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NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Dosage Unit Forms for the Administration of Medicaments and Diagnostic Agents

We, BIOREX LABORATORIES LIMITED, of 47/51, Exmouth Market, Rosebery Avenue, London, E.C.1., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention is concerned with improvements in or relating to dosage unit forms for the administration of medicaments and diagnostic agents and, more particularly, is concerned with dosage unit forms which are adapted to release their contents in the region of the pylorus.

Numerous types of dosage unit forms are already known which ensure the slow or rapid release of the contents thereof in the gastro-intestinal tract. The preparation of dosage unit forms of this type does not present any great difficulties when the active ingredients present therein are intended to be released in the stomach because the contents of the stomach remain therein for a considerable period of time and thus dosage unit forms in the stomach are subjected to the physical and chemical actions prevailing therein and can be formulated in such a manner as to ensure the release of the active ingredients of the dosage unit forms in the stomach. Dosage unit forms of this type can contain active ingredients intended either to be absorbed through the gastric mucosa or to exert a healing effect on the gastric mucosa, for example, in the case of the treatment of gastric ulcers.

Special problems, however, arise when it is desired that the dosage unit forms should release their contents in the pyloric region of the stomach and/or in the duodenum in order that the active materials present therein shall be absorbed in the duodenal region or that they be able to exert a heating effect on the duodenal mucosa. Every time the pyloric sphincter opens, a peristaltic wave in the stomach forces a portion of the contents thereof through the duodenum into the small intestine and it has hitherto been virtually impossible to prepare dosage unit forms which will ensure a release of their active ingredients in such a manner that the said active ingredients are able to come into contact, at an effective concentration, with the duodenol mucosa for any appreciable length of time.

It is an object of the present invention to provide new types of dosage units which will, with reasonable certainty, overcome the above-mentioned difficulties and are adapted to release therapeutically-active agents and/or diagnostic agents in the dosage units in or near the duodenum at high concentrations so that the said agents have a greater chance of remaining in contact with the duodenal mucosa for a sufficient length of time to enable them to act upon the duodenal mucosa, or to enable them to be of diagnostic utility in the duodenal region.

It has been known for a considerable period of time to administer medicaments orally in gelatine capsules but such capsules are readily dissolved in the stomach so that the contents thereof are released in the stomach. The result is that the contents of such gelatine capsules either may not reach the duodenum at all or may not reach the duodenum in a concentration which is high enough to be effective for the desired purpose.

According to the present invention, there is provided a dosage unit, for the administration of medicaments and diagnostic agents, which can be swallowed, comprising a distending

[*Price* 4*s.* 6*d.*]

agent which is either (a) a substance or mixture evolving gas on contact with gastric juice or (b) a substance which will exert an osmotic pressure when in aqueous solution or a mixture of (a) and (b), said distending agent being hermetically sealed in a polymeric, semi-permeable film which is resistant to attack by, but permeable to gastric juice, said dosage unit form swelling, without breaking when in contact with gastric juices, to such an extent as to be mechanically ruptured in the region of the pyloric sphincter.

According to one embodiment of the present invention, the dosage unit is not less than 20 mm. in overall length and swells, without bursting, when placed in simulated gastric juice for not less than 30 minutes to an increase in volume of at least 50% and, when so swollen, can be burst by a pressure of not less than 100 mm.Hg.

The dosage unit according to the present invention may, for example, be in the form of a sealed capsule of polymeric, semi-permeable material containing a therapeutically active agent and/or diagnostic agent and a distending agent or in the form of a compressed but easily disintegrated tablet containing a therapeutically-active agent and/or a diagnostic agent and a distending agent, said tablet being enclosed in a polymeric, semi-permeable material.

It is to be understood that the pyloric sphincter can vary somewhat in size from one subject to another. Furthermore, in the case of diseases of the pyloric region of the stomach and of the duodenum, the size of the pyloric sphincter may be increased or decreased. However, we have found that when the dosage units according to the present invention are swallowed, have become swollen in the stomach and subsequently pass into the pylorus, a statistically significant proportion of the dosage units are ruptured and the contents thereof are liberated, i.e. a sufficient portion of the dosage units are ruptured in the pyloric region to give the desired effect. Clinical trials have clearly indicated the efficacy of the dosage units according to the present invention for the administration of therapeutically active materials for the treatment of diseases of the duodenum. Valuable results have been obtained with the use of capsules of size 00. Capsules or coated tablets of this type can be formulated in such a manner that when they rupture, a very viscous solution is liberated which moves more slowly through the duodenum, thereby facilitating the contacting of these therapeutically active materials with the duodenal mucosa for a considerably longer period of time than would normally be the case.

Examples of non-toxic, polymeric, semi-permeable materials which can be used according to the present invention, after having been rendered resistant to gastric juice, include gelatine, partially or wholly hydrolysed polyvinyl acetate, copolymers of vinyl alcohol and viny acetate, ethers and esters of cellulose, such as ethoxy-cellulose, carbomethoxy-cellulose and methyl cellulose, and plant mucilages, such as agar agar and alginates, and mixtures of such polymeric, semi-permeable materials.

It is known that gelatine capsules which have been hardened or tanned with formaldehyde are liable to ageing. Recent investigations which we have carried out showed that only a small quantity of formaldehyde is consumed during the treatment of gelatine capsules with formaldehyde solutions. It is very probable that the progressive hardening of formaldehyde-treated gelatine capsules on storage is mainly due to the continued reaction of gelatine with residual formaldehyde. We have found that this disadvantage is avoided when capsules made from or tablets coated with gelatine or other polymeric, semi-permeable materials capable of being hardened or tanned with formaldehyde are, after treatment with formaldehyde, washed with a solvent, such as industrial methylated spirits or ethanol, to remove residual formaldehyde and then dried. Alternatively, residual formaldehyde can be inactivated with, for example, gaseous ammonia or a solution of ammonia in a non-aqueous or aqueous organic medium or a solution of an ammonium salt, such as ammonium carbonate, in a non-aqueous or aqueous-organic medium. The formaldehyde treatment has the effect of converting the polymeric material into a semi-permeable membrane which is insoluble in dilute acids, such as are encountered in the stomach, but which swells and permits the passage of small molecules, for example, water, mineral acids and inorganic electrolytes. Disaccharides, such as lactose, do not appear to pass through the semi-permeable membrane easily. Capsules and coated tablets comprising a polymeric, semi-permeable material treated with formaldehyde in this manner appear to provide good protection to their contents when these are known to be hygroscopic and sensitive to moisture and all these capsules and coated tablets appear to be stable for at least three months, whether stored in well-closed aluminium containers or exposed to the atmosphere.

As already indicated above, the dosage units according to the present invention must be hermetically sealed, prior to being tanned, hardened or otherwise rendered insoluble in gastric juice. This can be achieved, for example, in the case of capsules or coated tablets, by sealing them with a solution of gelatine or of another suitable adhesive, such as a cellulose ether, for example, a methyl cellulose, with or without the use of a plasticiser. The sealing can also be accomplished by placing a strip of polymeric, semi-permeable material over the join in the capsule. In the case of

tablets, these can be press-coated with a polymeric, semi-permeable material and then sealed with a jet of steam.

The formaldehyde treatment can be carried out with solutions of formaldehyde of any suitable strength in water or in aqueous-organic solvents, such as aqueous ethanol. It has been found to be convenient to use, for this treatment, commercial or B.P. solutions of formaldehyde, commonly referred to as formalin, i.e. 37—41 w/v aqueous solutions of formaldehyde which may contain a variable amount of methanol or ethanol.

The tanning or hardening of the gelatine or other appropriate polymeric materials can be carried out not only with the use of formaldehyde in the above-described manner but also with the use of other suitable, non-toxic reagents, such as tannic acid, ethylene oxide or glutaraldehyde. When using, for example, an aqueous solution of formaldehyde, this aqueous solution preferably also contains an organic solvent, such as methanol, ethanol, industrial methylated spirits isopropanol or acetone, the water allowing the reagent used to penetrate the colloid and the non-aqueous solvent preventing significant swelling of the capsule or coated tablet.

According to one embodment of the dosage units of the present invention, they can contain one or more components which are capable of evolving a non-toxic gas when in contact with gastric juice, provided, of course, that these components and the gas evolved are not incompatible with the active materials in the dosage units. The gas so evolved when the gastric juices permeate into the dosage units will then result in an increase in pressure in the interior of the dosage units, thereby preserving their shape and increasing their dimensions, and will also result in an explosion of the dosage units when they are subjected to mechanical stresses in the pylorus, with the result that the viscous solution resulting from the disintegration of the dosage units will forcibly impinge on the walls of the neighbouring mucosa and adhere thereto for some time. Examples of materials which may be incorporated into the dosage units and which are capable of evolving gas on contact with gastric juice, include sodium bicarbonate alone or in admixture with citric acid or tartaric acid.

If the swollen dosage units do not retain their shape after having been soaked in the gastric juices or if they are too hard and tough or if they are too soft and pliable, there is always the possibility that they will be able to pass through the pylorus without bursting. The presence of gas-releasing components in the dosage units assists the bursting of the swollen dosage units when passing through the pylorus. This retention of shape can also be ensured or assisted by including, in the dosage units, non-toxic compounds, such as water-soluble salts, for example, sodium chloride or potassium chloride, or sugars, for example, lactose, sucrose or mannitol, which will produce a high osmotic pressure in the interior of the dosage unit.

It is to be understood that any desired suitable therapeutically active agents and/or diagnostic agents may be placed in the new dosage units of the present invention. These dosage units are of particular value for treating duodenal ulcers with the disodium salt of glycyrrhetinic acid hemisuccinate (see our British Specification No. 843,133), which has already proved to be outstandingly successful in the treatment of gastric ulcers. This disodium salt is also known as carbenoxolone sodium and as "Biogastrone" (Registered Trade Mark).

The following Examples are given for the purpose of illustrating the present invention. All of the dosage units specifically exemplified have been shown to swell and rupture in the manner desired according to the present invention. It is to be understood that the capsules described in some of these Examples contain barium sulphate and not a therapeutically active ingredient in order that their behaviour in the stomach and duodenum could be followed radiologically. However, as explained above, the capsules can contain any desired suitable therapeutically active agents and/or diagnostic agents. Furthermore, all the capsules in the following Examples were hand-filled and also measured about 28 mm. in length. Unless otherwise stated, all the percentages are by weight.

EXAMPLE 1

Each capsule contains:

barium sulphate	750 mg.
sodium chloride	125 mg
lactose	600 mg.
tartaric acid	15 mg.
sodium bicarbonate	15 mg.

The capsules, which were "00" gelatine capsules, were sealed with aqueous glycerinated gelatine. They were placed in a solution of formaline (50%) and alcohol (50%) for 30 minutes and then placed in ethanol and tested under vacuum for leakage. After washing with alcohol, the capsules were dried.

The capsules were placed in a tablet disintegration tester with simulated gastric juice. They swelled rapidly as soon as they were in contact with simulated gastric juice. At the end of 30 minutes, the capsules were removed from the tester and their bursting pressure determined. It was about 600 mm.Hg.

These capsules were found, radiologically, to remain intact in the stomach but to rupture just before entering the duodenum

EXAMPLE 2

Each capsule contains:

tartaric acid	1%
sodium bicarbonate	1%
barium sulphate or carbenoxolone sodium	98%

In this formulation, the tartaric acid reacts with the sodium bicarbonate upon contact with simulated gastric juice and liberates carbon dioxide which would keep the capsule inflated. The capsule was sealed, hardened and further processed as in Example 1.

EXAMPLE 3

Each capsule contains:

lactose	50%
barium sulphate or carbenoxolone sodium	50%

Lactose, which is rapidly soluble in gastric juice, but the large molecule of which does not readily pass through the semi-permeable capsule wall, maintains a high osmotic pressure inside the capsule. The osmotic pressure inside the capsule is intended to keep it inflated. The capsule was sealed, hardened and further processed as in Example 1.

EXAMPLE 4

Each capsule contains:

"Modocoll E 1200"	20%
Sodium chloride	10%
barium sulphate or carbenoxolone sodium	70%

("Modocoll" is a Registered Trade Mark).

"Modocoll E 1200" (ethyl hydroxyethyl cellulose) forms a colloidal suspension inside the capsule and is thereby intended to maintain the rigidity of the swollen capsule. Sodium chloride was included to maintain the osmotic pressure at the initial stage and to retard the swelling of the "Modocoll". The capsule was sealed, hardened and further processed as in Example 1.

EXAMPLE 5

Each capsule contains:

carbenoxolone sodium	50 mg.
lactose	730 mg.
sodium chloride	100 mg.
"Modocoll E 1200"	100 mg.
sodium bicarbonate	10 mg.
tartaric acid	10 mg.

The ingredients were mixed and encapsulated in size "00" gelatine capsules. The capsules were sealed with glycerinated gelatine and then hardened and processed as in Example 1.

EXAMPLE 6

Each capsule contains:

carbenoxolone sodium	50 mg.
lactose	550 mg.
potassium chloride	100 mg.
"Modocoll E 1200"	50 mg.
sodium bicarbonate	15 mg.
anhydrous citric acid	35 mg.

The ingredients are all dried in an oven prior to use. The carbenoxolone sodium, being very hygroscopic, is dried in a vacuum at 80° C. The potassium chloride and citric acid are reduced to fine powders. The potassium chloride, citric acid powder and the "Modocoll" are mixed together and then half of the lactose gradually added (powder I). The sodium bicarbonate is mixed with the carbenoxolone sodium and gradually added to the other half of the lactose (powder II). Powders I and II are then mixed together. This final mixture is encapsulated in size "00" gelatine capsules which are then sealed with glycerinated gelatine. The capsules are then hardened and processed as in Example 1.

EXAMPLE 7

Gelatine capsule hardened with formaldehyde

The capsule, which is a size "00" gelatine capsule of suitable length, is filled with 800 mg. lactose and sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum and subsequently washed thoroughly with alcohol and dried.

The capsule would swell slowly in the stomach. The swollen capsule, since it could not normally pass the pyloric orifice, would release its contents when burst by the presence of the pylorus.

EXAMPLE 8

Capsule containing a water-soluble drug

The capsule contains:

carbenoxolone sodium	50 mg.
lactose	800 mg.

The capsule, which is a size "00" gelatine capsule of suitable length, is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried. This capsule possesses similar physical properties to that produced in Example 7.

EXAMPLE 9

Capsule containing a water-insoluble drug

The capsule contains:

barium sulphate	300 mg.
lactose	800 mg.

The capsule, which is a size "00" gelatine capsule, of suitable length, is sealed with an aqueous solution of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried. This capsule possesses similar physical properties to that produced in Example 7.

EXAMPLE 10

Capsule containing a gas-generating mixture

The capsule contains:

mannitol	800 mg.
tartaric acid	10 mg.
sodium bicarbonate	10 mg.

The capsule, which is a size "00" gelatine capsule of suitable length, is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried.

This capsule swells within 15 minutes, after contacting with simulated gastric juice. The capsule would release its contents by being burst by the pressure of the pylorus.

EXAMPLE 11

Capsule containing a viscosity-producing agent

The capsule contains:

"Modocoll E 1200"	80 mg.
tartaric acid	20 mg.
sodium bicarbonate	20 mg.
sucrose	680 mg.

The capsule, which is a size "00" gelatine capsule of suitable length, is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried.

EXAMPLE 12

Capsule containing a water-soluble drug

The capsule contains:

carbenoxolone sodium	50 mg.
spray-dried lactose	610 mg.
"Modocoll E 1200"	80 mg.
tartaric acid	20 mg.
sodium bicarbonate	20 mg.
magnesium stearate	20 mg.

The capsule, which is a size "00" gelatine capsule extended to a length of about 27 mm., is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried.

The dosage units described in the above Examples provide excellent protection for their contents when they are exposed to the atmosphere; although the contents are spoiled by contact with moisture, they appear to be quite stable inside the capsule which was exposed to the atmosphere for three months.

WHAT WE CLAIM IS:—

1. A dosage unit, for the adminstration of medicaments and diagnostic agents, which can be swallowed comprising a distending agent which is either (a) a substance or mixture evolving gas on contact with gastric juice or (b) a substance which will exert an osmotic pressure when in aqueous solution or a mixture of (a) and (b), said distending agent being hermetically sealed in a polymeric, semi-permeable film which is resistant to attack by, but permeable to gastric juice, said dosage unit form swelling, without breaking, when in contact with gastric juices, to such a size as to be mechanically ruptured in the region of the pyloric sphincter.

2. A dosage unit, for the administration of medicaments and diagnostic agents, of such a size that it can be swallowed, which is not less than 20 mm. in overall length and which swells, without bursting, when placed in simulated gastric juice for not less than 30 minutes to an increase in volume of at least 50% and which, when so swollen, can be burst by a pressure of not less than 100 mm. Hg., said dosage unit comprising a distending agent which is either (a) a substance or mixture evolving gas on contact with gastric juice or (b) a substance which will exert an osmotic pressure when in aqueous solution or a mixture of (a) and (b), said distending agent being hermetically sealed in a polymeric, semi-permeable film which is resistant to attack by, but permeable to gastric juice.

3. A dosage unit according to claim 1 or 2, wherein the distending agent is admixed with a therapeutically active agent and/or a diagnostic agent.

4. A dosage unit according to any of the preceding claims, said dosage unit being in the form either of a sealed capsule of polymeric, semi-permeable material containing a therapeutically active agent and/or a diagnostic agent and a distending agent or in the form of a compressed tablet, which easily disintegrates, containing a therapeutically active agent and/or a diagnostic agent and a distending agent and enclosed in a polymeric semi-permeable material.

5. A dosage unit according to any of the preceding claims, wherein the substance or mixture evolving gas when in contact with gastric juice is sodium bicarbonate alone or in mixture with citric acid or tartaric acid.

6. A dosage unit according to any of the preceding claims, wherein the substance capable of producing a high osmotic pressure in the interior of said dosage unit is water-soluble salt or a sugar.

7. A dosage unit according to any of the preceding claims, wherein the dosage unit takes the form of a size "00" capsule.

8. A dosage unit according to claim 1, substantially as hereinbefore described and exemplified.

9. A process for preparing a dosage unit according to any of claims 1—8, wherein the distending agent and optionally also a therapeutically active agent and/or a diagnostic

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EXAMPLE 10

Capsule containing a gas-generating mixture

The capsule contains:

mannitol	800 mg.
tartaric acid	10 mg.
sodium bicarbonate	10 mg.

The capsule, which is a size "00" gelatine capsule of suitable length, is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried.

This capsule swells within 15 minutes, after contacting with simulated gastric juice. The capsule would release its contents by being burst by the pressure of the pylorus.

EXAMPLE 11

Capsule containing a viscosity-producing agent

The capsule contains:

"Modocoll E 1200"	80 mg.
tartaric acid	20 mg.
sodium bicarbonate	20 mg.
sucrose	680 mg.

The capsule, which is a size "00" gelatine capsule of suitable length, is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried.

EXAMPLE 12

Capsule containing a water-soluble drug

The capsule contains:

carbenoxolone sodium	50 mg.
spray-dried lactose	610 mg.
"Modocoll E 1200"	80 mg.
tartaric acid	20 mg.
sodium bicarbonate	20 mg.
magnesium stearate	20 mg.

The capsule, which is a size "00" gelatine capsule extended to a length of about 27 mm., is sealed with a band of gelatine. It is placed in a solution of formalin (50%) and alcohol (50%) for 30 minutes, then tested for leakage in alcohol under vacuum, washed thoroughly with alcohol and dried.

The dosage units described in the above Examples provide excellent protection for their contents when they are exposed to the atmosphere; although the contents are spoiled by contact with moisture, they appear to be quite stable inside the capsule which was exposed to the atmosphere for three months.

WHAT WE CLAIM IS:—

1. A dosage unit, for the adminstration of medicaments and diagnostic agents, which can be swallowed comprising a distending agent which is either (a) a substance or mixture evolving gas on contact with gastric juice or (b) a substance which will exert an osmotic pressure when in aqueous solution or a mixture of (a) and (b), said distending agent being hermetically sealed in a polymeric, semi-permeable film which is resistant to attack by, but permeable to gastric juice, said dosage unit form swelling, without breaking, when in contact with gastric juices, to such a size as to be mechanically ruptured in the region of the pyloric sphincter.

2. A dosage unit, for the administration of medicaments and diagnostic agents, of such a size that it can be swallowed, which is not less than 20 mm. in overall length and which swells, without bursting, when placed in simulated gastric juice for not less than 30 minutes to an increase in volume of at least 50% and which, when so swollen, can be burst by a pressure of not less than 100 mm. Hg., said dosage unit comprising a distending agent which is either (a) a substance or mixture evolving gas on contact with gastric juice or (b) a substance which will exert an osmotic pressure when in aqueous solution or a mixture of (a) and (b), said distending agent being hermetically sealed in a polymeric, semi-permeable film which is resistant to attack by, but permeable to gastric juice.

3. A dosage unit according to claim 1 or 2, wherein the distending agent is admixed with a therapeutically active agent and/or a diagnostic agent.

4. A dosage unit according to any of the preceding claims, said dosage unit being in the form either of a sealed capsule of polymeric, semi-permeable material containing a therapeutically active agent and/or a diagnostic agent and a distending agent or in the form of a compressed tablet, which easily disintegrates, containing a therapeutically active agent and/or a diagnostic agent and a distending agent and enclosed in a polymeric semi-permeable material.

5. A dosage unit according to any of the preceding claims, wherein the substance or mixture evolving gas when in contact with gastric juice is sodium bicarbonate alone or in mixture with citric acid or tartaric acid.

6. A dosage unit according to any of the preceding claims, wherein the substance capable of producing a high osmotic pressure in the interior of said dosage unit is water-soluble salt or a sugar.

7. A dosage unit according to any of the preceding claims, wherein the dosage unit takes the form of a size "00" capsule.

8. A dosage unit according to claim 1, substantially as hereinbefore described and exemplified.

9. A process for preparing a dosage unit according to any of claims 1—8, wherein the distending agent and optionally also a therapeutically active agent and/or a diagnostic

agent is sealed in a polymeric, semi-permeable film which is gelatine, partially or wholly hydrolysed polyvinyl acetate, a copolymer of vinyl alcohol and vinyl acetate, an ether or ester of cellulose or a plant mucilage or a mixture of such polymeric, semi-permeable materials, and said polymeric, semi-permeable film is hardened or otherwise treated to render it resistant to attack by but permeable to gastric juices.

10. A process according to claim 9, wherein the said treatment comprises treatment with an aqueous solution of formaldehyde and residual formaldehyde then washed out with a solvent or inactivated.

11. A process according to claim 10, wherein the aqueous formaldehyde solution used for treatment additionally contains an organic solvent.

12. A process according to claim 11, wherein the organic solvent is methanol, ethanol, industrial methylated spirits, isopropanol or acetone.

13. A process according to any of claims 10—12, wherein the solvent used for washing out residual formaldehyde is ethanol or industrial methylated spirits.

14. A process according to claim 11, wherein the formaldehyde is inactivated with gaseous ammonia or a solution of ammonia or of an ammonium salt in a non-aqueous or aqueous organic medium.

15. A process according to any of claims 9—14 for preparing a dosage unit in the form of a capsule, wherein said capsule is hermetically sealed by treatment with a solution of gelatine or of a cellulose ether, with or without the use of a plasticiser, or by placing a strip of polymeric, semi-permeable material over the join in the capsule.

16. A process according to any of claims 9—14 for preparing a dosage unit in the form of a tablet coated with a polymeric, semi-permeable material, wherein the coating is produced by press-coating the tablet with a polymeric, semi-permeable material and then hermetically sealed with a jet of steam.

17. A process according to any of claims 9—16, wherein the therapeutically active agent is carbenoxolone sodium.

18. A process according to claim 9, substantially as hereinbefore described and exemplified.

19. A dosage unit according to claim 1, whenever prepared by the process according to any of claims 9—18.

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