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[54] **SOLID PHARMACEUTICAL FORMULATIONS CONTAINING HYDROXYPROPYL METHYL CELLULOSE**

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[22] Filed: **Oct. 25, 1972**

[21] Appl. No.: **300,745**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 5,140, Jan. 22, 1970, abandoned, which is a continuation-in-part of Ser. No. 626.968, March 30, 1967, abandoned.

[52] **U.S. Cl.**..... **424/19,** 424/127, 424/178, 424/180, 424/182, 424/201, 424/241, 424/242, 424/243, 424/258, 424/272, 424/285, 424/298, 424/310, 424/330, 424/362

[51] **Int. Cl.. A61k 17/00,** A61k 21/00, A61k 27/00

[58] **Field of Search** 424/19, 127, 178, 180, 424/183, 201, 241, 248, 243, 258, 272, 285, 298, 310, 330, 362

[56] **References Cited**

UNITED STATES PATENTS

2,887,440	5/1959	Greminger et al.	424/362 X
2,949,401	8/1960	Wershaw	424/362 X
3,181,998	5/1965	Kanig	424/362 X
3,312,594	4/1967	Cyr et al.	424/362 X
3,424,842	1/1969	Nurnberg	424/238 X

Primary Examiner—Albert T. Meyers
Assistant Examiner—Leonard Schenkman

[57] **ABSTRACT**

A solid pharmaceutical composition in which the carrier consists essentially of hydroxypropylmethylcellulose, or hydroxypropylmethylcellulose admixed with up to about 20% ethylcellulose, is prepared by compressing a mixture comprising one therapeutic agent and the hydroxypropylmethylcellulose powder which has been humidified to a moisture content of from about 5 to about 25% by weight at a low compression pressure. The solid pharmaceutical composition obtained will release the active ingredient contained therein evenly over a prolonged period, e.g. from about 1 to 8 hours.

3 Claims, No Drawings

SOLID PHARMACEUTICAL FORMULATIONS CONTAINING HYDROXYPROPYL METHYL CELLULOSE

CROSS-REFERENCE

This is a continuation-in-part of U.S. application Ser. No. 5,140, filed Jan. 22, 1970 now abandoned, which, in turn, is a continuation-in-part of U.S. application Ser. No. 626,968, filed Mar. 30, 1967, now abandoned.

DETAILED DESCRIPTION

Sustained release products of conventional character are well known to the art and have been found to have a number of advantages. Specifically, the release of the medication contained therein is uniform and continuous over a period of time, thereby avoiding the necessity of frequent administration of the medicament while at the same time achieving a desired blood level of active ingredient. The preparation of sustained release compositions often requires a rather substantial and complicated procedure and often the degree of predictability and the release pattern are less than optimum.

The use of cellulose derivatives such as hydroxypropylmethylcellulose as an ingredient in pharmacetical formulations is of course known. Thus U.S. Pat. No. 3,266,992 describes the incorporation of up to 30% of various cellulose derivatives such as methylcellulose, sodium carboxymethylcellulose and hydroxyethylcellulose, the particular derivative depending upon the nature of the therapeutic agent, into tablets to effect rapid disintegration thereof. U.S. Pat. No. 2,887,440 on the other hand discloses the use of hydroxypropylmethylcellulose in enteric coatings to prevent disintegration of the tablet core. It has also been recognized that methylcellulose might itself be a desirable material for certain pharmaceutical formulations but attempts at achieving such products have not met with success. Thus U.S. Pat. No. 2,949,401 recognizes the desirable properties of methylcellulose in a buccal tablet containing vitamin A but limits the amount to from 3 to 5%. Trotter and coworkers report several unsuccessful attempts at directly compressing methylcellulose into a troche and succeeded only by incorporating 25% superfine sugar with the methylcellulose. *Amer. Jour. Pharm*, February 1956, pp. 50–56. The combination of cellulose derivatives with large amounts of lactose is also described in U.S. Pat. No. 3,344,030. U.S. Pat. No. 3,590,117 reports the unsatisfactory nature of hydroxypropylmethylcellulose for troches. U.S. Pat. No. 3,312,594 describes troches containing carboxymethylcellulose but only in combination with equal amounts of pectin and gelatin.

The present invention relates to a long-acting sustained dosage unit, and the carriers and active ingredients in the composition thereof, presented in a solid coherent form. The long-acting dosage unit contains at least one active ingredient compressed with a mixture containing a moisturized carrier consisting esentially of 100 to 80% by weight of hydroxypropylmethylcellulose and optionally 0 to 20% by weight of ethylcellulose. The carrier ingredient during use gradually releases the active ingredient by contact with fluids, such as saliva, gastric juices, and other natural secretions and does so over an extended period, e.g., about 1 to 8 hours. In one aspect the invention comprises a long-acting troche, lozenge or tablet. The solid pharmaceutical form according to the present invention can however be utilized in other routes of administration in addition to buccal. Thus the solid form may be administered orally as a tablet to be swallowed or rectally or vaginally as a suppository.

Specifically, the carrier is hydroxypropylmethylcellulose which has been humidified under controlled conditions to a moisture content of from about 5 to about 25% by weight. This material, optionally containing ethylcellulose, can then be compressed at a low pressure, e.g. only 5 to 8 pounds per square inch, which, because of the moisture content, is sufficient to shape the material into a solid coherent pharmaceutical form such as a troche to be sucked or used in the oral cavity so as to effect a gradual release of the active therapeutic ingredient which is absorbed through the oral mucosa through the blood stream. Higher degrees of compression, e.g., up to about 30 pounds per square inch, yield a harder and more long lasting composition as might be desired for example in a suppository to be inserted in the rectum or vagina, or a tablet to be simply swallowed.

According to the present invention it has now been found that a reliable and effective long acting sustained action solid dosage unit can be very simply made by compressing an appropriate amount of practically any desired active ingredient or medicament with a premoisturized hydroxypropylmethylcellulose powder or with a mixture of a combination of moisturized hydroxypropylmethylcellulose and ethylcellulose powder. The release time, the dosage unit and pattern of release can be controlled by the relative amounts of hydroxypropylmethylcellulose and ethylcellulose employed, the size and weight of the tablet product, the degree of compression or a combination thereof, bearing in mind that a high degree of moisturization permits the use of low compression pressures, and visa versa, for the blend of active ingredient and cellulose powder and that increased compression increases the composition's span of action. It is thus an important feature of the present invention that a sustained release product can be readily and easily prepared containing, as the sole carrier, varying amounts of hydroxypropylmethylcellulose and ethylcellulose having a predetermined moisture content and that by controlled variation of the moisture content of the alkylated cellulose carrier powder, the duration of the release period of the active medicament held in the compacted tablet may be controlled. The release of the active ingredient is, therefore, controlled by the size and the weight, moisture content and degree of compression pressure exercised on the lozenge, suppository or tablet at the time it is being formed from the pre-wetted powder and active medicament.

In general, the long acting carrier products of the present invention are produced by combining the appropriate amount of active ingredient into the shape of troches, lozenges, tablets or suppositories with a mixture of from about 100–80% by weight of hydroxypropylmethylcellulose and from about 0–20% by weight of ethylcellulose. The product can also contain adjuvants such as a synthetic sweetening agent as for example saccharin, a nontoxic food grade color such as FD&C Yellow No. 10, a flavoring agent such as cherry flavor and a preservative such as p-methylbenzoic acid. The only criterion for the addition of such materials is that they do not tend to dehydrate

the product before or after it is tableted by compression techniques.

Specific techniques for the manufacture and use of the long acting carrier will be set forth in greater detail below but an illustration of the improved activity of the product may briefly be noted by the following illustration. For example, a 5 grain lozenge when held in the mouth will release its active ingredient in a regular manner over a period of one and one-and-one-half hours by dissolution or disintegration of the lozenge by the saliva fluids. If the same lozenge is inserted in the upper cavity of the mouth, the release then can be extended to 3 hours. Moreover a shaped product or tablet of the present invention which has a weight of about 10 grains is noted to take almost twice as long to release its active ingredient as a 5 grain product.

When used as a lozenge, release through the action of the saliva is continuous and the active ingredient then passes through the gastro-intestinal tract into the blood stream. However, when the composition is positioned in the buccal pouch, absorption of the active ingredient takes place through the mucosa membrane lining the pouch directly through the capillaries in the blood stream.

A similar pattern can be observed when the solid pharamaceutical form takes the form of a suppository. Here again the exclusive carrier has highly desirable properties in that it is non-irritating, substantially neutral and adherent.

While the solid pharmaceutical forms of the present invention intended for oral administration; i.e., tablets to be swallowed, will be subjected to the effects of both gastric and intestinal fluids and mechanical wear within the gastrointestinal tract, a prolonged rate of release is also seen here.

The invention has flexibility and versatility dependent upon the particular nature of the active ingredient which is to be dispensed, the treatment or condition for which the active ingredient is indicated, the route of administration and the desired length of release time of the active ingredient. It has been found that one may for example prepare a 50 lb. mixture for the production of long acting troches from a composition indicated in the following Table:

TABLE

No.	Make of Materials	Lbs.	Ozs.	Grs.
1	0.10% Calcium Cyclamate			350
2	1.00% Cherry Flavor		8	
3	0.10% Methyl Paraben			350
4	0.01% Propyl Paraben			35
5	0.50% Lake Dye Red No. 2		4	
6	Mixture of 85% Methocel HG 60 (20% of H_2O), premium viscosity 50 and 15% Ethylcellulose N50	49	2	140

With respect to the foregoing Table, it is to be understood that the calcium cyclamate ingredient can be replaced by sodium cyclamate or other suitable food grade, nontoxic synthetic sweetening agent such as saccharin. A different flavoring material obviously can be substituted for the cherry flavor and other approved colors can be used in place of the Lake Dye Red No. 2. It is further to be understood that the invention is not limited to the preferred use of 85% by weight hydroxypropylmethylcellulose and 15% by weight of ethylcellulose because variations in the relative proportions are not only permissible but are intended as these variations affect the release time and pattern of the active ingredient.

In preparing troches from the above mixture, items 1, 2, 3 and 4 are weighed out and thoroughly mixed. Item 5, which is the food grade dye, is placed in a mortar and rubbed with some of the mixture of Items 1, 2, 3 and 4 following which the remainder of Items 1, 2, 3 and 4 is added and the rubbing is conducted until a homogenous blend is obtained. Item 6, which is the specified cellulose powder mixture, is added to the previously produced mixtures of Items 1, 2, 3, 4 and 5 and the entire composition is blended until uniformity is achieved. The uniform dry mixture of ingredients is then spread out on trays and thoroughly sprayed with a 35% mixture of ethanol and distilled water. The thus treated mixture is allowed to dry overnight and is then ground on a Fitzpatrick mill to an average 20–40 mesh particle size. The powder derived from the Fitzpatrick mill is next placed on trays which trays are put into a steam room and held there overnight under conditions of very high humidity for the express purpose of creating in the previously dry blend, certain moisture levels which are important in the ultimate performance of each tablet in simultaneously maintaining its integrity and sustained even release of active ingredient. As a means of maintaining the desired humidity at a fixed level in the powder, trays filled with water are placed in the steam room to maintain the even consistency of the humidity level to insure adequate wetting of the powder. The room temperature is about 75°F and humidity is maintained between about 78 to 82% for 24 hours (overnight). The resulting material will have a moisture content from about 20 to about 25% by weight.

After a constant moisture level is thus achieved, the active ingredient is added and the entire batch of material is placed in the hopper of a conventional tableting machine which is set up with half-inch punches and dies and the machine is adjusted and regulated for 8 pounds of pressure per square inch and for product size. In this manner, 7½ grain or 10 grain tablets preferably, are produced and by following the same procedure, but suitably further adjusting the machine, 12 grain or other size tablets are produced.

Alternatively, the procedure is carried out by introducing the hydroxypropylmethylcellulose or a mixture of the hydroxypropylmethylcellulose with ethylcellulose into an oven chamber having an exhaust aperture which is at that time in closed or shut position. The chamber is provided with a heating unit and a forced air blower, which is inoperative at this stage of the procedure, the heat and forced air being applied at a subsequent stage. The material to be processed is placed in thin layers (not more than ¼ inch thick) on trays of the oven chamber which are lined with heat-resistant parchment paper and the trays are placed on racks in the oven chamber using only alternate shelves, thereby providing a predetermined amount of spacing between the layers of material being treated. There is then placed within the oven chamber a humidifier equipped with a humidistat which is pre-set to maintain humidity in the oven chamber at 85 – 90%, the humidifier being filled with sufficient distilled or deionized water to last for 24 to 36 hours. The humidifier is now activated and the oven chamber is closed and the process is allowed to proceed under the 85 –90% humidity for a minimum

of 24 hours. Humidification can be continued for up to 36 hours or even longer if desired, although there is no special advantage in exceeding 36 hours and unduly extended times are apt to be uneconomical, but the treatment should be continued at least about 24 hours. The humidifier is then removed from the oven chamber, the exhaust aperture opened by manipulation of the valve and the forced air blower is activated thereby applying heat at a controlled temperature in the range of 100° to 120°F (43° to 49°C). The moisture content will then decrease, depending upon the length of time the material is treated with the hot air. At the end of 12 hours for example the moisture content of the treated material is at its lowest limit of the range, about 5%. This is not an exact limit since this added moisture content can be as low as 4 or 4½%, as determined by a standard moisture determination apparatus. The 12-hour period just referred to is also approximate as the duration of the period may vary somewhat above or below 12 hours, but it has been found in practice that the period should not exceed approximately 12 hours.

When the required added moisture content is achieved, the treated material is removed from the oven and passed through a No. 2 stainless steel screen employing a Fitzpatrick mill and processed as described above.

Variations in the two extremes are of course readily apparent, the critical factor being that the hydroxypropylmethylcellulose is so treated that its moisture content is stabilized at a higher level than is normally encountered.

The hydroxypropylmethylcellulose preferably employed is identified as Methocel HG 60 which is a commercial methylcellulose product manufactured by the Dow Chemical Company, Midland, Michigan and has a methoxyl percentage of 28 to 30%, a hydroxypropoxyl percentage of 7 to 12%, is soluble in water and organic solvents, has a normal gel temperature of 60°F and demonstrates an average viscosity of 50 centipoises (range 40 to 60, 2% aqueous solution).

As regards the ethylcellulose, this material corresponds to that defined in the National Formulary XIII with a standard ethoxy content ranging between 44.0 and 51.0%, preferably 48–49.5%, by weight. The preferred material corresponds to ethylcellulose N50, the number N50 indicating the viscosity in centipoises of a 5% by weight solution of the product in a 80/20 toluene/ethanol solvent at a temperature of 25°C. These viscosity numbers are indicative of the size of the ethylcellulose molecules, the larger the molecule, the greater the viscosity and can be further referred to in the standard charts on the products which are readily available.

The active ingredient may be of any suitable nature such as insulin, vitamins, hormones, analgesics, local anesthetics, epinephrine, antiinflammatory steroids, progestational agents, antibiotics, antiseptics, antimycotics, antacids and the like. The nature of the therapeutic agent is not critical and any drug, or stable combination of drugs, can be incorporated into these novel pharmaceutical forms. This is particularly important since some active medicaments such as insulin, antidiuretic hormones and epinephrine become inactivated when incorporated into conventional or previously known sustained release products where the products are swallowed and the release occurs in the gastric fluids or in the intestinal fluids or in a combination of both. Some active agents such as ACTH, epinephrine, vitamin B_{12}, iron insulin, antidiuretic hormones, prednisolone and nitroglycerine as well as antiobesity agents and antacids can, in accordance with the present invention, be administered via the transmucosal absorption route. However those therapuetic agents which are active when swallowed, can also be administered in the new pharmaceutical carrier of the present invention, the composition being used exactly like a conventional tablet. Similarly, antimicrobial agents such as furazolidone and nifuroxime can be administered in a vaginal suppository. Products of the present invention are also useful as demulcents in the treatment of painful ulcerations, inflammations, and irritations. These effects have been shown by in vitro and in vivo clinical tests.

Moreover, it can be shown by X-ray studies a tablet prepared according to the present invention for very long release, while gradually dissolving remains coherent for most of its passage through the gastro-intestinal tract. Hence a tablet of the moisturized hydroxypropylmethylcellulose and barium sulfate (as an X-ray contrast agent) having a total weight of 600 mg, a diameter of 12.7 mm, a thickness of 3.15 mm and a hardness of 6.6 lbs/in^2 can still be seen in X-rays for more than 5 hours after administration. A typical progression is as follows:

1 hr.	small intestine
1 hr. 35 min.	do.
2 hr. 20 min.	do.
5 hr. 10 min.	caecum

Since the therapeutic agent is being continuously released, the observed period of activity will be even longer than this.

The invention is further illustrated by the following non-limitative examples:

EXAMPLES 1–11

SUSTAINED RELEASE TROCHE FORMULATIONS

50 LB. MIXTURE FOR 50,000 TABLETS AT 7 GRAINS

EXAMPLE 1

PREDNISOLONE, 4 MG.

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Prednisolone		7	60
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 20% by weight	48	11	80

EXAMPLE 2

EPINEPHRINE, 1 MG

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Epinephrine		1	330
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60	49		245

EXAMPLE 2-Continued

EPINEPHRINE, 1 MG

No.	Make of Materials	Lbs.	Ozs.	Grs.
	hydroxypropylmethylcellulose, premium,viscosity 50 moisture 20% by weight			

EXAMPLE 3

DIBUCAINE, 3 MG

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Dibucaine		5	150
2.	0.10% Calcium cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose premium,viscosity 50 moisture 20% by weight	48	12	440

EXAMPLE 4

BENZOCAINE, 20 MG

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Benzocaine	2	3	300
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose premium, viscosity 50 moisture 20% by weight	46	14	290

EXAMPLE 5

TRIAMCINOLONE ACETONIDE, 0.25 MG

No.	Make of Materials	Lbs.	Ozs.	Grs
1.	Triamcinolone Acetonide			188
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose premium, viscosity 50 moisture 20% by weight	49	1	402

EXAMPLE 6

HEPARIN, 50 MG

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Heparin	5	8	165
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose premium, viscosity 50, moisture 20% by weight	35	5	210
8.	Ethocel N50 ethylcellulose	9	2	70

EXAMPLE 7

VITAMIN B_{12}, 1000 MCG

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Vitamin B_{12}		1	330
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcelluose premium, viscosity 50 moisture 20% by weight	41	10	195
8.	Ethocel N50 ethylcellulose	8	3	345

EXAMPLE 8

INSULIN, 250 INT. UNITS

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Insulin		1	330
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50 moisture 20% by weight			

EXAMPLE 9

SODIUM BICARBONATE, 0.3 GM — GRAIN TABLETS

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	Sodium Bicarbonate	33	1	23
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose premium, viscosity 50 moisture 20% by weight	53		
8.	Ethocel N50 ethylcellulose	13	14	412

EXAMPLE 10

d-DESOXYEPHEDRINE HYDROCHLORIDE, 5 MG

No.	Make of Materials	Lbs.	Ozs.	Grs.
1.	d-Desoxyephedrine Hydrochloride		8	390
2.	0.10% Calcium Cyclamate			350
3.	1.00% Cherry Flavor		8	
4.	0.10% Methyl Paraben			350
5.	0.01% Propyl Paraben			35
6.	0.50% Lake Dye Red No. 2		4	
7.	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50 moisture 20% by weight	49	7	45

In examples 1 – 10, the calcium cyclamate can be replaced by 0.1 the amount of sodium saccharin while the Lake Dye Red No. 2 can be replaced by another pharmaceutically acceptable coloring agent or omitted altogether from the formulation.

EXAMPLE 11
REPRESENTATIVE RELEASE PATTERNS

260 individual tests have been made on 31 subjects with both lozenges and tablets inserted either in the buccal pouch on held sublingually, and show the following results:

LOZENGES	
1. Partial dissolution time	Medium range per 1/10 gram carrier, 15.8 to 21.5 minutes.
2. Total dissolution time.	Medium range per 7 grain lozenge, 81 to 108 minutes.
3. Total dissolution time.	Medium range per 14 grain tablet, 158 to 215 minutes.

TABLETS INSERTED IN BUCCAL POUCH OR USED SUBLINGUALLY	
1. Partial dissolution time.	Medium range per 1/10 gram carrier, 29.4 to 42.1 minutes.
2. Total dissolution time.	Medium range per 7 grain tablet, 149 to 212 minutes.
3. Total dissolution time.	Medium range per 14 grain tablet, 294 to 421 minutes.

EXAMPLE 12

	Analgesic Tablet Ingredients	mg/tablet
1	Aspirin powder U.S.P.	525.0
2	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 5% by weight	325.5
3.	Glycine	45.0
4.	Syloid 244 micron size silica	4.5

Ingredients 1, 2 and 3 are mixed in a bowl into which ingredient 4 is added after screening and the whole blended for 20 minutes and compressed in a tableting machine having a one-half inch die size and a one-half inch punch to make tablets with an average weight of 0.9 g and a thickness of 0.210 ± 0.01 inch. The hardness of the tablet was 22–28.6 lbs/square inch.

EXAMPLE 13

	Antihistamine Tablet Ingredients	mg/tablet
1	Chlorpheniramine maleate U.S.P.	12.60
2	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 4½% by weight	509.20
3	Methyl paraben U.S.P	0.52
4	Propyl paraben U.S.P.	0.06
5	Syloid 244 micron size silica	2.63

Ingredient 2 was placed in a container and ingredients 1, 3, 4 and 5 were weighed out and added after screening and the whole blended for 20 minutes. The compression into tablets was conducted on a tableting machine using a die size of seven-sixteenths inch with a pound of seven-sixteenths inch to obtain a tablet thickness of 0.250 ± 0.01 inch with a tablet hardness of 22–28.6 lbs/square inch. Each tablet weighed 0.525 g.

EXAMPLE 14

	Laxative Tablet Ingredients	mg/tablet
1	Phenolphthalein U.S.P.	33.0
2	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 5% by weight	513.64
3	Methyl paraben U.S.P.	0.55
4	Propyl paraben U.S.P.	0.06
5	Syloid 244	2.75

Ingredients 1 and 2 were placed in a stainless steel vessel to which, after screening, were added ingredients 3, 4 and 5 and the whole blended for 20 minutes and compressed as in Example 13. The tablet thickness was 0.250 ± 0.01 inch and the hardness was 22.2 lbs/square inch. Each tablet weighed 0.55 g.

EXAMPLE 15

	Laxative Tablet Ingredients	mg/tablet
1	Phenolphthalein U.S.P.	66.0
2	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 4% by weight	480.64
3	Methyl paraben U.S.P.	0.55
4	Propyl paraben U.S.P.	0.06
5	Syloid 244	2.75

The same procedure was followed as in Example 13 with the same results.

EXAMPLE 16

	Vitamin Tablet Ingredients	mg/tablet
1	Ascorbic acid, U.S.P., powder	105
2	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 5% by weight	691
3	Syloid 244	4

Ingredients 1 and 2 were weighed out as in the preceding examples and placed into a stainless steel bowl into which ingredient 3 was added after screening and the whole blended for 20 minutes and compressed as previously described. The tablets had a thickness of 0.210 ± 0.01 inch and a hardness of 22.2–28.6 lbs/square inch. Each tablet weighed 0.8 g.

EXAMPLE 17

	Ingredients	Amount/Suppository
1	Furazolidone	0.005 g
2	Nifuroxime	0.007 g
3	Methocel HG 60 hydroxypropylmethylcellulose, premium, viscosity 50, moisture 7.5% by weight	1.988 g

The ingredients are thoroughly mixed and compressed in a similar fashion to that described above utilizing however a suppository mold to yield a vaginal suppository weighing 2 g.

EXAMPLE 18

	Ingredients	Amount/Suppository
1	Prednisolone	5.25 mg
2	Methocel HG 60 hydroxypropylmethylcellulose premium, viscosity 50, moisture 7.5% by weight	1131.90 mg
3	Syloid 244	2.85 mg

The above ingredients are mixed and thoroughly blended for 30 minutes and then compressed to form rectal suppositories of 1.14 g each.

What is claimed is:

1. A method of preparing a long-acting compressed buccal composition for the administration of transmucosally absorbed therapeutic agents consisting essentially of the therapeutic agent and a carrier which comprises subjecting an effective amount of a dry carrier consisting of from 80 to 100% of hydroxypropyl methyl cellulose having a methoxyl content of 28 to 30% and a hydroxypropyl content of 7 to 12% and from 20 to 0% of ethyl cellulose having an ethoxy content of 48 to 49.5% to controlled humidity for a time sufficient to establish a moisture content of from about 5 to about 25%, mixing the moisturized carrier with a therapeutically effective amount of the therapeutic agent and compressing the mixture into solid shaped units at a pressure of from about 5 to about 8 pounds per square inch.

2. The product prepared by the process of claim **1.**

3. The product of claim **1** which additionally contains a synthetic sweetening agent, a coloring agent, a flavoring agent and a preservative.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,870,790

DATED : March 11, 1975

INVENTOR(S) : Hans Lowey & Herbert Henry Stafford

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In Examples 6, 7 and 9, the last line of each should read N50 Ethylcellulose by deleting "Ethocel".

Signed and Sealed this

Tenth Day of August 1976

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks