Sept. 17, 1968 R. A. CAIN ET AL 3,402,240

MEDICINAL TABLET AND PROCESS OF MAKING SAME

Filed June 25, 1957

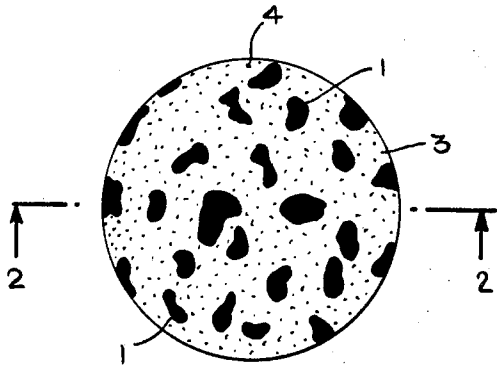

FIG. 1

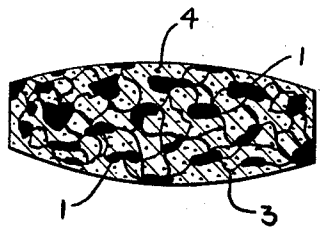

FIG. 2

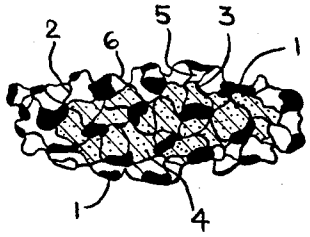

FIG. 3

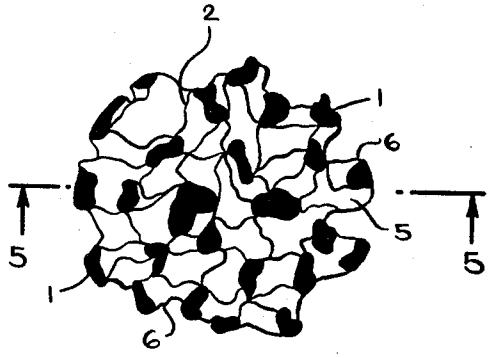

FIG. 4

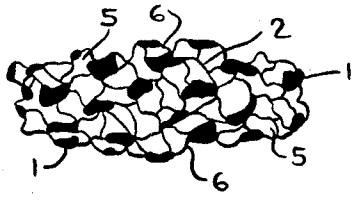

FIG. 5

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United States Patent Office 3,402,240
Patented Sept. 17, 1968

3,402,240

MEDICINAL TABLET AND PROCESS OF MAKING SAME

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Filed June 25, 1957, Ser. No. 667,908
4 Claims. (Cl. 424—22)

The object of this invention is to provide a tablet containing a predetermined amount of a therapeutic active agent or drug to be administered to a patient and when taken internally will initially release a small but therapeutically effective portion of the agent or drug and thereafter continue to slowly and gradually release the agent or drug over many hours.

Such slow release provides desirable body or blood levels of the active ingredient or ingredients, thereby providing a single administration which remains active particularly during normal periods of work or sleep which is desirable as the necessity of taking repeated doses in shorter periods is eliminated.

The tablet of this invention is useful in putting up and administrating many therapeutic agents and drugs some of which, for illustrative purposes, are organic nitrites, sympathomimetic amines, barbituric acid derivatives, salicylates, xanthine derivatives, and many others.

In preparing such tablets standard mixing machines, tableting machines and other standard equipment, with which pharmaceutical houses are provided, may be used.

The tablet of this invention comprises a matrix substantially insoluble in gastric and intestinal juices, a therapeutically bland or inert filler or extender and an active therapeutic agent or agents or drugs. The matrix is constituted of such materials as carnauba wax, candelilla wax, esparto wax, or ouricury wax, which have melting points between about 68° and 90° C. Other materials which can be used are spermaceti, stearic acid and other edible hard and non-toxic waxes and materials mixed with one or more of the first mentioned group of waxes to provide a matrix having a melting point between approximately 65° and 90° C. These relatively low melting point materials can be satisfactorily mixed with carnauba wax or some other high melting point wax to provide a material for the matrix having the desired melting points. Synthetic waxes such as Durawax 1032 (M.P. about 84–86° C.) can also be used as the matrix. For practical purposes carnauba wax is preferred.

The filler or extender may be any one of the standard materials used in making medicinal tablets, such as calcium or sodium phosphate dibasic, magnesium stearate (serving also as a lubricant in tableting), calcium phosphate tribasic, talc, calcium oxide, calcium stearate, sodium stearate and starch and mixtures thereof as now used in the making of tablets and methylcellulose (serving also as a swelling agent in the gastrointestinal tract).

The active therapeutic agent or drug may be such as are generally used in medicine, examples whereof in treating known diseases are:

Coronary and circulatory medicaments

Erythrityl tetranitrate (Erythrol Tetranitrate, Merck).
Pentaerythritol tetranitrate (Warner-Chilcott).
Mannitol hexanitrate (Hexanitrol and Manartal).
Glyceryl trinitrate (U.S.P.).
Triethanolamine trinitrate biphosphate (Metamine).

Analgesics

Neocinchophen (Novatophan).
Acetophenetidin and acetyl salicylic acid, phenobarbital and hyoscyamine sulfate (Phenophen).
Antipyrine.

Salicylamide.
Sodium, potassium, magnesium and lithium salicylate.

Barbiturates and related hypnotics

Acetylcarbromal (Abasin).
Allyl-isopropyl-barbituric acid and acetophenetidin (Allonal).
Isoamyl-ethylbarbituric acid (Amytal).
Monosodium-isoamyl-ethyl barbiturate (Sodium Amytal).
Carbromal and sodium pentobarbital (Carbrital).
Cyclopentonyl allylbarbituric acid (Cyclopal).
N-methyl cyclohexenylmethyl barbituric acid and acetyl salicylic acid (Evicyl).
N-methylethylphenylbarbituric acid (Mebaral).
3-methyl-5,5-phenylethylhylantoin (Mesantoin).
5N-butyl-5-ethylbarbituric acid (Neonal).
Mono sodium 5-allyl-5-(1 methyl butyl) barbiturate (Seconal Sodium).
5-ethyl-5-(1 methyl propyl) barbituric acid (Butabarbital).
Barbital (Veronal).
Amobarbital.
Trimethadione.

Sympathomimetic compounds

Neo-synephrine hydrochloride phenobarbital and aminophylline (Adnephrin).
D1-alpha methyl-beta-phenylethylamine sulfate (Benzedrine Sulfate).
D-alpha methyl-beta-phenylethylamine sulfate (Dexedrine Sulfate).
Benzylephedrine phenobarbital and theophylline (Franol).
1-(3′,4′-dihydroxyphenyl) - 2 - isopropylamino - ethanol hydrochloride (Isuprel).
d-Desoxyephedrine hydrochloride (Methedrine).
Beta (ortho - methoxyphenyl) - isopropylmethylamine (Orthoxine Hydrochloride).
p - Hydroxy - alpha - methylphenethylamine hydrobromide (Poredrine Hydrobromide).
p-Methylamino-ethanolphenol tartrate (Sympatol).

Parasympathomimetic compounds

Acetyl-beta-methylcholine bromide (Mecholyl Bromide).
3-dimethylcarbamoxyphenyl trimethyl ammonium bromide (Prostigmin Bromide).
Bethanechol chloride (Urecholine Chloride).

Sulfonamides

Sulfadizine and sulfamerazine (Diamerzine).
Sulfadiazine and sulfathiazole (Disulfa-Vess).
Succinylsulfathiazole (Sulfasuxidine).
Sulfadiazine, sulfamerazine and sulfamethazine (Terfonyl).

Histamine and antihistamine like agents

Phenazoline hydrochloride (Antistine).
Diphenhydramine hydrochloride (Benadryl).
Chloroprophenpyridamine maleate (Chor-Trimeton).
N,N-dimethyl-N′-benzyl-N′-(alpha-pyridylethylenediamine hydrochloride (Pyribenzamine).
2-methyl-9-phenyl-2,3,4,9-tetra-hydro-1-pyridindene hydrogen tartrate (Thephorin).
Aspirin or sodium salicylate.

Cardiac glycosides

Digitoxin (Cardigin).
Lanatoside C (Cedilanid).
Glycosides of digitalis leaves (Digalin).

Alkaloids

Meperidine hydrochloride (Demerol Hydrochloride).
Ethylmorphone hydrochloride (Dionin).
Dihydrocodeinone bitartrate (Hycodan Bitartrate).
Chloroquine diphosphate (Aralen Diphosphate).
Chloroguanide hydrochloride (Guanatol Hydrochloride).
Quinidine sulfate (Quincardine).
Hyoscyamine hydrobromide (Delkadon).
Homatropine methyl bromide and sodium phenobarbital (Homabital).
Atropine methyl nitrate (Eumydrin).
Beta diethylaminoethyl fluorene-9-carboxylate hydrochloride (Pavatrine).
Benzazoline hydrochloride (Priscoline).
Diphenylacetyl diethylaminoethanol hydrochloride (Trasentine).

Central nervous system stimulants

Theobromine sodium acetate (Agurin).
Theophylline-calcium salicylate (Phyllicin).
Theobromine and luminol (Theominol).
Theophylline isopropanolamine (Theopropanol).

Hormone

Ethinyl estradiol.

Antibiotics

Aluminum penicillin.
Bacitracin (Baci-Troche).
Chloramphenicol (Chloromycetin).
Procaine penicillin (Duracillin).
Gramacidin (Gramolets).
Potassium penicillin G (Neocillin).
Sodium penicillin G (Penalev Tablets).
Tyrothricin.
Aecreomycin hydrochloride.

The foregoing therapeutic agents and drugs are given only as examples of preparations and compounds which can be used in the tablets of this invention. The proportions of the active agent in each aforementioned product are known and are set forth in Remington's Practice of Pharmacy (10th ed.) to which reference is made.

The amount of the active agent can be increased as the pharmaceutical manufacturer may in his judgment determine and may be increased to as much as 50% over the amount set forth in the following examples or as set forth in the aforementioned publication.

The following is a detailed description of the materials used and the procedure followed in preparing the tablets using the specific active ingredients referred to in Example 1 hereof.

(1) The selected wax, preferably carnauba, in amount of 44 lbs. and 1 oz., in powdered form, is passed through a #30 mesh screen.

(2) Calcium phosphate tribasic, in amount of 61 lbs. and 11 oz., talc 8 lbs. and 13 oz., together with the carnauba wax of step 1, are mixed in a standard mixer for 15 minutes.

(3) Glucose in amount of 8 lbs. and 13 oz. and about 18,000 cc. of deionized water are stirred together with a paddle to facilitate dissolving the glucose and when nearly dissolved the mixture is stirred with an electric mixer until complete solution is obtained.

(4) The glucose solution is added to the mixed dry powders in the mixer in four equal amounts with fifteen minutes of stirring between each addition. If necessary, to obtain satisfactory granulation, an additional amount of deionized water may be found necessary.

(5) Mixing is continued for about one and one-half hours after the last addition of the glucose solution.

(6) The moist granulation is removed from the mixer and spread on trays and partially dried in an oven at 130° F.

(7) The partially dried granulation is passed through an oscillator fitted with a #6 sieve, then spread on trays and again dried in an oven at 120° F. for 4 or 5 hours until perfectly dry.

(8) Magnesium stearate in amount of 10 lbs. and 12 oz., 1 lb. and 10 oz. of methylcellulose and 9 lbs. and 4 oz. of pure triethanolamine trinitrate biphosphate are mixed to a uniform powder mixture.

(9) The dry granulation of step 7 is passed through an oscillator fitted with a #30 sieve and the uniform powder mixture of step 8 is added thereto intermittently.

(10) The granulation of step 9 is then transferred to a mixer and mixed for one hour.

(11) It is preferred to take a small portion of the granulation and convert it into tablets and make an initial assay thereof.

(12) The granulation of step 10 is then converted into tablets by the use of a standard tableting machine, such as a Stokes Rotary Tablet Machine.

The finished tablets will comprise the matrix consisting of an aggregate of the ground carnauba wax having interconnecting voids therein, in which are embedded an intimate mixture of the active ingredient and the filler.

Each tablet thus prepared consists of wax, about 30.45%; active ingredient, about 6.10%; filler, about 57.35%; and glucose as a binder, about 6.10%.

It is to be noted that the amount of wax is comparatively high with respect to the amount of active ingredient and filler.

Such a tablet as it comes from the tableting machine will have exposed on its surfaces part of the matrix, part of the filler and small particles of the active ingredient. The matrix forms a skeleton in the spaces of which the filler and active ingredient particles are distributed in mixed intimate relation.

When a tablet is taken into the human system the gastrointestinal juices will first attack the surface of the tablet and leach out the particles of the active ingredient lying on the surfaces of the tablet which will forthwith give the patient an initial therapeutic action. The gastrointestinal juices will continue to attack the filler and active ingredient and gradually and slowly leach or remove them from the tablet. Such process of leaching out the active ingredient will proceed, together with the removal of the filler, at a very slow and substantially uniform rate. The material of the matrix is not substantially affected by the processes of the stomach and intestines, retaining substantially its matrix form. Inasmuch as the active material is embedded throughout the matrix, and in the filler, the release thereof is slow but continuous and will provide a body or blood level of the active ingredient over the entire period during which the leaching operation takes place. A tablet such as above described having a weight of between 150 and 165 mg. will give the required action of the active ingredient over a period of from 8 to 9 hours, sufficient to provide a patient with medication during normal sleeping or working periods. In fact, the therapeutic effect of the active ingredient will continue for a number of hours after the leaching-out process has been substantially completed.

The accompanying drawings illustrate a tablet in its various phases from directly after tableting to completion of the leaching-out of the active ingredient and the removal of the filler as appears from treatment of tablets in simulated gastrointestinal juices in a standard device for so testing tablets.

FIG. 1 represents a face view of a finished tablet as it comes from the tableting machine; FIG. 2 is a cross-section on the line 2—2 of FIG. 1; FIG. 3 is a section of the tablet after about 1 hour of treatment in simulated gastric juice; FIG. 4 is a face view of the matrix after the tablet has been treated in simulated intestinal juice and the active ingredient leached therefrom; FIG. 5 is a cross-section on the line 5—5 of FIG. 4.

The waxy material 1 of the matrix 2 constitutes about 31% of the tablet by weight, the filler 3 constitutes about 57%, the active ingredient 4 about 6.10%, and the balance

binder (not represented). As the active ingredient is leached out of the matrix and filler removed, at the surface of the matrix the matrix exhibits a series of voids 5 which as leaching and removal of filler continues become more and more deep until after a period of from 8 to 9 hours the matrix represents the skeleton shown in FIGS. 4 and 5 exhausted substantially of active ingredients, filler and binder. The matrix when exhausted retains its general contour with the edges 6 thereof chipped due to the tumbling action which takes place during treatment but retaining its identity as a matrix.

The following examples illustrate the invention.

EXAMPLE 1

The vasodilator, comprising triethanolamine trinitrate biphosphate, for treating angina pectoris to prevent attacks or reduce their number and severity, is administered over prolonged periods. Each of such tablets, made as hereinbefore set forth, has the following ingredients:

	Mg.
Carnauba wax	50.00
Magnesium sterarate	12.00
Triethanolamine trinitrate biphosphate	10.00
Calcium phosphate, tribasic and talc	80.00
Methylcellulose	2.00
Glucose (binder)	10.00

The filler in the finished tablet is comprised of magnesium stearate, calcium phosphate tribasic, talc and methylcellulose, each of the first and last mentioned agents also performing another function as indicated heretofore.

Each finished tablet weighs 164 mg.; is about 3.2 mm. thick; has a hardness of 4–6 kg. (determined by a Monsanto Hardness Tester) and a diameter of about five-sixteenths of an inch.

When tested for 1 hour in simulated gastric juice and then for 7 hours in simulated intestinal juice, the weight of the wax is about 47 mg.; the recovered filler removed from the matrix and found in juices, about 63 mg.; the active ingredient has been substantially entirely leached out and the binder has been eliminated. About 6% of the matrix has been lost but structurally it remains intact.

Further examples of the contents of various pharmaceutical tablets which can be made by the use of this invention and following the several steps above set forth follow:

In each of the following examples, 2 to 11, the tablets are prepared in the same manner as the tablets of Example 1, substituting in place of the active ingredient of Example 1 the specific active ingredient named in each individual example. In such tablets the wax should range between 28% and 32% of the total weight of the tablet. The remaining ingredients are varied proportionally from the amounts set forth in Example 1.

EXAMPLE 2

An analgesic containing per tablet 2½ grs. of aspirin.

EXAMPLE 3

A barbiturate preparation may be prepared containing per tablet 10 mg. of barbituric acid derivatives and 2.5 mg. of homatropine methyl bromide.

EXAMPLE 4

A sympathomimetic compound containing per tablet 5 mg. of d-desoxyephedrine hydrochloride.

EXAMPLE 5

A parasympathomimetic compound containing per tablet 5 mg. of bethanediol chloride.

EXAMPLE 6

An antihistamine containing per tablet 4 mg. of chlorprophenpyridamine maleate.

EXAMPLE 7

A cardiac glycoside containing per tablet 0.2 mg. of digitoxin.

EXAMPLE 8

An alkaloid preparation containing per tablet 2.5 mg. of homatropine methyl bromide and 15 mg. of sodium phenobarbital.

EXAMPLE 9

A stimulant for the central nervous system containing per tablet 5 grs. of theobromine and one-half gr. of luminal.

EXAMPLE 10

A hormone preparation containing 0.05 mg. of ethinyl estradiol.

EXAMPLE 11

An antibiotic containing 50,000 units of aluminum penicillin.

A specific example has been set forth as illustrative of each class of medicinal preparations referred to heretofore. Any particular pharmaceutical, therapeutic agent or drug which is administrated in a solid form (in contradistinction to those administered in the form of solutions, suspensions, elixirs, syrups, or like liquid types) and as to which a slow, gradual and continuous release of the active ingredient is desired, can be prepared in tablet form following the disclosure of this invention.

Many therapeutic preparations are prepared as to which slow and continuous release of the active ingredient has no particular advantage. Tablets with such ingredients could be prepared according to this invention but would not have any particular advantages in therapy. Other preparations require that the whole dosage be made quickly available for therapeutic action. As to the latter this invention would not be advantageous.

The amount of the active ingredient or ingredients per tablet of any particular medicinal preparation may be equal to the amounts now employed or such amounts may be increased as medical advice deems desirable even up to doubling the amount of the active ingredient or ingredients.

The tablets may be given an enteric coating should it be desired that they pass through the stomach into the intestines without being acted upon by the gastric juices. They may also be given a coating of edible shellac or such other coating or treatment as is usual in the manufacture of medicinal tablets.

It will be evident from the foregoing specification that the matrix must be resistant to the gastric and intestinal juices and must not disintegrate in such juices, or in either of them, nor disintegrate by the physical action of the gastrointestinal tract upon matter entering such tract. It is further evident that the matrix must have voids or channelling therein filled with an active ingredient and a filler or extender but nevertheless be in the form of a continuous skeleton-like frame from the voids or channelling whereof the gastrointestinal juices slowly and continuously leach out the active ingredient which is made continuously available in the human system for its value in therapy.

These advantages are accomplished by forming the tablets from a mixture of the named ingredients in which, when tableted, the several ingredients take a definite relation to each other. Actually the matrix, in its skeleton form with voids or channelling, is cast or formed by the presence of the filler, carrying the active ingredient in intimate mixture therewith, insuring that the material of the matrix does not per se form a solid body or form a solid coating on the surface of the tablet which, did that occur, would defeat the purposes of this invention.

Throughout this specification the term "tablet" has been used to identify the product but such use is to be understood as not referring to the shape but rather to the

fact that the product is in solid form without regard to its particular shape or configuration and is to be so interpreted in the claims.

We claim:

1. A medicinal tablet for oral administration comprising a continuum of a non-toxic matrix in skeleton form, said matrix consisting essentially of wax which has a melting point between about 65° and about 90° C. and is insoluble in digestive juice, and said matrix having in the interstices thereof interconnected canals and ducts, the canals and ducts being filled with a drug and leachable filler, the canals and ducts being continuous to the outer surfaces of the tablet so that a portion of said drug and filler extends to and is exposed on an outer surface of said tablet, the matrix resisting disintegration in digestive juices and retaining substantially its original tablet form during the entire leaching out period, said tablet requiring a period of at least about 8 hours for the drug to be substantially completely leached therefrom by the action of said digestive juice.

2. A tablet according to claim 1 wherein the said wax is carnauba wax.

3. A medicinal tablet for oral administration comprising a continuum of an indigestible, non-toxic matrix in skeleton form, said matrix comprising from about 28 percent to about 32 percent of carnauba wax having a melting point between about 65° C. and 90° C., said matrix having in the interstices thereof an intimate mixture of an active ingredient, triethanolamine trinitrate biphosphate, and filler, a portion of said active ingredient and filler extending to and being exposed on an outer surface of said tablet, the matrix resisting disintegration in gastric and intestinal juices, active ingredient on said surface quickly leaching out in gastric juices and active ingredient and filler slowly and continuously leaching out of said interstices in intestinal juices, the matrix retaining substantially its original tablet form during the entire leaching out period, said tablet requiring a period of about 8 hours for the active ingredient to be substantially leached therefrom by the action of said gastric and intestinal juices.

4. A medicinal tablet of the character set forth in claim 3 wherein the tablet contains about 10 mg. of triethanolamine trinitrate biphosphate.

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