, wherein the tablet matrix is formulated so as to be erodible on exposure to fluid present within the mouth.

4. A method as claimed in claim 3, wherein the tablet matrix includes a water soluable cellulose derivative, preferably hydroxy- propylmethyl cellulose or a mixture of hydroxypropyl- methyl celluloses.

5. A method as claimed in claim 3, wherein the tablet matrix includes an ethyl cellulose and a salt of carboxymethyl cellulose, preferably the sodium salt.

6. A method as claimed in any of the preceding claims, wherein the antibiotic agents are selected to have a narrow spectrum of activity and to be substantially active only against selected potentially pathogenic organisms.

7. A method of preparing a pharmaceutical tablet or lozenge, comprising admixing at least two non-absorbable antibiotic agents, with a tablet matrix for providing controlled and sustained release of said agents, wherein the antibiotic agents are not absorbable, in a substantial quantity, through a normal and untraumatized human or animal digestive tract, and are selected from the group comprising non-absorbable aminoglycosides, non-absorbable polymyxins, non-absorbable antifungal polyenes, and non-absorbable substituted imidazole derivatives, and the tablet or lozenge is arranged for providing controlled release of said antibiotic agents into the mouth and gastro-intestinal tract, from a buccal or sub-lingual location.

8. A method as claimed in claim 2 or claim 7, wherein at least three antibiotic agents, which, preferably, belong to different ones of the classes set out in claims 2 and 7 are admixed with the tablet matrix.

9. A method as claimed in claim 2, 7 or 8, wherein the non-absorbable aminoglycosides include non-absorbable forms of tobramycin, framycetin, neomycin, netilmicin, gentamicin, and streptomycin; the non-absorbable polymyxins include colistin sulphate and sulphur methylated colistin; the antifungal polyenes include nystatin and amphotricin B and; the non-absorbable substituted imidazole derivatives include non-absorbable forms of ketoconazole, miconazole and clotrimazole.

10. A method as claimed in any of the preceding claims, wherein the tablet matrix comprises a salivation promotion agent, an inert tablet filler and an inert tablet lubricant.

11. A method as claimed in claim 1, wherein the antibiotic agents are selected for treating the digestive tract of immunocompromised patients, such as those with leukaemia or HIV infection, or others who have undergone transplant surgery.

12. A method as claimed in claim 1, wherein one of the antibiotic agents is benzyl- metronidazole.

13. A method as claimed in any of the preceding claims, wherein a tablet lubricant selected from magnesium stearate, stearic acid, sodium fumarate and colloidial silicon dioxide is included in the tablet matrix.

14. A method as claimed in any of the preceding claims, wherein the tablet matrix includes a non-carigenic sugar, preferably sorbitol, mannitol, xylitol or a mixture thereof.

15. A method as claimed in claim 14, wherein less than 100 mg of non-carigenic sugar is included in the tablet or lozenge.

16. A method as claimed in any of claims 1 to 15, characterised in that the tablet is prepared as a buccal tablet.

17. A tablet retaining device for use with a pharmaceutical tablet or lozenge prepared by a method as claimed in any of the preceding claims, comprising means engagable to a patient and means for accommodating and retaining a pharmaceutical tablet or lozenge, wherein the device is arranged to hold a tablet or lozenge in a location within a patient's mouth from which an active ingredient, from the tablet or lonzenge, is releasable by the action of the patient's saliva, or other fluid within the mouth.

18. A device as claimed in claim 17, arranged to hold a tablet or lozenge in a buccal location, between a patient's gum and lip.

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19. A device as claimed in either of claims 17 and 18 wherein the means engageable to a patient comprise a clip for resiliently gripping a tooth or teeth.

20. A device as claimed in either of claims 18 and 19 wherein the means for accommodating the tablet or lozenge comprises a clip for resiliently gripping the tablet or lozenge.

21. A device as claimed in claim 20, wherein each of said clips comprises a pair of resiliently partable jaw plates.

22. A device as claimed in claim 21, wherein a leg member extends between the clips and provides one jaw plate for each clip.

23. A device as claimed in claim 21 or 22, wherein at least one of the jaw plates of the tablet clip is perforated.

24. A device as claimed in claim 23, wherein the tablet clip is dimensioned to hold a plurality of tablets.

25. A device as claimed in any of claims 17 to 24 wherein said device is moulded from a resilient plastic resin material.

26. A device as claimed in any of claim 17 to 25, further comprising a pharmaceutical tablet or lozenge prepared by a method as claimed in any of claims 1-16.

27. A method as claimed in claim 16, wherein the tablet or lozenge is formed to be suitable for adminstration in a device as claimed in any of claims 17 to 25.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Pharmazeutische Tablette oder Pastille, umfassend wenigstens zwei nicht-absorbierbare antibiotische Stoffe in Verbindung mit einem Tabletten-Grundgerüst, um eine kontrollierte und verzögerte Freisetzung der Stoffe in einer wesentlichen Menge, wobei die antibiotischen Stoffe nicht absorbierbar sind, durch einen normalen und nicht-traumatisierten menschlichen oder tierischen Verdauungstrakt zur Verfügung zu stellen, und die Tablette oder Pastille so angeordnet ist, daß sie eine kontrollierte und verzögerte Freisetzung einer prophylaktischen Dosis der antibiotischen Stoffe von einem buccalen oder sublingualen Ort in den Mund und den gastrointestinalen Trakt zur Verfügung stellt, um einen menschlichen oder tierischen Verdauungstrakt selektiv zu dekontaminieren.

2. Pharmazeutische Tablette oder Pastille nach Anspruch 1, wobei die nicht-absorbierbaren antibiotischen Stoffe aus der Gruppe ausgewählt sind, bestehend aus nicht-absorbierbaren Aminoglycosiden, nicht-absorbierbaren Polymyxinen, nicht-absorbierbaren anti-fungizid wirkender Polyene und nicht-absorbierbaren substituierten Imidazol-Derivaten.

3. Pharmazeutische Tablette oder Pastille nach Anspruch 1 oder Anspruch 2, wobei das Tabletten-Grundgerüst so formuliert ist, daß sie bei Einwirkung von im Mund vorhandener Flüssigkeit erudierbar ist.

4. Pharmazeutische Tablette oder Pastille nach Anspruch 3, wobei das Tabletten-Grundgerüst ein wasserlösliches Zellulose-Derivat, vorzugsweise Hydroxypropylmethyl-Zellulose oder ein Gemisch aus Hydroxypropylmethyl-Zellulosen, enthält.

5. Pharmazeutische Tablette oder Pastille nach Anspruch 3, wobei das Tabletten-Grundgerüst eine Ethylzellulose und ein Salz von Carboxymethyl-Zellulose, vorzugsweise das Natriumsalz, enthält.

6. Pharmazeutische Tablette oder Pastille nach einem der vorhergehenden Ansprüche, wobei die antibiotischen Stoffe so ausgewählt sind, daß sie ein enges Wirkungsspektrum haben und im wesentlichen nur gegen ausgewählte, potentielle pathogene Organismen wirksam sind.

7. Pharmazeutische Tablette oder Pastille, umfassend wenigstens zwei nicht-absorbierbare antibiotische Stoffe in Verbindung mit einem Tabletten-Grundgerüst, um eine kontrollierte und verzögerte Freisetzung der Stoffe in einer wesentlichen Menge, wobei die antibiotischen Stoffe nicht absorbierbar sind, durch einen normalen und nicht-traumatisierten menschlichen oder tierischen Verdauungstrakt zur Verfügung zu stellen, und die aus der Gruppe ausgewählt sind, umfassend nicht-absorbierbare Aminoglycoside, nicht-absorbierbare Polymyxine, nicht absorbierbare anti-fungizid wirkender Polyene und nicht-absorbierbarer substituierte Imidazol-Derivate, und die Tablette oder Pastille so angeordnet ist, daß sie eine kontrollierte Freisetzung der antibiotischen Stoffe in den Mund und gastrointestinalen Trakt, von einem buccalen oder sub-lingualen Ort aus, zur Verfügung stellt.

8. Pharmazeutische Tablette oder Pastille nach Anspruch 2 oder Anspruch 7, wobei die Tablette oder Pastille drei anitbiotische Stoffe enthält, die vorzugsweise zu verschiedenen der Klassen, die in den Ansprüchen 2 und 7 dargelegt sind, gehören.

9. Pharmazeutische Tablette oder Pastille nach den Ansprüchen 2, 7 oder 8, wobei die nicht-absorbierbaren Aminoglycoside nicht-absorbierbare Formen von Tobramycin, Framycetin, Neomycin, Netilmicin, Gentamicin und Streptomycin enthalten; die nicht-absorbierbaren Polymyxine Colistinsulfat und Schwefel-methyliertes Collstin enthalten; die antifungizid wirkenden Polyene Nystatin und Amphotricin B enthalten; und die nicht-absorbierbaren substituierten Imidazol-Derivate nicht absorbierbare Formen von Ketoconazol, Miconazol und Clotrimazol enthalten.

10. Pharmazeutische Tablette oder Pastille nach einem der vorhergehenden Ansprüche, wobei das Tabletten-Grundgerüst einen Stoff zur Förderung des Speichelflusses, einen inerten Tabletten-Füllstoff und ein inertes Tabletten-Gleitmittel umfasst.

11. Pharmazeutische Tablette oder Pastille nach Anspruch 1, wobei die antibiotischen Stoffe zum Behandeln des Verdauungstraktes von Patienten, deren Immunsystem gefährdet ist, wie solche mit Leukämie oder einer HIV-Infektion, oder andere, die sich einer Transplantations-Operation unterzogen haben, ausgewählt sind.

12. Pharmazeutische Tablette oder Pastille nach Anspruch 1, wobei einer der antibiotischen Stoffe Benzylmetronidazol ist.

13. Pharmazeutische Tablette oder Pastille nach einem der vorhergehenden Ansprüche, weiter umfassend ein Tabletten-Gleitmittel, ausgewählt aus Magnesiumstearat, Stearinsäure, Natriumfumarat und kolloidalem Siliciumdioxid.

14. Pharmazeutische Tablette oder Pastille nach einem der vorhergehenden Ansprüche, wobei das Tabletten-Grundgerüst einen nicht-karigenen Zucker, vorzugsweise Sorbitol, Mannitol, Xylitol oder ein Gemisch daraus, enthält.

15. Pharmazeutische Tablette oder Pastille nach Anspruch 14, wobei die Tablette oder die Pastille weniger als 100 mg eines nicht-karigenen Zuckers umfasst.

16. Tablette oder Pastille nach einem der Ansprüche 1 bis 15, dadurch gekennzeichnet, daß die Tablette eine Buccaltablette ist.

17. Vorrichtung zum Halten einer Tablette zur Verwendung mit einer pharmazeutischen Tablette oder Pastille nach einem der vorhergehenden Ansprüche, umfassend Vorrichtungen, die an einem Patienten angebracht werden können, und Vorrichtungen zum Aufnehmen und Halten einer pharmazeutischen Tablette oder Pastille, wobei die Vorrichtung angeordnet ist eine Tablette oder Pastille an einem Ort im Mund des Patienten zu halten, von dem ein Wirkstoff, von der Tablette oder der Pastille, durch die Einwirkung des Speichels des Patienten, oder anderer Flüssigkeit im Mund, freigesetzt werden kann.

18. Vorrichtung nach Anspruch 17, angeordnet, um eine Tablette oder Pastille an einem buccalen Ort zwischen dem Zahnfleisch und der Lippe eines Patienten zu halten.

19. Vorrichtung nach einem der Ansprüche 17 und 18, wobei die Vorrichtungen, die an einem Patienten angebracht werden können, eine Klammer zum elastischen Erfassen eines Zahnes oder Zähne umfasst.

20. Vorrichtung nach einem der Ansprüche 18 und 19, wobei die Vorrichtungen zum Aufnehmen der Tablette oder Pastille eine Klammer zum elastischen Erfassen der Tablette oder Pastille umfasst.

21. Vorrichtung nach Anspruch 20, wobei jede der Klammern ein Paar elastische, teilbare Klemmbacken-Platten umfasst.

22. Vorrichtung nach Anspruch 21, wobei ein Schenkel zwischen die Klammern hindurchführt und eine Klemmbacken-Platte für jede Klammer zur Verfügung stellt.

23. Vorrichtung nach den Ansprüchen 21 oder 22, wobei wenigstens eine der Klemmbacken-Platten der Tabletten-Klammer perforiert ist.

24. Vorrichtung nach Anspruch 23, wobei die Tabletten-Klammer dimensioniert ist eine Vielzahl von Tabletten zu halten.

25. Vorrichtung nach einem der Ansprüche 17 bis 24, wobei die Vorrichtung aus einem elatischen Kunstharz gebildet wird.

26. Vorrichtung nach einem der Ansprüche 17 bis 25, weiter umfassend eine pharmazeutische Tablette oder Pastille nach einem der Ansprüche 1-16.

27. Pharmazeutische Tablette oder Pastille nach Anspruch 16, angeordnet zur Verabreichung in einer Vorrichtung nach einem der Ansprüche 17 bis 25.

28. Verwendung einer Zusammensetzung, umfassend wenigstens zwei nicht-absorbierbare antibiotische Stoffe, die nicht in einer wesentlichen Menge durch einen normalen und nicht-traumatisierten menschlichen Verdauungstrakt absorbierbar sind, in Verbindung mit einem Tabletten-Grundgerüst, daß so angeordnet ist, daß es eine kontrollierte und verzögerte Freisetzung einer prophylaktischen Dosis der Stoffe in den Mund und den gastrointestinalen Trakt von einem buccalen oder sublingualen Ort zur Verfügung stellt, bei der Herstellung eines Arzneimittels zur prophylaktischen und selektiven Dekontamination des menschlichen oder tierischen Verdauungstraktes.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Zubereitung einer pharmazeutischen Tablette oder Pastille, mit einem Beimischen von wenigstens zwei nicht-absorbierbaren antibiotischen Stoffen mit einem Tabletten-Grundgerüst, um eine kontrollierte und verzögerte Freisetzung der Stoffe in einer wesentlichen Menge, wobei die antibiotischen Stoffe nicht absorbierbar sind, durch einen normalen und nicht-traumatisierten menschlichen oder tierischen Verdauungstrakt zur Verfügung zu stellen, und die Tablette oder Pastille so angeordnet ist, daß sie eine kontrollierte und verzögerte Freisetzung einer prophylaktischen Dosis der antibiotischen Stoffe von einem buccalen oder sublingualen Ort in den Mund und den gastrointestinalen Trakt zur Verfügung stellt, um einen menschlichen oder tierischen Verdauungstrakt selektiv zu dekontaminieren.

2. Verfahren nach Anspruch 1, wobei die nicht-absorbierbaren antibiotischen Stoffe aus der Gruppe ausgewählt sind, bestehend aus nicht-absorbierbaren Aminoglycosiden, nicht-absorbierbaren Polymyxinen, nicht-absorbierbaren anti-fungizid wirkender Polyene und nicht-absorbierbaren substituierten Imidazol-Derivaten.

3. Verfahren nach Anspruch 1 oder Anspruch 2, wobei das Tabletten-Grundgerüst so formuliert ist, daß sie bei Einwirkung von im Mund vorhandener Flüssigkeit erudierbar ist.

4. Verfahren nach Anspruch 3, wobei das Tabletten-Grundgerüst ein wasserlösliches Zellulose-Derivat, vorzugsweise Hydroxypropylmethyl-Zellulose oder ein Gemisch aus Hydroxypropylmethyl-Zellulosen,

enthält.

5. Verfahren nach Anspruch 3, wobei das Tabletten-Grundgerüst eine Ethylzellulose und ein Salz von Carboxymethyl-Zellulose, vorzugsweise das Natriumsalz, enthält.

6. Verfahren nach einem der vorhergehenden Ansprüche, wobei die antibiotischen Stoffe so ausgewählt sind, daß sie ein enges Wirkungsspektrum haben und im wesentlichen nur gegen ausgewählte, potentielle pathogene Organismen wirksam sind.

7. Verfahren zur Zubereitung einer pharmazeutischen Tablette oder Pastille, umfassend ein Beimischen von wenigstens zwei nicht-absorbierbaren antibiotischen Stoffen mit einem Tabletten-Grundgerüst, um eine kontrollierte und verzögerte Freisetzung der Stoffe in einer wesentlichen Menge, wobei die antibiotischen Stoffe nicht absorbierbar sind, durch einen normalen und nicht-traumatisierten menschlichen oder tierischen Verdauungstrakt zur Verfügung zu stellen, und die aus der Gruppe ausgewählt sind, umfassend nicht-absorbierbare Aminoglycoside, nicht-absorbierbare Polymyxine, nicht absorbierbare anti-fungizid wirkender Polyene und nicht-absorbierbarer substituierte Imidazol-Derivate, und die Tablette oder Pastille so angeordnet ist, daß sie eine kontrollierte Freisetzung der antibiotischen Stoffe in den Mund und gastrointestinalen Trakt, von einem buccalen oder sub-lingualen Ort aus, zur Verfügung stellt.

8. Verfahren nach Anspruch 2 oder Anspruch 7, wobei zumindest drei anitbiotische Stoffe, die vorzugsweise zu verschiedenen der Klassen, die in den Ansprüchen 2 und 7 dargelegt sind, gehören, dem Tabletten-Grundgerüst beigemengt sind

9. Verfahren nach den Ansprüchen 2, 7 oder 8, wobei die nicht-absorbierbaren Aminoglycoside nicht-absorbierbare Formen von Tobramycin, Framycetin, Neomycin, Netilmicin, Gentamicin und Streptomycin enthalten; die nicht-absorbierbaren Polymyxine Colistinsulfat und Schwefelmethyliertes Colistin enthalten; die anti-fungizid wirkenden Polyene Nystatin und Amphotricin B enthalten; und die nicht-absorbierbaren substituierten Imidazol-Derivate nicht absorbierbare Formen von Ketoconazol, Miconazol und Clotrimazol enthalten.

10. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Tabletten-Grundgerüst einen Stoff zur Förderung des Speichelflusses, einen inerten Tabletten-Füllstoff und ein inertes Tabletten-Gleitmittel umfasst.

11. Verfahren nach Anspruch 1, wobei die antibiotischen Stoffe zum Behandeln des Verdauungstraktes von Patienten, deren Immunsystem gefährdet ist, wie solche mit Leukämie oder einer HIV-Infektion, oder andere, die sich einer Transplantations-Operation unterzogen haben, ausgewählt sind.

12. Verfahren nach Anspruch 1, wobei einer der antibiotischen Stoffe Benzylmetronidazol ist.

13. Verfahren nach einem der vorhergehenden Ansprüche, weiter umfassend ein Tabletten-Gleitmittel, ausgewählt aus Magnesiumstearat, Stearinsäure, Natriumfumarat und kolloidalem Siliciumdioxid.

14. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Tabletten-Grundgerüst einen nicht-karigenen Zucker, vorzugsweise Sorbitol, Mannitol, Xylitol oder ein Gemisch daraus, enthält.

15. Verfahren nach Anspruch 14, wobei in der Tablette oder Pastille weniger als 100 mg eines nicht-karigenen Zuckers enthalten ist

16. Verfahren nach einem der Ansprüche 1 bis 15, dadurch gekennzeichnet, daß die Tablette als eine Buccaltablette zubereitet ist.

17. Vorrichtung zum Halten einer Tablette zur Verwendung mit einer pharmazeutischen Tablette oder Pastille, zubereitet nach einem Verfahren nach einem der vorhergehenden Ansprüche, umfassend Mittel, die an einem Patienten eingreifen können, und Mittel zum Aufnehmen und Halten einer pharmazeutischen Tablette oder Pastille, wobei die Vorrichtung angeordnet ist, eine Tablette oder Pastille an einem Ort im Mund des Patienten zu halten, von dem ein Wirkstoff, von der Tablette oder

der Pastille, durch die Einwirkung des Speichels des Patienten, oder anderer Flüssigkeit im Mund, freigesetzt werden kann.

18. Vorrichtung nach Anspruch 17, angeordnet, um eine Tablette oder Pastille an einem buccalen Ort zwischen dem Zahnfleisch und der Lippe eines Patienten zu halten.

19. Vorrichtung nach einem der Ansprüche 17 und 18, wobei die Vorrichtungen, die an einem Patienten angebracht werden können, eine Klammer zum elastischen Erfassen eines Zahnes oder Zähne umfasst.

20. Vorrichtung nach einem der Ansprüche 18 und 19, wobei die Vorrichtungen zum Aufnehmen der Tablette oder Pastille eine Klammer zum elastischen Erfassen der Tablette oder Pastille umfasst.

21. Vorrichtung nach Anspruch 20, wobei jede der Klammern ein Paar elastische, teilbare Klemmbacken-Platten umfasst.

22. Vorrichtung nach Anspruch 21, wobei ein Schenkel zwischen die Klammern hindurchführt und eine Klemmbacken-Platte für jede Klammer zur Verfügung stellt.

23. Vorrichtung nach den Ansprüchen 21 oder 22, wobei wenigstens eine der Klemmbacken-Platten der Tabletten-Klammer perforiert ist.

24. Vorrichtung nach Anspruch 23, wobei die Tabletten-Klammer dimensioniert ist eine Vielzahl von Tabletten zu halten.

25. Vorrichtung nach einem der Ansprüche 17 bis 24, wobei die Vorrichtung aus einem elatischen Kunstharz gebildet wird.

26. Vorrichtung nach einem der Ansprüche 17 bis 25, weiter umfassend eine pharmazeutische Tablette oder Pastille, zubereitet nach einem Verfahren nach einem der Ansprüche 1-16.

27. Verfahren nach Anspruch 16, wobei die Tablette oder Pastille ausgebildet wird, um in einer Vorrichtung nach einem der Ansprüche 17 bis 25 verabreicht werden zu können.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Comprimé ou pastille pharmaceutique comprenant au moins deux agents antibiotiques non absorbables, en association avec une matière de base de comprimé, pour procurer une libération réglée et prolongée desdits agents, les agents antibiotiques n'étant pas absorbables en importante quantité par un tube digestif humain ou animal normal et non traumatisé, et le comprimé ou la pastille étant disposé de manière à fournir une libération réglée et prolongée d'une dose prophylactique desdits agents antibiotiques, à partir d'une localisation gingivo-jugale ou sublinguale et s'effectuant dans la bouche et le tractus gastro-instestinal, pour la décontamination sélective d'un tube digestif humain ou animal.

2. Comprimé ou pastille pharmaceutique selon la revendication 1, dans lequel les agents antibiotiques non absorbables sont choisis parmi des aminoglycosides non absorbables, des polymyxines non absorbables, des polyènes antifongiques non absorbables et des dérivés d'imidazole substitués non absorbables.

3. Comprimé ou pastille pharmaceutique selon la revendication 1 ou 2, dans lequel la matière de base du comprimé est formulée de manière a être érodable lors de l'exposition à un liquide présent dans la bouche.

4. Comprimé ou pastille pharmaceutique selon la revendication 3, dans lequel la matière de base du comprimé comprend un dérivé de cellulose soluble dans l'eau, de préférence l'hydroxypropylméthylcellulose ou un mélange d'hydroxypropylméthylcelluloses.

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5. Comprimé ou pastille pharmaceutique selon la revendication 3, dans lequel la matière de base du comprimé comprend une éthylcellulose et un sel de carboxyméthylcellulose, de préférence le sel sodique.

6. Comprimé ou pastille pharmaceutique selon l'une quelconque des revendications précédentes, dans lequel les agents antibiotiques sont choisis de manière à avoir un spectre étroit d'activité et à n'être pratiquement actifs que contre des organismes potentiellement pathogènes choisis.

7. Comprimé ou pastille pharmaceutique comprenant au moins deux agents antibiotiques non absorbables en association avec une matière de base de comprimé, pour procurer une libération réglée ou prolongée desdits agents, les agents antibiotiques n'étant pas absorbables en importante quantité à travers un tube digestif humain ou animal normal et non traumatisé, et étant choisis parmi des aminoglycosides non absorbables, des polymyxines non absorbables, des polyènes antifongiques non absorbables et des dérivés d'imidazole substitués non absorbables, et le comprimé ou la pastille étant disposé de manière à procurer une libération réglée desdits agents antibiotiques dans la cavité buccale et le tractus gastro-intestinal, à partir d'un emplacement gingivo-jugal ou sublingual.

8. Comprimé ou pastille pharmaceutique selon la revendication 2 ou 7, caractérisé en ce que ledit comprimé ou ladite pastille comprend trois agents antibiotiques qui appartiennent de préférence à différentes classes parmi celles indiquées dans les revendications 2 et 7.

9. Comprimé ou pastille pharmaceutique selon la revendication 2, 7 ou 8, dans lequel les aminoglycosides non absorbables comprennent des formes non absorbables de la tobramycine, la framycétine, la néomycine, la nétilmicine, la gentamicine et la streptomycine; les polymyxines non absorbables comprennent la colistine sulfate et la colistine sulfométhylée; les polyènes antifongiques comprennent la nystatine et l'amphotricine B, et les dérivés d'imidazoles substitués non absorbables comprennent des formes non absorbables de kétoconazole, miconazole et clotrimazole.

10. Comprimé ou pastille pharmaceutique selon l'une quelconque des revendications précédente, dans lequel la matière de base du comprimé comprend un agent favorisant la salivation, un excipient inerte pour comprimés et un lubrifiant inerte pour comprimés.

11. Comprimé ou pastille pharmaceutique selon la revendication 1, dans lequel les agents antibiotiques sont choisis pour le traitement du tube digestif de patients immunocompromis, tels que ceux atteints de leucémie ou d'infection par le HIV, ou d'autres qui ont subi une chirurgie de greffe.

12. Comprimé ou pastille pharmaceutique selon la revendication 1, dans lequel l'un des agents antibiotiques est le benzylmétronidazole.

13. Comprimé ou pastille pharmaceutique selon l'une quelconque des revendications précédentes, comprenant un lubrifiant pour comprimés choisi parmi le stéarate de magnésium, l'acide stéarique, le fumarate de sodium et la silice colloïdale.

14. Comprimé ou pastille pharmaceutique selon l'une quelconque des revendications précédentes, dans lequel la matière de base du comprimé comprend un sucre non cariogène, de préférence le sorbitol, le mannitol, le xylitol ou un mélange de ceux-ci.

15. Comprimé ou pastille pharmaceutique selon la revendication 14, caractérisé en ce que le comprimé ou la pastille comprend moins de 100 mg de sucre non cariogène.

16. Comprimé ou pastille pharmaceutique selon l'une quelconque des revendications 1 à 15, caractérisé en ce que le comprimé est un comprimé gingivo-jugal.

17. Dispositif de maintien de comprimé pour utiliser avec un comprimé ou une pastille pharmaceutique selon l'une quelconque des revendications précédentes, comprenant un moyen insérable sur un patient et un moyen pour loger et retenir le comprimé ou la pastille pharmaceutique, le dispositif étant disposé de manière à maintenir le comprimé ou la pastille en un emplacement dans la bouche d'un patient, à partir duquel un composant actif, provenant du comprimé ou de la pastille, peut être libéré sous l'action

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de la salive du patient ou d'un autre liquide dans la cavité buccale.

18. Dispositif selon la revendication 17, monté de manière à maintenir un comprimé ou une pastille en un emplacement buccal, entre la gencive et la lèvre d'un patient.

19. Dispositif selon l'une quelconque des revendications 17 et 18, dans lequel le moyen insérable sur un patient comprend une pince pour la prise élastique d'une dent ou de dents.

20. Dispositif selon l'une quelconque des revendications 18 et 19, dans lequel le moyen destiné à recevoir le comprimé ou la pastille comprend une pince pour la prise élastique du comprimé ou de la pastille.

21. Dispositif selon la revendication 20, dans lequel chacune desdites pinces comprend une paire de plaques mâchoires pouvant être écartées élastiquement.

22. Dispositif selon la revendication 21, dans lequel un élément allongé s'étend entre les pinces et procure une plaque mâchoire pour chaque pince.

23. Dispositif selon la revendication 21 ou 22, dans lequel au moins l'une des plaques mâchoires de la pince pour comprimé est perforée.

24. Dispositif selon la revendication 23, dans lequel la pince pour comprimé a des dimensions permettant de maintenir plusieurs comprimés.

25. Dispositif selon l'une quelconque des revendication 17 à 24, caractérisé en ce que ledit dispositif est moulé à partir d'une matière plastique élastique.

26. Dispositif selon l'une quelconque des revendications 17 à 25, comprenant en outre une comprimé ou une pastille pharmaceutique selon l'une quelconque des revendications 1 à 16.

27. Comprimé ou pastille pharmaceutique selon la revendication 16, disposé pour l'administration dans un dispositif selon l'une quelconque des revendications 17 à 25.

28. Utilisation d'une composition comprenant au moins deux agents antibiotiques non absorbables qui ne sont pas absorbables en importante quantité par un tube digestif humain normal et non traumatisé, en association avec une matière de base de comprimé disposée de matière à fournir une libération réglée et prolongée d'une dose prophylactique desdits agents, dans la bouche et le tractus gastrointestinal, à partir d'un emplacement gingivo-jugal ou sublingual, dans la fabrication d'un médicament pour la décontamination prophylactique et sélective du tube digestif humain ou animal.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de fabrication d'un comprimé ou d'une pastille pharmaceutique, comprenant le mélange d'au moins deux agents antibiotiques non absorbables, en association avec une matière de base de comprimé, pour procurer une libération réglée et prolongée desdits agents, les agents antibiotiques n'étant pas absorbables en importante quantité par un tube digestif humain ou animal normal et non traumatisé, et le comprimé ou la pastille étant disposé de manière à fournir une libération réglée et prolongée d'une dose prophylactique desdits agents antibiotiques, à partir d'une localisation gingivo-jugale ou sublinguale et s'effectuant dans la bouche et le tractus gastro-instestinal, pour la décontamination sélective d'un tube digestif humain ou animal.

2. Procédé selon la revendication 1, dans lequel les agents antibiotiques non absorbables sont choisis parmi des aminoglycosides non absorbables, des polymyxines non absorbables, des polyènes antifongiques non absorbables et des dérivés d'imidazole substitués non absorbables.

3. Procédé selon la revendication 1 ou 2, dans lequel la matière de base du comprimé est formulée de manière a être érodable lors de l'exposition à un liquide présent dans la bouche.

4. Procédé selon la revendication 3, dans lequel la matière de base du comprimé comprend un dérivé de cellulose soluble dans l'eau, de préférence l'hydroxypropylméthylcellulose ou un mélange d'hydroxypropylméthylcelluloses.

5. Procédé selon la revendication 3, dans lequel la matière de base du comprimé comprend une éthylcellulose et un sel de carboxyméthylcellulose, de préférence le sel sodique.

6. Procédé selon l'une quelconque des revendications précédentes, dans lequel les agents antibiotiques sont choisis de manière à avoir un spectre étroit d'activité et à n'être pratiquement actifs que contre des organismes potentiellement pathogènes choisis.

7. Procédé de fabrication d'un comprimé ou d'une pastille pharmaceutique comprenant au moins deux agents antibiotiques non absorbables avec une matière de base de comprimé, pour procurer une libération réglée ou prolongée desdits agents, les agents antibiotiques n'étant pas absorbables en importante quantité à travers un tube digestif humain ou animal normal et non traumatisé, et étant choisis parmi des aminoglycosides non absorbables, des polymyxines non absorbables, des polyènes antifongiques non absorbables et des dérivés d'imidazole substitués non absorbables, et le comprimé ou la pastille étant disposé de manière à procurer une libération réglée desdits agents antibiotiques dans la cavité buccale et le tractus gastro-intestinal, à partir d'un emplacement gingivo-jugal ou sublingual.

8. Procédé selon la revendication 2 ou 7, dans lequel on mélange avec la matière de base du comprimé au moins trois agents antibiotiques qui, de préférence, appartiennent à différentes classes parmi celles indiquées dans les revendications 2 et 7.

9. Procédé selon la revendication 2, 7 ou 8, dans lequel les aminoglycosides non absorbables comprennent des formes non absorbables de la tobramycine, la framycétine, la néomycine, la nétilmicine, la gentamicine et la streptomycine; les polymyxines non absorbables comprennent la colistine sulfate et la colistine sulfométhylée; les polyènes antifongiques comprennent la nystatine et l'amphotricine B, et les dérivés d'imidazole substitués non absorbables comprennent des formes non absorbables de kétoconazole, miconazole et clotrimazole.

10. Procédé selon l'une quelconque des revendications précédente, dans lequel la matière de base du comprimé comprend un agent favorisant la salivation, un excipient inerte pour comprimés et un lubrifiant inerte pour comprimés.

11. Procédé selon la revendication 1, dans lequel les agents antibiotiques sont choisis pour le traitement du tube digestif de patients immunocompromis, tels que ceux atteints de leucémie ou d'infection par le HIV, ou d'autres qui ont subi une chirurgie de greffe.

12. Procédé selon la revendication 1, dans lequel l'un des agents antibiotiques est le benzylmétronidazole.

13. Procédé selon l'une quelconque des revendications précédentes, dans lequel est inclu dans la matière de base du comprimé un lubrifiant pour comprimés choisi parmi le stéarate de magnésium, l'acide stéarique, le fumarate de sodium et la silice colloïdale.

14. Procédé selon l'une quelconque des revendications précédentes, dans lequel la matière de base du comprimé comprend un sucre non cariogène, de préférence le sorbitol, le mannitol, le xylitol ou un mélange de ceux-ci.

15. Procédé selon la revendication 14, dans lequel moins de 100 mg de sucre non cariogène sont inclus dans le comprimé ou la pastille.

16. Procédé selon l'une quelconque des revendications 1 à 15, caractérisé en ce que le comprimé est fabriqué sous forme d'un comprimé gingivo-jugal.

17. Dispositif de maintien de comprimé pour utiliser avec un comprimé ou une pastille pharmaceutique fabriqués par un procédé selon l'une quelconque des revendications précédentes, comprenant un

moyen insérable sur un patient et un moyen pour loger et retenir le comprimé ou la pastille pharmaceutique, le dispositif étant disposé de manière à maintenir le comprimé ou la pastille en un emplacement dans la bouche d'un patient, à partir duquel un composant actif, provenant du comprimé ou de la pastille, peut être libéré sous l'action de la salive du patient ou d'un autre liquide dans la cavité buccale.

18. Dispositif selon la revendication 17, monté de manière à maintenir un comprimé ou une pastille en un emplacement buccal, entre la gencive et la lèvre d'un patient.

19. Dispositif selon l'une quelconque des revendications 17 et 18, dans lequel le moyen insérable sur un patient comprend une pince pour la prise élastique d'une dent ou de dents.

20. Dispositif selon l'une quelconque des revendications 18 et 19, dans lequel le moyen destiné à recevoir le comprimé ou la pastille comprend une pince pour la prise élastique du comprimé ou de la pastille.

21. Dispositif selon la revendication 20, dans lequel chacune desdites pinces comprend une paire de plaques mâchoires pouvant être écartées élastiquement.

22. Dispositif selon la revendication 21, dans lequel un élément allongé s'étend entre les pinces et procure une plaque mâchoire pour chaque pince.

23. Dispositif selon la revendication 21 ou 22, dans lequel au moins l'une des plaques mâchoires de la pince pour comprimé est perforée.

24. Dispositif selon la revendication 23, dans lequel la pince pour comprimé a des dimensions permettant de maintenir plusieurs comprimés.

25. Dispositif selon l'une quelconque des revendication 17 à 24, caractérisé en ce que ledit dispositif est moulé à partir d'une matière plastique élastique.

26. Dispositif selon l'une quelconque des revendication 17 à 25, comprenant en outre une comprimé ou une pastille pharmaceutique selon l'une quelconque des revendications 1 à 16.

27. Procédé selon la revendication 16, dans lequel le comprimé ou la pastille est formé de manière à être approprié à l'administration dans un dispositif tel que revendiqué dans l'une quelconque des revendications 17 à 25.