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SUSTAINED RELEASE PHARMACEUTICAL TABLETS

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ABSTRACT OF THE DISCLOSURE

A sustained release pharmaceutical tablet characterized by a substantially constant rate of drug release comprising: (a) a medicament; (b) a hydrophobic dissolution retardant; (c) an acid-insoluble release agent; and (b) a water-soluble or dispersible binder.

BACKGROUND OF THE INVENTION

This invention relates to novel orally administrable dosage forms. In particular, it relates to the preparation of sustained release tablets capable of disintegrating at a constant and uniform rate.

Although many of the newer drugs now being prescribed are extremely effective, in many instances serious side-effects are encountered with conventional dosage forms, even at low dosage levels. As a consequence, it is advantageous to carefully control the rate of release of medicaments of this type. One means of overcoming this problem is to employ dosage forms that are capable of slowly releasing the medicament at a reasonably uniform and constant rate.

In addition, such dosage forms enable the physician to more carefully regulate the level of drug administration to the patient. A further advantage of sustained release dosage forms to the patient is the fact that a lesser number of them need be taken during the course of treatment.

Where oral administration is desired, one means for obtaining the above objective is to employ capsules or tablets which release the drug at a uniform rate during the capsule's passage through the gastro-intestinal tract.

In the past this object has been achieved by admixing one or more inert ingredients with the drug in such a manner that these inactive materials interfere with the disintegration of the tablet or the dissolution of the drug. An obvious form of such a tablet is one wherein a core containing the active ingredient is surrounded by a layer of inert materials. For example, the tablet may be coated with an enteric substance, in which case the tablet passes unchanged through the stomach and disintegrates in the intestinal tract. Alternatively, tablets can be composed of several alternate layers of medicament and inert material. In this manner, as each alternate protective layer disintegrates the patient receives a further dose of medicament. However, tablets of this type suffer from the disadvantage of not providing a uniform and constant drug release. Furthermore, such tablets are difficult to prepare with precision so that in many instances the desired dosage level cannot be assured.

The present invention describes sustained release dosage forms which will provide a uniform and constant liberation of medicament.

SUMMARY OF THE INVENTION

This invention comprises a sustained release pharmaceutical tablet comprising: (a) a medicament; (b) a hydrophobic dissolution retardant; (c) an acid insoluble release agent; and (d) a water soluble or dispersible binder. The product of this invention is characterized by having a substantially constant erosion rate in gastro-intestinal fluid wherein the medicament is released at a constant and uniform rate.

This invention further comprises a sustained release pharmaceutical tablet containing up to 70% by weight of a medicament, 15–50% by weight of a hydrophobic dissolution retardant, 0.1–5.0% by weight of an acid-insoluble release agent and 5–15% by weight of a water soluble or dispersible binder.

DETAILED DESCRIPTION OF THE INVENTION

I have now discovered a dosage pharmaceutical formulation that will provide a sustained release of medicament. The formulation comprises an intimate uniform blend of a water soluble or insoluble medicament, a hydrophobic dissolution retardant, an acid-insoluble release agent, and a water soluble or dispersible binder. Other customary tablet ingredients such as fillers, colorants, lubricants, stabilizers and excipients can also be included in the formulation as required. Tabletting of this blend provides a pharmaceutical tablet wherein the aforesaid constituents are uniformly dispersed throughout the tablet matrix. Alternatively, the blend can be formulated into a capsular form as well.

The range of the basic ingredients can be varied over a considerable latitude and yet will provide an orally administrable dosage form having a constant and uniform rate of disintegration. Thus, the following ranges have been found to be effective (the percentages are by weight): up to 70% of medicament; 15–50% of hydrophobic dissolution retardant; 0.1–5% of acid insoluble release agent; and 5–15% of a water soluble binder.

A preferred formulation would comprise about 5–25% of medicament; 20–30% of hydrophobic dissolution retardant; 0.5–1.0% of acid-insoluble release agent; and 7.5–11% of water-soluble binder.

An outstanding advantage of the present invention is the fact that a mixture of water soluble and insoluble medicaments can be incorporated into the blend and after tableting each individual medicament will be released from the tablet at a uniform and constant rate. Thus we have prepared a sustained release dosage form containing theophylline, ephedrine sulfate and hydroxyzine hydrochloride, wherein each pharmaceutical has been found to be released in simulated intestinal fluid at a reasonably constant and uniform rate.

Various types of medicaments can be used in the instant invention, such as antihistamines, hypoglycemics, antidepressants, coronary vasodilators, bronchodilators, sedatives, decongestants, antispasmodics, vitamins, and the antibiotics.

The hydrophobic dissolution retardants, by virtue of their water insolubility, function by retarding the dissolution and diffusion of the drug from the tablet or granulates into the gastro-intestinal fluid. Among the hydrophobic dissolution retardants that we have found effective are the natural and synthetic waxes, resins and plastics. Of these we prefer carnauba wax, beeswax, spermaceti, and the commercial product Sterotex K–100, which is a hydrogenated cottonseed oil available from Capital City Products, Columbus, Ohio.

Enteric substances, insoluble in the acidic stomach juices, are the preferred acid-insoluble release agents. Of these we prefer cellulose acetate phthalate and the other acetate phthalates; the esters of the carbohydrate polymers; and the phthalic acid derivatives of polyacrylic acid.

The effect of the water-soluble or dispersible binder is to insure a uniform release of the drug. Although the binders of choice are the polyvinyl pyrrolidones, acacia and other water-soluble or dispersible binders well known to those skilled in the art, may be used.

As previously stated, besides the above essential ingredients other conventional tableting ingredients may also be included in the blend. Thus, antioxidants, e.g., ascorbic acid, sodium metabisulfite; lubricants, e.g., talc, magnesium stearate and sodium lauryl sulfate; fillers e.g., calcium diphosphate; and colorants are generally added to further improve the product. Nevertheless, it should be understood that the inclusion of the hydrophobic dissolution retardant, the acid-insoluble release agent, and the water-soluble or dispersible binder, in amounts constituting an effective ratio, within the ranges previously indicated, constitute the critical features of the present invention.

The tablets can be prepared from the blended ingredients in the usual manner, e.g., dry blending followed by compression into tablets, or dry slugging and granulating the blended ingredients prior to compressing them into tablets, etc. The tablets may also be prepared by first wet granulating the blend with a suitable solvent or binder solution or dispersion, such as alcohol or polyvinyl pyrrolidone colloidal solution.

The tablet erosion studies are conducted with the tablet distintegration apparatus described in U.S.P. XVII. Simulated gastro-intestinal fluids, the preparation of which are described in U.S.P. XVII, are used in the test. The tablets are placed in the apparatus and initially contacted with simulated gastric juices for one hour. The weight loss of the tablets is then determined. The gastric juice is then removed, simulated intestinal fluid is added to the apparatus, and the course of the disintegration of the tablets is followed over the course of the next few hours by periodically determining the weight loss of the tablets. The drug dissolution rate is also determined in this test by periodically assaying the amount of drug that dissolves in these fluids over the course of several hours. The drug dissolution rate ran also be determined by the in vitro test for timed-release capsules and tablets outlined in the second supplement of N. F. XII.

The following examples are provided to further illustrate the scope of the present invention; however, they should not be considered as limiting the scope thereof.

EXAMPLE I

The ingredients listed below are dry blended and directly compressed into tablets on a rotary or single punch tableting machine:

	Grams/ 4,000 tablets	Milligram/ tablet
Metamine and dicalcium phosphate [1]	146.80	36.70 (5.25%) [1]
Dicalcium phosphate	383.08	95.77
Light brown dye	0.52	0.13
Cab-O-Sil [2]	8.00	2.00
Magnesium stearate	12.00	3.00
Carnauba wax	197.60	49.40 (23.5%)
Polyvinylpyrrolidone Type "C" [3]	84.00	21.00 (10%)
Cellulose acetate phthalate	8.00	2.00 (0.95%)
Total weight, ca	840	210

[1] Representing 30% active potency. 17.5% of total blend.
[2] Anhydrous particulate silica available from Cabot Corporation, 125 High Street, Boston, Massachusetts.
[3] Available from the Cabot Corp.

144 tablets are tested in the disintegration test described in U.S.P. XVII. For the first hour the tablets are contacted with gastric juice and for the remaining time with intestinal juice. At the end of each hour's testing, the apparatus containing the tablets is placed in a beaker containing fresh gastro-intestinal fluid. The fluid containing the dissolved drug is filtered and an aliquot is taken and quantitatively assayed by a suitable method. The quantity of drug determined to have dissolved in the total amount of gastro-intestinal fluid is converted to percent of total drug contained in the aggregate of tablets by dividing with the total amount of drug represented by the aggregate of tablets, and multiplying by 100%.

The pertinent results are given in the table below.

DRUG DISSOLUTION RATE

Time/hours	Cumulative amount of metamine released, percent	Amount of metamine released/ hour, percent
1 [1]	39.0	39.0
2	50.7	11.7
3	59.9	9.2
4	71.1	11.2
5	82.2	11.1
6	92.4	10.2
7	98.9	6.5

[1] First hour in gastric juice; thereafter in intestinal fluid.

EXAMPLE II

All of the ingredients below, except the lubricant magnesium stearate are dry-blended for 15 minutes.

	Grams 5,000 tablets	Mg./Tablet
Metamine at 100% and 10% overage	55.00	11.00 (5.5%)
Dicalcium phosphate	516.85	103.37
Light brown dye	0.65	0.13
Cab-O-Sil	10.00	2.00
Magnesium stearate	5.00	1.00
Carnuba Wax 60 mesh	300.00	60.00 (30%)
Polyvinylpyrrolidone Type C	100.00	20.00 (10%)
Cellulose acetate phthalate	12.50	2.50 (1.25%)
Total weight, ca	1,000	200

The particles are passed through a 40 mesh screen using a Fitzmill, hammers leading at medium speed. The mixture is reblended for 30 minutes and moistened with 50 g. of methanol in a Hobart blender. The moist mixture is passed through a 40 mesh screen (Fitzmill, hammers leading at medium speed). The final mixture is air dried without heat for 30–45 minutes. The magnesium stearate is then added and the mixture is blended for 5 to 10 minutes. The tablets are prepared by compressing on a rotary tablet press using $\frac{5}{16}$ in. standard round concave punches and dies, to a thickness of 0.141 ± 0.005 in. thick and a hardness of 7 kg. (Pfizer tester).

The rate of drug dissolution is determined in the same manner as detailed above.

DRUG DISSOLUTION RATE

Time/hours	Cumulative amount of metamine released, percent	Amount of metamine released hour, percent
1 [1]	35.02	35.02
2	43.76	8.74
3	50.72	6.96
4	56.67	5.95
5	64.79	8.12
6	77.55	12.76

[1] First hour in gastric juice; thereafter in intestinal fluid.

EXAMPLE III

With the exception of magnesium stearate, the ingredients listed below are dry-blended for 15 minutes and passed through a 40 mesh screen:

Metamine and dicalcium phosphate [1]	183.50	36.70 (5.5%)
Butabarbital	247.86	49.57 (24.8%)
Dicalcium phosphate	150.64	30.128
FD&C Blue No. 1, Lake (11%)	0.50	0.10
Cab-O-Sil	10.00	2.00
Magnesium stearate	5.00	1.00
Carnauba Wax, 60 Mesh	285.00	57.00 (28.5%)
Polyvinylpyrrolidone type C	100.00	20.00 (10%)
Cellulose acetate phthalate	17.50	3.50 (1.75%)
Total weight, ca	1,000	200

[1] Representing 30% active potency—18.3% of total blend.

The ingredients are reblended for 30 minutes and moistened with 75 g. of 2B ethanol. The mixture is stirred in a Hobart mixer until nearly dry and passed through a 40 mesh screen and reblended. The mixture is then air dried until the odor of the solvent is no longer detectable, and the lubricant is added. The mixture is briefly blended

and compressed into tablets under the following conditions: the dry powder granulates are placed in the hopper without further processing and compacted into tablets using 5/16 in. standard round concave punches and dies on a rotary tablet press to a hardness of 7 kg. (Pfizer tester).

The rate of drug dissolution is detrmined identically to the previously described method:

DRUG DISSOLUTION RATES

Time/hours	Cumulative amount of metamine released, percent	Amount of metamine released/ hour, percent	Cumulative amount of butabarbital released, percent	Amount of butabarbital realeased/ hour, percent
1 [1]	26.1	26.1	11.06	11.06
2	36.9	10.8	22.89	11.83
3	47.7	10.8	32.98	10.09
4	60.4	12.7	41.3	8.32
5	70.8	10.4	48.56	7.26
6	80.0	9.2	54.37	5.81
7	90.5	10.5	60.47	6.10

[1] First hour in gastric juice; thereafter in intestinal fluid.

EXAMPLE IV

The ingredients tabulated below are blended together under the following conditions: All except the metamine and the lubricant are preblended, passed through a 40 mesh screen in a Fitzmill, hammers leading at high speed. The mixture is reblended, half the lubricant is added, and the blend is briefly mixed again prior to slugging. The slugs are granulated on a stokes or other suitable oscillating granulator. Fines (<60 mesh) are separated and thoroughly blended with the metamine. This mixture containing the active drug is blended with the remainder, the dry granulation. The remaining half of magnesium stearate is added to the total blend of granules, followed by brief reblending. Tablets are prepared by compressing on a rotary tablet press in accordance with previously defined procedures.

	Gram/ 10,000 tablets	Milligrams/ tablet
Metamine and dicalcium phosphate blend [1]	428.85	42.89 [1] (6.14%)
Butabarbital	495.72	49.57 (23.6%)
Dicalcium phosphate	343.93	34.39
FD&C Blue No. 1, Lake (11%)	2.00	0.20
Cab-O-Sil	21.00	2.10
Magnesium stearate	31.50	3.15
Sterotex K-100 [2]	315.00	31.5 (15.0%)
Polyvinyl pyrrolidone, type C	315.00	31.5 (15.0%)
Dextrose	52.50	5.25
Cellulose acetate phthalate	63.00	6.30 (3.00%)
Talc	31.50	3.15
Total, ca	2,100	210

[1] Representing 30% active potency, 20.4% of total blend.
[2] Hydrogenated cottonseed oil available from Capital City Products Co., Columbus, Ohio.

RATE OF DISINTEGRATION

Time/hours	Percent weight loss	Percent hourly change
1 [1]	28.97	
2	41.43	12.46
3	57.42	15.99
4	70.04	12.62
5	84.38	14.34
6	94.34	9.96

[1] First hour in gastric juice; thereafter in intestinal fluid.

The rate of drug dissolution is as follows:

DRUG DISSOLUTION RATES

Time/hours	Cumulative amount of metamine released, percent	Amount of metamine released/ hour, percent	Cumulative amount of butabarbital released, percent	Amount of butabarbital released/ hour, percent
1 [1]	28.3	28.3	14.6	14.6
2	35.4	7.1	30.7	16.1
3	43.5	8.1	43.6	12.9
4	53.3	9.8	56.4	12.8
5	63.4	10.1	69.5	13.1
6	73.2	9.8	82.9	13.4
7	82.4	9.2	94.9	12.0

[1] First hour in gastric juice; thereafter in intestinal fluid.

EXAMPLE V

With the exception of magnesium stearate, the ingredients listed below are blended together for 30 minutes in a suitable blender, after passage through a 40 mesh screen on a Fitzmill comminator. A portion of the magnesium stearate (1.5%) is added, and the mixture is briefly blended and slugged with ½ in. standard round flat punches and dies to a hardness of 8 kg. and 400 mg. weight. The slugs are granulated through an 18 mesh screen on an oscillating granulator. The remainder of the magnesium stearate is blended into the resultant granulation. The blend is compressed on a suitable tablet press, to a weight of 512.5 mg. for a hardness of 10 kg. (Pfizer tester).

	Grams/ 2,000 tablets	Milligrams/ tablet
Theophylline	400	200 (39%)
Ephedrine sulfate	100	50 (9.75%)
Hydroxyzine dihydrochloride	50	25 (4.87%)
Dicalcium phosphate	30	15
Cab-O-Sil	10	5
Sterotex K-100	260	130 (25.4%)
Cellulose acetate phthalate	10	5 (0.98%)
Polyvinylpyrrolidone, type C	100	50 (9.75%)
Talc	40	20
Magnesium stearate	25	12.5
Total weight, ca	1,025	512.5

RATE OF DISINTEGRATION

Time/hours	Cumulative percent weight loss	Percent hourly change
1 [1]	22.9	22.9
2	39.8	16.9
3	55.5	15.7
4	73.9	18.4
5	89.8	15.9

[1] First hour in gastric juice; thereafter in intestinal fluid.

DRUG DISSOLUTION RATE

Time/hours	pH	Cumulative amount of theophylline released, percent	Amount of theophylline released/ hour, percent	Cumulative amount of ephedrine released, percent	Amount of ephedrine released/ hour, percent
½	1.3	14.3		32.7	
1 [1]	1.3	22.7	22.7	45.3	45.3
2	2.5	37.9	15.2	62.4	17.1
3	6.8	50.1	12.2	74.7	12.3
4	7.25	62.8	12.7	87.3	12.6
5	7.50	75.4	12.6	96.1	8.8

[1] First hour in gastric juice; thereafter in intestinal fluid.

Time/hours	pH	Cumulative amount of hydroxyzine dihydrochloride released, percent	Amount of hydroxyzine dihydrochloride released/ hour, percent
½	1.3	26.1	
1 [1]	1.3	36.4	36.4
2	2.5	50.9	14.5
3	6.8	58.7	7.8
4	7.25	67.0	8.3
5	7.5	76.2	9.2

[1] First hour in gastric juice; thereafter in intestinal fluid.

EXAMPLE VI

The ingredients listed below are blended and tableted according to the procedure in Example V.

	Grams/ 2,000 tablets	Milligrams/ tablet
Theophylline	500	250 (50%)
Ephedrine sulfate	130	65 (13%)
Hydroxyzine dihydrochloride	70	35 (7%)
Sterotex K-100	150	75 (15%)
Cellulose acetate phthalate	10	5 (0.1%)
Polyvinylpyrrolidone Type C	80	40 (8%)
Dicalcium phosphate	20	10
Cab-O-Sil	10	5
Talc	16	8
Magnesium stearate	14	7
Total weight, ca	1,000	500

The rate of disintegration and rate of drug dissolution of these tablets are found to be constant and uniform when determined according to the tests described in the preceding examples.

EXAMPLE VII

The ingredients listed below are blended and tableted according to the procedure of Example V.

	Grams/ 2,000 tablets	Milligrams/ tablet
Theophylline	350	175 (35%)
Ephedrine sulfate	70	35 (7%)
Hydroxyzine dihydrochloride	30	15 (3%)
Sterotex K-100	200	100 (20%)
Cellulose acetate phthalate	50	25 (5%)
Polyvinylpyrrolidone Type C	150	75 (15%)
Dicalcium phosphate	50	25
Cab-O-Sil	10	5
Talc	50	25
Magnesium stearate	40	20
Total weight, ca	1,000	500

The rate of disintegration and rate of drug dissolution of these tablets are found to be constant and uniform when determined according to the tests described in the preceding examples.

EXAMPLE VIII

The ingredients listed below are blended and tableted according to the procedure of Example V.

	Grams/ 2,000 tablets	Milligrams/ tablet
Theophylline	200	100 (20%)
Ephedrine	70	35 (7%)
Hydroxyzine dihydrochloride	30	15 (3%)
Sterotex K-100	500	250 (50%)
Cellulose acetate phthalate	30	15 (3%)
Polyvinylpyrrolidone Type C	100	50 (10%)
Cab-O-Sil	10	5
Dicalcium phosphate	30	15
Talc	10	5
Magnesium stearate	20	10
Total weight, ca	1,000	500

The rate of disintegration and rate of drug dissolution of these tablets are found to be constant and uniform when determined according to the tests described in the preceding examples.

EXAMPLE IX

The procedure of Examples VI–VIII is repeated with substantially the same results, replacing the Sterotex K-100 with the following ingredients:

Carnauba wax
Spermaceti
Hydrogenated castor oil
Shellac

EXAMPLE X

The procedures of Examples VI to IX are repeated with substantially the same results replacing the cellulose acetate phthalate with starch acetate phthalate.

EXAMPLE XI

The ingredients below are blended and tableted in the manner described in the previous examples.

	Grams/ 10,000 tablets	Milligram/ tablet [1]
Metamine and dicalcium phosphate [1]	367.60	36.76 (4.8%)
Dicalcium phosphate	891.60	89.16
Light brown dye	1.3	0.13
Cab-O-Sil	21	2.1
Magnesium stearate	42	4.2
Sterotex K-100	462	46.2 (20.08%)
Polyvinylpyrrolidone Type C	210	21.0 (9.13%)
Cellulose acetate phthalate	63	6.30 (2.74%)
Talc	31.5	3.15
Dextrose	21	2.10
Dried corn starch	189	18.90
Total Weight, ca	2,300	230

[1] Representing 30% active potency. 16% of total blend.

Tests A, B, and C below are conducted with the disintegration aparatus described in USP XVII. In Tests A and B, the tablets are contacted with gastric juice to 1 hour and then with intestinal fluid to 4 hours. At the end of the 4 hour period the tablets are contacted with fresh intestinal fluid to 7 hours. In Test C the tablets are contacted with gastric juice for the first hour and thereafter with intestinal fluid, with hourly change to fresh fluid.

Test A.—144 tablets

Time/hours:	Amount of metamine released/time interval
1	33.3
4	16.3
7	20.4
Total	70.0

Test B.—48 tablets

Time/hours:	Amount of metamine released/time interval
1	34.2
4	12.5
7	19.2
Total	65.9

Test C.—144 tablets

Time/hours:	Amount of metamine released/time interval
1	30.4
2	6.6
3	2.8
4	3.8
	13.2
5	5.7
6	5.2
7	5.2
	16.1
Total	59.7

Test D

This test is conducted according to the procedure in N.F. XII, using 12 tablets per screw cap bottle.

	Metamine dissolution rate determined from residue assay		Metamine dissolution rate determined from solution assay	
Time/ hours	Cumulative amount of metamine released, percent	Amount of metamine released/ time interval	Cumulative amount of metamine released, percent	Amount of metamine released/ time interval
1	39.9	39.9	38.7	38.7
2	55.2	15.3	52.0	13.3
3.5	68.0	12.8	64.5	12.5
5	79.0	11.0	79.5	15.0
7	90.0	11.0	92.4	12.9

What I claim is:

1. A sustained released pharmaceutical tablet essentially containing, uniformly dispersed throughout the tablet matrix, about 5 up to 70% by weight of a medicament, 5–50% by weight of a hydrophobic dissolution retardant selected from the group consisting of hydrogenated cottonseed oil, hydrogenated castor oil, carnauba wax, beeswax, spermaceti, and shellac, 0.1–5.0% by weight of an enteric acid-insoluble release agent selected from the group consisting of cellulose acetate phthalate, starch acetate phthalate and a phthalic acid derivative of polyacrylic acid, and 5–15% by weight of a water-soluble or dispersible binder, effective to insure a uniform release of the medicament, selected from the group consisting of polyvinyl pyrrolidone and acacia.

2. A sustained release pharmaceutical tablet according to claim 1 comprising: (a) 5–6% by weight of triethanolamine trinitrate biphosphate; (b) 22–25% by weight of carnauba wax; (c) 0.80–1.20% by weight of cellulose acetate phthalate; and (d) 8–12% by weight of polyvinylpyrrolidone.

3. A sustained release pharmaceutical tablet according to claim 1 comprising: (a) 5–7% by weight of triethanolamine trinitrate biphosphate; (b) 22–25% by weight of butabarbital; (c) 13–17% by weight of hydrogenated cottonseed oil; (d) 2–4% by weight of cellulose acetate phthalate; and (e) 13–18% by weight of polyvinylpyrrolidone.

4. A sustained release pharmaceutical tablet according to claim 1 comprising: (a) 37–41% by weight of theophylline; (b) 8–11% by weight of ephedrine sulfate; (c) 4–6% by weight of hydroxyzine dihydrochloride; (d) 23–26% by weight of cottonseed oil; (e) 0.8–1.2% by weight of cellulose acetate phthalate; and (f) 8–12% by weight of polyvinylpyrrolidone.

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